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Contents

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PRESIDENT'S PAGE

Protecting the Mental Health of Our Young Patients

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In the last few years, the discourse around mental health has been taking precedence on a global scale. People seem to be more aware about the appearance of mental duress in their loved ones, much like we used to be with the overt exhibition of fever and fatigue in a family member, back in the day. While many in my generation still struggle to perfectly verbalize our thoughts on these topics, the younger generation is making a welcome shift towards identifying and articulating one's own mental state and its interlinkage with productivity in other spheres of life. While pondering over this, I was struck by the gap in the benefits of this shift for our young patients who are too young to process these emotions, let alone articulate them.

Evidence suggests that about 20% of the world's population is neurodiverse. This could include being on the autism spectrum disorder, having attention deficit hyperactivity disorder (ADHD), dyslexia, dyspraxia, Tourette syndrome, amongst others. Two things struck me instantly as I read this statistic. First, about how this implies that every fifth patient of mine is, on some level, perhaps spending a confused childhood, trying to understand how he/she does not fit into the standard schema of what is expected from an ideal child. Such a thought – usually persistent throughout childhood – can be terrifying and traumatizing. Second, looking back (to over three and half decades ago) to my medical college days, I am struck by how, while we were trained to become extremely vigilant about the smallest signs and symptoms of any physical atypicality in our patients, little time was spent trying to understand the subtle signs of neurodivergence in a child. Pediatricians are often the first point of contact for the parent for any health-related concern of the child. Although we are aware about the importance of mental health and well-being in a child, we ourselves often lack awareness regarding how it translates to a child's development and how we could play an influential role in identifying when a child is undergoing mental health difficulties. I am now spending more time trying to understand how, as a clinician, I can be more attentive towards the nature of my patient's mental health.

Neurodivergence, much like any other aspect of our physiology, is an ever-developing phenomenon, which is why it can manifest in a wide range through early infancy, childhood and adolescence. Naturally, this variability also leads to differing challenges through every stage, and so, there cannot be a generalized protocol that we could follow for every child. Hence, it becomes important to just understand a few key markers that we could watch for in our everyday practice. Mindfulness is the key here. A lot of us are parents ourselves, and just like it takes practice and patience to change a long-term sticky habit, it takes active effort to accept thoughts or behaviors that go against the traditional criteria of 'normal' behaviors. It also goes to show that any change becomes difficult to implement with time, so identifying certain aberrations in a child's development due to mental health reasons becomes all the more important, as early sensitization of parents and early intervention gives the best prognosis to a child.

Early infancy is a period where we know the purest indicator of mental health are developmental milestones. During routine check-ups, a question or two about the child's attachment patterns, temperament, nature of reciprocal interaction, and social attitudes can reveal a lot about the child's early developmental markers. In such a situation, we guide the parents towards a developmental pediatrician or occupational therapy just as simply as prescribing medication. Here, if we take a few extra minutes to stress on the importance of these early interventions, it goes a long way in ensuring compliance. Parents are still hesitant to visit psychologists, counselors or therapists unprompted, due to the stigma still attached to a psychological diagnosis. As pediatricians, our word can be a convincing behavior change communication. Many children with developmental delays grow up to have either borderline intellectual functioning or are slow learners in academics. Early sensitization for the parents on the display of mildly neurodivergent behavior can save a lot of pressures that the toddler will subsequently face in the next developmental phase - as a child.

After the home, the school occupies the center stage in a child's life. As a country, we have always been

dangerously obsessed with good marks, as we look at academic performance as the highest reflection of our child's intelligence. We are all aware about the reflection of this attitude in the disheartening student suicide rates in India. Within the context of learning disabilities, ignorance of parents, teachers (and often doctors), together with the competitive nature of the world, unfair expectations from the child, and the endless unproductive distractions available to the child is a recipe for developing a depressive, or anxious personality for a child struggling with their own neurodivergence. At such times, equipping the parents with the basic information and guiding them towards the right direction can go a long way. A question about the child's academic performance, social interaction or play or behavioral patterns can reveal underlying mental health stress like anxiety or sadness. A child is too young to understand and process her own emotions so she would find it difficult to express if she is feeling sad. Children are often embarrassed about these emotions too since we are yet to normalize feeling sad/anxious and these emotions are often looked at negatively or as a sign of a weak mind. Hence a child's behavior and any deviation from it becomes an important marker for diagnosis. Stress induces an inflammatory cascade and can induce somatic complaints which mimic physical ailments and if the symptoms coincide with missing examinations, bunking school or tuitions, they suggest a psychological association. In adolescence, although your patients can perhaps communicate their problems to you, they will trust you as a doctor only if they find your attitude towards them accommodating and accepting at least in comparison to their parents. As pediatricians, simple counseling to parents on these matters during routine check-ups can have a huge impact on the household conversations. Further, if the child is present and overhears you verbalizing these thoughts to her parents, the child can look up to you as a positive role model, and the clinic becomes a safe space.

As pediatricians, we often watch our patients grow up right before our eyes. I now have several former patients who come to me with toddlers of their own. These are patients who have made me a part of their key milestones – coming into the clinic with sweets upon passing exami-nations, finding a job, a wedding invite, and then babies of their own. After decades of practice, I have come to believe that pediatricians are uniquely posed to observe the entirety of someone's childhood. Just by being slightly more perceptive and observant about developmental markers as much as physical markers in everyday clinical practice, we could be making the most significant contribution to a patient's life.

NOTICE

IAP-ICP RESEARCH GRANTS 2023

The Indian Academy of Pediatrics (IAP) and Indian College of Pediatrics (ICP) announce IAP-ICP Research Grants 2023, to foster a research environment amongst the undergraduate medical students, pediatric postgraduate students, young pediatric faculty, and practicing pediatricians, for carrying out a research project related to child health. Applications are invited from interested researchers for the following categories of grants.

1. Undergraduate Pediatric Research Grant: 10 grants of Rs. 10,000/each
   (Who can apply: MBBS Students)
2. Postgraduate Pediatric Research Grant: 4 grants of Rs. 25,000/each
   (Who can apply: MD/DNB Pediatrics Students)
3. Young Researcher Grant: 4 grants of Rs. 25,000/each
   (Who can apply: Young (age <40 years) faculty/ Residents/Tutors in Medical Colleges/Hospitals, within 5 years of completing postgraduation in Pediatrics)
4. Practicing Pediatrician Research Grant: 8 grants of Rs. 25,000/each
   (Who can apply: Life members of IAP in office practice)
5. Pediatricians in small institutes: 4 grants of Rs. 25,000/- each
   (Who can apply: Pediatricians in level 1 and level 2 health care institutes)

The details of the grant scheme are available on IAP (*www.iapindia.org*) and ICP (*icpindia.org.in*) websites.

Last date of receiving project proposals with completed application forms is 30th June, 2023.

INVITED COMMENTARY

Investigating Probiotics in the Management of Childhood Functional Constipation: A Never-Ending Story?

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Over the past two decades, several studies have evaluated the effectiveness of probiotics in the management of childhood functional constipation (FC). A recently published systematic review by the Cochrane Collaboration concluded that there is still insufficient evidence to draw conclusions as to whether probiotics are effective in improving defecation parameters such as defecation frequency and stool consistency or achieving global treatment success [1]. Despite inconclusive results from studies thus far, researchers have continued their search to find a probiotic strain or a combination of probiotic strains that positively affect childhood FC. In this issue of the journal, Lojanatorn, et al. [2] report the results of a pilot randomized controlled trial evaluating the effect of four weeks of once daily administration of *B.clausii* as single treatment in children (1-5 years of age) with FC according to the Rome IV criteria. The primary outcome was treatment success, defined as 'at least three defecations per week and a stool consistency on the Bristol stool chart of at least three.' Treatment success did not differ between both groups after two and four weeks, nor did defecation frequency, stool consistency or other parameters related to defecation. Thus, they concluded that the probiotic strain *B.clausii* was not more effective than placebo in the treatment of childhood FC after two and four weeks of treatment [2].

To support their hypothesis of the influence of the gut microbiota in childhood FC, Lojanatorn, et al. [2] referred to a previous study in adults with FC [3]. That study showed that the prevalence of methanogenic gut flora was higher in adults with slow transit constipation compared to FC with normal colonic transit times and controls, and did not differ between patients with FC with normal colonic transit times and controls. In addition, patients with FC (both slow transit and normal transit) produced significantly more methane following a carbohydrate challenge compared to controls. Patients with slow transit constipation showed higher methane production compared to patients with FC with normal colonic transit times [3]. Although Attaluri, et al. [3] demonstrated an association between methanogenic flora and colonic transit, the authors could not provide evidence for a causative role. In contrast, these findings may even result from slower gastrointestinal transit times, rather than suggest a causative role of methanogenic flora in the development of FC, as was pointed out by the authors of the original study [3]. In addition, these findings do not implicate that the particular probiotic strain *B.clausii* would be helpful in managing FC. More importantly, the study by Attaluri, et al. [3] was conducted in adults and does not provide evidence that gut dysbiosis plays a role in the pathogenesis of childhood FC nor that probiotics would be effective in the management of childhood FC.

Studies evaluating gut microbiota composition in children with FC have resulted in inconsistent findings and no FC-specific gut microbiota signature has been identified for this patient group yet [4]. The discrepancy in findings on microbiota composition may be contributed by different factors, including differences in study design, such as sample collection and storage, applied analytical techniques, and lack of standardization [5]. Moreover, in children, both the pathogenesis of FC and the development of the gut microbiota during the first years of life differ to a great extent from the situation in adults and consequently, results from adult studies are not necessarily applicable to the pediatric population. Whether the gut microbiota plays a role in the pathogenesis of childhood FC and, if so, in what manner, still needs to be elucidated.

In the study by Lojanatorn, et al. [2], the choice for *B.clausii* seems to be based on the concept that most *Bacillus* spp. can produce lactic and short-chain fatty acids from carbohydrate fermentation, resulting in a lower pH within the colonic lumen, which would theoretically increase peristalsis. However, no studies in the pediatric

population have shown an effect of *B.clausii* on transit times or stool composition thus far. On the contrary, a recent study investigating the application of *B.clausii* in children (6-17 years) with irritable bowel syndrome reported no differences in defecation frequency, nor a softening effect on stool consistency compared to placebo [6]. Lack of identification of microbial signatures linked to childhood FC, including their role in the pathogenesis, limits the evidence-based application of microbiota-based interventions, including probiotics, in children with FC. Therefore, the theoretical basis on which the interventional study by Lojanatorn, et al. [2] is based, including the selection of *B.clausii*, seems thin. Unfortunately, the authors did not longitudinally analyze the composition of the gut microbiota, before and after treatment. In addition, no other microbiota-derived out-come measures, such as stool pH or methane production, were taken into account. This impairs the evaluation of the hypotheses on which the choice for *B.clausii* and the selected dosing regimen were based.

In general, it could be questioned if administration of a single probiotic strain can influence the gut microbiota in a sufficient manner to influence defecation patterns. If the gut microbiota would play a role in childhood FC, then a more impactful manipulation of the gut microbiota might be needed, for instance through the administration of probiotic or synbiotic mixtures or even fecal microbiota transplants (FMT) [7,8]. However, before children are exposed to invasive experimental treatments such as FMT, a better understanding of the role of the gut microbiota in the development of childhood FC is essential. Also, the hypotheses on which such treatment strategies are based need to be tested and well-established in the pediatric population first.

In conclusion, a deeper understanding of the potential role of gut microbiota in the pathophysiology of childhood FC needs to be acquired first, in order to allow the design of future RCTs. In such trials, the choice for probiotics or other microbiota-based interventions, including the dosing regimens, needs to be based on evidence that is relevant to the studied population.

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INVITED COMMENTARY

Probiotics for Functional Constipation in Children: Does it Help?

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Functional constipation (FC) is a common problem in children, accounting for 3% of visits to general pediatric clinics, and up to 30% visits to pediatric gastroenterologists in developed countries [1]. The main factor involved in the pathogenesis in children is withholding behavior, usually occurring after experiencing painful defecation. Withholding of feces leads to prolonged fecal stasis in the rectum, with resultant absorption of fluids and hardening of stools. Successive retention of stools in the rectum makes them larger. As the cycle is repeated, successively greater amounts of larger and harder stools are built up in the rectum and passed with even greater pain accompanied by severe "stool withholding maneuvers."

Conventional treatment of children with FC involves non-pharmacological interventions such as parent education, toilet training, and high-fiber diet in combination with pharmacological interventions such as laxatives. According to the 2014 guidelines developed by the European and North American Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN), polyethylene glycol (PEG) is the drug of choice [2]. When PEG is not sufficient, other laxatives (lactulose), may be considered as a second-choice treatment. In a proportion of patients; however, these treatment options do not provide sustained relief of symptoms. Data have shown that 10% of children with functional constipation take laxatives for longer than 12 months, and 40% are still symptomatic despite the use of laxatives [3]. Approximately 50% of children with functional constipation have had at least one relapse within the first 5 years after initial recovery [4]. Therefore, other therapeutic options such as probiotics are being sought. In adults, experimental studies have shown that constipation is often associated with dysbiosis of gut microbiota, consisting of the modified abundance of certain taxa of the colonic microbiome [5]. For example, some data have suggested the decreased abundance of *Bifidobacteria*, *Lactobacillus*, *Bacteroides*, and *Prevotella* [5]. One recent study in children showed that in those with FC, the most discriminative species were *Bacteroides fragilis*, *Bacteroides ovatus*, *Bifidobacterium longum*, *Parabacteroides* species (increased), and *Alistipes finegoldii* (decreased) [6]. However, it remains to be determined if these alterations are a cause or a consequence of altered gut motility. Probiotics are also believed to improve peristalsis and reduce intestinal stasis by modifying the gut microbiota, increasing the production of lactate and short-chain fatty acids, and reducing luminal pH. Considering the potential role of the microbiota, there is a question as to whether modulating the gastrointestinal microbiota plays a role in the management of FC.

The study by Lojanatorn, et al. [7] in this issue of *Indian Pediatrics*, examined the efficacy of *Bacillus clausii* in treating FC in 38 children aged between 1-5 years (20 in the probiotics arm and 18 in placebo arm). In this open-label, double-blinded, placebo-controlled study, children were assigned to receive either *B. clausii* or placebo, once daily for 28 days. At 4 weeks follow-up, the Bristol stool chart grade increased significantly in both groups, compared to baseline. Use of rectal enema decreased over time only in the *B. clausii* group (40% in first 2-week vs 15% between 2-4 weeks, P=0.003) while the placebo group did not show any reduction in rectal enema use (27% each, P>0.99). Neither group showed any reduction in abdominal pain. The primary outcome of the study, treatment success rates (defined as atleast three defecations/week and stool consistency atleast grade 3 on Bristol stool chart) were comparable at 2 weeks and 4 weeks follow-up. Hence, the authors concluded that a 4-week treatment with *B. clausii* was not more effective than a placebo in children with FC.

Different systematic reviews and meta-analyses that studied the role of probiotics in children with FC concluded that there is not enough evidence for the recommendation of probiotics for FC [4,8,9]. The meta-analysis by Wojtyniak, et al. [4] included 7 RCTs and 515 participants with significant heterogeneity with respect to study population, probiotic strains, dosages, study duration, and follow-up. The pooled results of two RCTs (n=108) that investigated the efficacy of *Lactobacillus rhamnosus casei* Lcr35 showed no significant difference between

probiotics and the placebo group [4]. Another meta-analysis by Jin, et al. [8] involving four RCTs and 382 children with FC reported that there were no significant differences in treatment success, spontaneous bowel movements per week, fecal incontinence episodes per week, straining at defecation and use of laxatives between probiotics and placebo. Interestingly, abdominal pain and use of rectal enema were significantly less in the probiotics arm, similar to findings of the present study [7]. One trial evaluated the effectiveness of *L. rhamnosus* GG, and one, *Bifidobacterium lactis* DN-173010; neither probiotic was significantly more efficacious than placebo. In another meta-analysis of six RCTs involving 498 children, Huang, et al. [9] showed that the use of probiotics significantly increased the stool frequency. Although, the authors of this meta-analysis have claimed a significant improvement in stool frequency with probiotics, the 95% confidence intervals clearly indicate that the difference was not significant. Also, there was significant heterogeneity among the studies (I^2 =84%), each RCT was from a different country and had a small sample size, and most studies used separate probiotic species (2 *L. rhamnosus* GG, 2 *L. rhamnosus Lcr35 casei*, 1 *L. sporogenes*, 1 *B. lactis* DN-173010), which might have influenced the validity and reliability of the conclusions.

Guerra, et al. [10] carried out a crossover double-blind trial in 59 Brazilian children with FC according to Rome III criteria. The patients were randomized into two groups to receive either a goat yogurt supplemented with 10^9 colony-forming units/mL of *B. longum* daily or only the yogurt for a period of 5 weeks. Afterward, the groups were inter-crossed for another 5 weeks. Both treatment groups demonstrated improvement in defecation frequency, compared to the baseline. However, the improvement obtained with probiotics was significantly higher [10]. In the second phase of treatment, the group initially treated with probiotics showed worsening stool consistency when using only yogurt. However, the difference was not significant. The study concluded that an improvement in defecation frequency was observed using both supplemented and non-supplemented yogurt, but an additional improvement with *B. longum* supplementation was obtained. Coccorullo, et al. [11] performed a double-blind randomized placebo-controlled study in 44 formula-fed infants with a diagnosis of FC. One group received supplementation with the probiotic *L. reuteri* (DSM 17938) and the other group received a placebo. *L. reuteri* was administered at a dose of 10^8 colony-forming units in 5 drops of oil suspension once per day for 8 weeks. Infants treated with *L. reuteri* had a significantly higher defecation frequency than placebo after 2, 4, and 8 weeks of treatment. The results were graphically presented without reporting absolute numbers, and there was no mean difference for outcome measures between the two groups [11].

To conclude, current limited evidence does not support the use of probiotics in the treatment of FC in children. ESPGHAN/NASPGHAN guidelines recommend against the use of probiotics in FC. Further research with well-established and homogeneous methodologies is needed to determine causal relationships between functional constipation and alteration of fecal microbiota, as well as the efficacy of using probiotics to treat children and adolescents.

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INVITED COMMENTARY

Community-Acquired Acute Kidney Injury in Hospitalized Children: Do Not Miss the Diagnosis!

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Acute kidney injury (AKI) is an abrupt decline in glomerular filtration rate that could lead to health consequences in children in both the short- and -long term [1]. In fact, in the short-term, AKI may increase the length of the hospitalization, and the morbidity and mortality of patients; while, in the long-term, it exposes to an increased risk of chronic kidney disease (CKD). Even a mild AKI, indeed, doubles the risk of CKD during the follow-up [2].

AKI is a common condition in hospitalized children. Reports have shown that AKI can worsen several common pediatric disorders with an AKI prevalence of about 25% in acute gastroenteritis [3], 20% in community-acquired pneumonia [4], 45% during type 1 diabetes mellitus onset [5], and around 7% in acute appendicitis [6]. In this issue of *Indian Pediatrics*, Ashish, et al. [7] evaluated frequency, etiology, outcomes and risk factors for mortality in Indian children with community-acquired AKI (AKI already present at the time of hospitalization). Interestingly, the authors found that 7.7% of the hospitalized children presented with AKI. Diarrheal diseases with dehydration and sepsis were the most common causes of community acquired AKI. Among the 215 patients presenting with AKI, 11.2% died, 78.1% had complete kidney recovery while 10.7% had partial or absent kidney recovery at discharge [7]. For the 23 patients with partial or absent kidney recovery, a 3-month follow-up was also available and the authors found that 10 of them developed CKD (3 becoming dialysis-dependent) [7].

This study gives a picture of the prevalence of the community-acquired AKI in an urban pediatric tertiary care hospital in India providing relevant information for the daily clinical practice. It underscores, indeed, that the overall prevalence of AKI as a complication of common pediatric illnesses is not negligible [7]. The awareness of pediatricians about this topic is relevant in our opinion because AKI, especially in its milder forms, is often undiagnosed [3-6]. In fact, in our research experience, we frequently noticed that the AKI diagnosis was made only retrospectively when analyzing the data for research purpose [3,4,6]. Moreover, the data provided by the authors [7] further support the need of a post-discharge follow-up for children who presented with an AKI episode, in order to accurately detect clinical signs suggesting the evolution toward CKD.

In the AKI pathophysiology, the early stage occurs when the renal blood flow decreases (functional prerenal AKI) causing ischemia and adenosine triphosphate depletion in the renal tubular cells leading to an acute renal tubule cell injury and dysfunction. The acute tubular injury determines an adaptive fall in glomerular filtration rate due to renal vasoconstriction in order to compensate for failure to reabsorb filtered solute. If ischemia persists, the renal tubular damage evolves to overt acute tubular necrosis shifting the AKI from functional to intrinsic [5]. Therefore, being aware of the AKI pathophysiology in the most common pediatric conditions (i.e., dehydration in children with acute gastroenteritis [3] and type 1 diabetes mellitus onset [5] or systemic inflammation in children with community-acquired pneumonia [4] or acute appendicitis [6]) is important to avoid the onset of this complication and to prevent the progression of AKI from functional to intrinsic.

The Kidney Disease/Improving Global Outcomes provides specific criteria to diagnose AKI [1]. The diagnosis can be made on the basis of serum creatinine and urinary output criteria. AKI is defined as either an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to be occurred within the 7 prior days, or urine volume <0.5mL/kg/h for 6 hours [1]. While these data are easily available in adulthood, in children they could not be easily obtained unless using an invasive approach, not always achievable or justifiable in pediatrics. In fact, especially in case of mild clinical pictures who apparently do not require seriate blood sample collections for biochemical analyses or vesical bladder catheterization for urine output quantifica-

tion (in non-toilet trained patients), a mild AKI diagnosis could be missed. Moreover, the real increase of the serum creatinine value compared with measured baseline serum creatinine seems to be challenging, considering that healthy children rarely undergo to creatinine measurements. To overcome these issues, both for research and clinical purpose, height- and age-based methods to estimate the basal serum creatinine on the basis of glomerular filtration rate normative values have been proposed and validated in children [8-11]. To avoid daily bedside calculations, we have designed a table with the back-calculation of basal serum creatinine for children both on the basis of height- and age-based methods [12,13] (**Table I**).

Table I Estimated Basal Serum Creatinine on the Basis of Normative eGFR Values

On the basis of height[1]		Age (y)	*On the basis of age*[2]	
Height (cm)	Cr (mg/dL)		Cr (mg/dL)	
			Male	Female
70,00	0.34	0.5	0.36	0.37
90,00	0.35	1	0.30	0.30
105,00	0.36	2	0.26	0.26
110,00	0.38	3	0.29	0.28
115,00	0.39	4	0.31	0.31
120,00	0.41	5	0,33	0.33
125,00	0.43	6	0.35	0.35
130,00	0.45	7	0.37	0.38
135,00	0.46	8	0.40	0.40
140,00	0.48	9	0.42	0.42
145,00	0.50	10	0.45	0.45
150,00	0.52	11	0.48	0.48
155,00	0.53	12	0.52	0.50
160,00	0.55	13	0.56	0.53
165,00	0.57	14	0.60	0.55
170,00	0.58	15	0.65	0.58
175,00	0.60	16	0.69	0.60
180,00	0.62	17	0.73	0.62
185,00	0.64	18	0.76	0.63
190,00	0.65	19	0.79	0.65

[1]Calculated on the basis of CKiD equation [12]; [2]Calculated on the basis of age equation [13].

In conclusion, AKI is common in hospitalized children. Being aware that AKI could complicate several common pediatric conditions could improve the children's care by making an early diagnosis, in order to prevent AKI progression and, through a specific post-discharge follow-up, to early detect the progression to CKD. The paper appearing in this issue of the journal [7] further emphasizes these considerations, making pediatricians aware of the importance of early diagnosis of AKI in children.

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INVITED COMMENTARY

Hypertension in Nephrotic Syndrome: A Pressing Concern

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High blood pressure is often detected in patients with nephrotic syndrome, at the onset of the illness, following therapy with prednisolone, and/or during long-term follow-up. A review of cardiovascular outcomes in proteinuric glomerulopathies showed that the prevalence of hypertension ranges from 7% to 41% in steroid sensitive nephrotic syndrome, compared to 13% to 58% in patients with steroid resistance [1]. In patients with steroid sensitive disease, high blood pressure was found in 65% to 95% of patients with edema, which persisted in 19% to 34% following steroid induced remission [2,3]. The prevalence of hypertension is highest in patients with frequent relapses or steroid dependence, and in those with family history of essential hypertension [1,3]. Masked hypertension, which is in itself associated with adverse cardiovascular outcomes, is reported in 16% to 40% of such patients. [4,5]

Hypertension in nephrotic syndrome may be attributed to intrinsic renal and non-renal causes, as well as extrinsic reasons. The chief renal causes include primary salt and water retention, fluid overload, glomerulosclerosis related decline in glomerular filtration rate, and proliferative glomerulonephritis. Important extrarenal factors contributing to hypertension are therapy with corticosteroids or calcineurin inhibitors, and dyslipidemia [1]. Hypertension has long-term cardiovascular consequences, including left ventricular hypertrophy and atherosclerosis, and leads to end-organ injury, such as retinopathy and progressive kidney disease. Almost one-third of children with primary hypertension show echocardiographic evidence of left ventricular hypertrophy, underscoring the importance of detection and appropriate management of hypertension in children [6].

A prospective single-center observational study, published in this issue of the *Journal* [7], aimed to evaluate the prevalence of hypertension in 83 children with infrequently relapsing nephrotic syndrome during a relapse and following 4-weeks of prednisolone therapy. The authors also evaluated if hypertension was associated with family history, dyslipidemia, or end organ damage. Blood pressure was measured in the clinic as the mean of three recorded values, and hypertension was defined as per standard guidelines [8]. The authors found that almost one-third (32.5%) of patients had hypertension during disease relapse, which persisted in one-quarter of cases (8.6%) following 4-weeks of prednisolone therapy. Amongst hypertensive patients, 29% had a family history of hypertension, and ~50% had history of hypertension at disease onset or during a previous relapse. While a proportion of patients showed abnormal left ventricular geometry, concentric left ventricular hypertrophy was uncommon. These findings are noteworthy, since clinic hypertension was found in ~30% patients with active disease, compared to an estimated population prevalence of ~4% for primary hypertension [9]. However, it would be important to emphasize few issues of relevance for practicing clinicians and researchers.

The eligibility criteria state that inclusion was limited to patients who were receiving antihypertensive medications for 3-months or longer. In order to determine the prevalence of hypertension in infrequent relapsers, it would have been appropriate to include all patients with infrequent relapses, irrespective of antihypertensive therapy. While the use of antihypertensive medications might have led to underestimation of the prevalence of hypertension, the true prevalence might indeed have been lower were all the patients with infrequent relapses included. Secondly, patients with hypertension appear to have had more severe relapses, as indicated by serum and urine biochemistry. A prolonged duration of disease and delayed therapy of relapse might influence the severity of relapse and result in hemodynamic aberrations, including hypertension. Thirdly, in order to negate the influence of corticosteroid therapy on hypertension, repeat blood pressure values should have been estimated a few months remote from the relapse. Further, the value of detecting transient hypertension is uncertain, since persistent hypertension is more likely to correlate with cardiovascular outcomes than acute hypertension associated with a relapse compared to casual clinic blood pressure records, ambulatory blood pressure monitoring (ABPM) is a comprehensive technique to detect

abnormal blood pressure in adults and children [10]. Its advantages include reproducibility, better correlation with end organ injury, and cost-effectiveness. ABPM is optimal in diagnosing and confirming high blood pressure records, white coat hypertension and masked hypertension, and helps optimize antihypertensive medications [10]. Its application in children is currently limited by availability of child validated equipment, and lack of normative data that reflects racial and ethnic diversity [8]. However we emphasize that prospective studies to classify and determine the true prevalence of hypertension should ideally be based on ABPM. In absence of ABPM, home blood pressure measurements using oscillometric devices have been advocated. However, the sensitivity, specificity and positive and negative predictive values of home measurements are rather modest, when compared to ABPM [11]. Expert groups therefore suggest using home blood pressure monitoring as an adjunct to casual blood pressure and ABPM following the diagnosis of hypertension.

In conclusion, findings of this and other reports suggest that acute but transient hypertension is common during relapses of steroid sensitive nephrotic syndrome. Prospective studies on prevalence of hypertension should have broad-based inclusion criteria and avoid confounders that might affect outcomes. It is necessary to follow up these patients, preferably when in remission and off corticosteroids, to determine if hypertension indeed persists and determine risk(s) for adverse cardiovascular outcomes.

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PERSPECTIVE

Recurring Outbreaks of Circulating Vaccine-derived Polioviruses: Implications for Global Poliovirus Immunization Strategy

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The incidence of polio has decreased by more than 99.9% and currently, only two countries are endemic for wild poliovirus. However, increasing outbreaks of circulating vaccine-derived poliovirus globally in the last few years, with the latest ones in high-income, exclusive inactivated polio virus vaccine (IPV)-using countries have brought out a new dimension to the end game of polio eradication. The inability of the current IPV to induce efficient mucosal immunity in the intestine is likely to be one of the key reasons behind the silent transmission of the polio virus in these countries. New challenges demand concerted global efforts with renewed vigor to cross the last mile. We need to aggressively cover up areas of under-vaccination and continue large-scale genomic surveillance. Further, the availability of a novel oral polio vaccine (nOPV2), and the likely availability of Sabin IPV and a more refined IPV with mucosal adjuvant in the near future is likely to go a long way in achieving this remarkable feat.

Keywords: *Novel oral polio vaccine, Polio end game, Polio eradication.*

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Since the beginning of polio eradication efforts in 1988, the incidence of polio has decreased by 99.9%. Currently, only two countries are endemic for wild poliovirus: Pakistan and Afghanistan [1]. However, the persistence of wild poliovirus (WPV) in these two countries is not the only challenge faced by the Global Polio Eradication Initiative (GPEI), the recurring outbreaks of circulating vaccine-derived poliovirus (cVDPV) in many countries have further complicated the task. Several such cVDPV outbreaks have been reported, mostly in low- or middle-income countries and always in populations with poor vaccine coverage [2]. Although all three types of polioviruses can cause cVDPV, over 90% of these cVDPV outbreaks are caused by the type-2 virus (cVDPV2) [3]. Since the last type 2 wild poliovirus (WPW2) case was seen in 1999 [4], and over 90% of VDPV outbreaks and over 40% of cases of vaccine-associated paralytic poliomyelitis (VAPP) were documented to be caused by OPV2, OPV2 was withdrawn globally – in a coordinated manner, among all OPV-using countries in April, 2016 [3]. Thus, trivalent OPV (tOPV) was replaced by bivalent OPV (bOPV) globally, the 'global switch.'

Was the Global Switch A Failure?

While in 2017-2020, type 1 WPV (WPV1) transmission was limited to endemic countries only (Afghanistan and Pakistan), in 2021-2022 non-endemic countries, Malawi and Mozambique also reported a few confirmed cases of WPV [1]. Unexpectedly, rather than decreasing, the number of cVDPV2 outbreaks also increased significantly after the trivalent OPV (tOPV)-to-bivalent OPV (bOPV) switch. There were only two countries (with 96 cases) with VDPV outbreaks in 2017, 5 countries (71 cases) in 2018, and 15 countries (251 cases) in 2019. Overall, there have been more than 2600 cVDPV2 paralytic cases out of 100 VDPV2 outbreaks from at least 70 independent emergences affecting at least 38 countries in the last six years [2].

The global switch from tOPV to bOPV with the removal of type 2 was one of the key elements of GPEI's 'polio endgame.' However, cessation of Sabin type-2 poliovirus from tOPV for routine immunization along with shortages of IPV led to low population immunity against type-2 poliovirus, giving a foothold to the virus in many communities. Unsurprisingly, few experts are now calling the 'global switch' a failure, owing to poor risk management and sub-optimal coordination of OPV cessation [5].

Vaccine-Derived Polio in IPV-Using High-Income Countries: A Cause for Concern

The recent detection of poliovirus in sewage samples and new outbreaks of cVDPV in some of the non-OPV-using developed countries like Israel, England, and the USA has turned global attention again toward polio eradication and polio immunization strategies [6]. While paralytic cases were reported from Israel (single case, unvaccinated) and the US (single case, unvaccinated), England reported cVDPV2 (the first evidence of polio transmission since

1984) in the sewage only. Though, over 30 countries have reported cases or isolates of VDPVs in 2022 [3], those in Israel, the UK, and the USA have received greater attention since these are high-income countries with excellent Water, Sanitation, and Hygiene (WASH) infrastructure and good overall IPV coverage. These countries had eliminated WPV long back and are not using OPV for over 18 years. Moreover, genotyping of the isolates from these three countries was found to be genetically linked (>99.0% identity), indicating a common source in an unknown fourth country, still using OPV. This incident indicates multi-country, community transmission [7] and is thus of grave concern.

Why outbreaks of cVDPVs in IPV-using countries?

The above incidents have amply demonstrated that the terminal 0.1% of the eradication initiative, the 'end game,' is going to be as challenging as the first 99%. But the most concerning aspect is why IPV-using countries are facing outbreaks of cVDPVs despite excellent immunization coverage. Though large inter-state and intra-state variations in the vaccination coverage in some regions and growing vaccine hesitancy among certain communities may have a significant impact, the key reason might be the failure of the current IPV to induce effective mucosal immunity in the intestine that provides resistance to poliovirus replication and shedding upon oral exposure to the live virus – vaccine or wild. While the inactivated vaccine offers excellent individual protection against paralytic disease to the vaccinees by virtue of high titers of serum-neutralizing antibodies, it fails to prevent viral transmission, especially the poliovirus replication at the intestinal border, which may explain the silent transmission of poliovirus in some developed countries [8].

Intestinal Mucosal Immunity: The Key Determinant of Polio Transmission

The concept of mucosal immunity is distinct from the serum response, and the notion that transudation of serum antibodies to the intestinal border elicits mucosal resistance to viral shedding in IPV-immunized individuals does not hold in the light of new understanding about intestinal mucosal responses. Early studies also suggested that the transudation of serum antibodies makes a minimal contribution to total antibody concentrations in the mucosa [9]. Recent studies have proved that IgA, particularly the isotype IgA1, mediates the mucosal neutralization of poliovirus at the intestinal border [10].

The mucosal immunity at the gut level is induced by secretory IgA, mucosal IgG, and to some extent through tissue-resident memory T (TRM) cell populations. In the absence of enteric IgA against poliovirus in older children and adults, TRM cells may provide some resistance to poliovirus replication in the intestine through cytokine-mediated recruitment of both innate and adaptive immune cells [11]. However, the IgA at the intestinal border is the most abundant antibody providing the first-line defense against invading pathogens. Mucosal IgA level correlates with viral neutralization in the gut, not the mucosal IgG level [12]. A recent paper examining SARS-CoV-2 nasal IgA responses after natural infection and vaccination concludes that parenteral vaccination after COVID-19, boosted nasal and plasma IgG but had a limited impact on nasal IgA [13].

Traditionally, IPV is known to elicit excellent mucosal immunity at the pharynx that helps in curbing 'oral-oral' virus transmission, the main mode of poliovirus circulation in countries having temperate climates. However, due to poor mucosal immunity at the intestinal level, the imported live virus could circulate unhindered in the intestines of IPV-immunized individuals. In a recent study, children aged 1-5 years who had already received up to four doses of IPV were challenged with a mOPV2 dose. Only about one-third of children developed type-2 specific neutralization titers (>32) in their stools and continued to shed the vaccine virus in the stools even after the second challenge dose [14]. Studies have even shown that vaccine naïve children excrete less amount of vaccine virus for a shorter duration following the second challenge dose of the same strain of OPV than IPV-immunized children [8,15]. Many studies on mucosal immunity conducted recently in a few Latin American countries and Europe conclude that initial receipt of IPV during the primary immunization schedule may lead to compromised development of intestinal immunity that results in greater shedding after a live polio vaccine challenge in older children than those who received OPV during their primary immunization series [8]. These studies further demonstrate that the type-specific enteric antibodies to poliovirus in infants are stimulated by the replication of the live virus in the intestine. In vaccine-naïve children, receipt of an IPV-only primary series is insufficient to induce significant levels of enteric IgA and virus-neutralizing activity in the absence of OPV. This limitation of IPV regarding intestinal immunity was known since the early 60s, and has got huge implications for the polio eradication initiative [15].

Another factor that may have facilitated the transmission of poliovirus in vaccinated individuals is the finding that mucosal immunity in the intestine either fails to develop or wanes progressively, after primary series of vaccination in older children, adolescents, and adults, thus creating an 'immunological gap' in this population [8]. Though, this defect in intestinal immunity is starker with IPV, studies have shown that even OPV reci-

pients experience partial waning after a year of primary series [16]. The transient nature of mucosal IgA response is further confirmed in the above-cited SARS-CoV-2 study, wherein nasal IgA levels waned after nine months of natural infection and could not be induced by subsequent intramuscular vaccination [13]. Studies conducted in adult popu-lations who had received IPV during the primary infant series demonstrated the absence of polio neutralizing antibodies and enteric IgA in stools following mOPV1/nOPV2 challenges despite excellent serum-neutralizing antibodies response [8]. This phenomenon may explain the involvement of the adult population in the transmission of the polio virus noted in the recent outbreaks of cVDPV in IPV-using countries.

HOW TO TACKLE THE GROWING MENACE OF VDPV: THE WAY OUT

Reaching the unreached

Maintaining high coverage of available vaccines has been the crux of GPEI which has led to the eradication of two of the three WPVs. However, recent outbreaks like that in New York have clearly demonstrated that pockets of under-vaccination exist even in highly immunized countries and can pose a serious threat to the program. It is imperative to tackle these on a war footing, with a special focus on the last person in the queue: the zero-dose children, those who have not received a single dose of any basic vaccine.

Continuing large scale genomic surveillance

Right from the early phase of GPEI, genotyping of specimens isolated from cases and from the community played a crucial role in the whole program. However, paralysis is a relatively rare outcome of poliovirus infection and can be a lagging marker for significant circulation. Detection and the pro-active management of outbreaks in Israel and the UK have demonstrated that identification of silent transmission by viral culture and/or molecular surveillance of wastewater is going to be crucial, going forward.

Development of novel vaccines

Novel oral polio vaccine against type 2 (nOPV2): Both OPV and IPV are effective and time-tested vaccines. However, increasing instances of VDPV have amply demonstrated their drawbacks: rare risk of reversion of virulence of vaccine strains with OPV, and lack of intestinal immunity with IPV: both contribute to the threat of VDPV. The GPEI experts realized the need of developing a safer alternative that keeps the merits of OPV intact. The development of a new OPV, a 'novel' OPV against the type-2 virus (nOPV2), must be viewed as an effort in this regard [17]. The new nOPV2 contains up to five more mutations in its genome than the existing vaccine, which are needed to regain neurovirulence [18]. The nOPV2 has been rolled out in Africa without any safety signal, even after the administration of over 500 million doses.

Till recently, mOPV2 was being used for tackling cVDPV outbreaks, which ironically re-introduces OPV2 in the community that can further lead to the emergence of new VDPV strains. The use of nOPV2 in place of mOPV2 for this purpose would be a lot safer. The CDC, USA is also contemplating its use in areas with persistent poliovirus circulation to tackle the ongoing cVDPV outbreak [19]. Deployment of nOPV2 and the availability of nOPV types 1 and 3 in future should help diminish the threat of future VDPV outbreaks.

Mucosal IPV: While the development of nOPV is an attempt to solve one of the major limitations of the Sabin-OPV, innovations are similarly needed to develop better IPV also. Development of Sabin-IPV can lead to ease of manufacturing of IPV as it would require less stringent biosafety measures to handle Sabin strains instead of WPVs [20]. However, this move does not address one critical issue: the failure of IPV to induce efficient intestinal immunity. A large meta-analysis concludes that while tOPV/bOPV effectively limits the viral replication in the intestine, the addition of one or more doses of either fIPV or full-dose IPV will not increase intestinal immunity to the type-2 virus, hence, will not prevent transmission or circulation of type 2 poliovirus [21].

Several hypotheses are offered to explain the lack of intestinal IgA responses observed in older children and adults with a history of childhood IPV: active suppression of intestinal IgA by IPV given during infancy, inadequate T cell-mediated stimuli for IgA induction, immune tolerance in the intestine, and the suppressive effects of T-regulatory cells (Tregs). Recent studies have indicated that Tregs play an essential role in shaping mucosal IgA responses to infections and vaccination [8].

Certain adjuvants could help enhance mucosal immunity, potentially mimicking the protection against intestinal virus shedding seen with OPV. One such adjuvant is LT(R192G/L211A) or dmLT, a heatlabile enterotoxin of *Escherichia coli*-based mucosal vaccine antigen that has been shown to modulate human Tregs and Th17 cells to induce strong antigen-specific Th17 responses that enhance mucosal IgA production. The dmLT enhances intestinal immunity when included in IPV immunization by ID or IM delivery in animal studies [22]. GPEI is conducting clinical trials of dmLT co-administered with IPV in adults that will provide valuable information on the impact of targeted modulation of cellular responses for induction of long-lived polio-specific mucosal IgA and virus-

neutralizing responses in the intestine.

Development of new polio vaccines: The GPEI is also exploring the possibility of developing some new, non-infectiously (non-live virus) produced polio vaccines based on mRNA and virus-like particles (VLPs) technology. Development of these vaccines may offer considerably more opportunities for managing polio endgame risks, particularly during the post-eradication era [5].

ARE THERE OTHER OPTIONS?

Going back to Sabin tOPV: Some modelling studies suggest that the current trajectory for eradication of type 2 Sabin virus is not on its way even with the use of nOPV2 [5]. Though the new nOPV2 has been aggressively employed to tackle emerging cVDPV2 outbreaks, particularly in OPV-using countries, there is still no real-world data from these countries. There are speculations on the performance of this new nOPV2 – it may perform better than or equal to mOPV2 depending on its effectiveness in real populations. Since the GPEI has selected a low dose nOPV formulation for use in the field [17,23], the overall effectiveness of the new nOPV2 may be less than the existing mOPV2. Further, there may be different relative take rates for the three types of OPV when combined with the current bOPV. Modelling by Thomson, et al. [5] suggests that abruptly ending all OPV use in 2023 and relying exclusively on IPV to prevent paralysis would lead to re-established endemic transmission of poliovirus with a significantly large number of polio cases, particularly type 1 and 2. They find betterexpected health and economic outcomes associated with ending IPV use and restarting tOPV, given the current global performance on OPV cessation in OPV-using countries [5].

Abandoning global polio eradication and settling for control: Few experts have recently urged the WHO/GPEI to consider refocusing on eradicating poliomyelitis as a disease, rather than eradicating the virus itself [24]. Unarguably, the GPEI has delivered immense good to mankind with a 99·9% reduction in the global incidence of polio, saving more than 1·5 million lives and an estimated 16 million people from paralysis. Two of the three serotypes of WPV types 2 and 3 have been certified as eradicated worldwide. Thus, the demand of abandoning eradication at this juncture may not only prove to be highly demoralizing to the entire scientific community and health workers but may also jeopardize the future effort to eradicate any life-threatening disease.

CONCLUSIONS

Though the GPEI has succeeded in bringing WPV transmission to an extremely low level, the silent circulation of live polioviruses in countries with high IPV immunization coverage demonstrates the limited ability of the IPV to stop poliovirus transmission. Through the development of nOPV2, the GPEI has made a great stride to address one of the key limitations of the live polio vaccine, it is time to address the dwindling mucosal immunity at the intestinal border, the major limitation of the current generation of the IPV. The GPEI needs to urgently address the threat posed by cVDPVs by improving geno-mic surveillance, investing in a more efficient IPV and closing the immunity gaps since the 'window of oppor-tunity' will not remain open indefinitely.

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PERSPECTIVE

Active Bleeding Control - Can Pediatricians Stem the Tide of Lives Lost From Trauma Through 'Stop the Bleed' Training?

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Trauma is a global challenge and India has one of the highest trauma deaths in the world. Despite the United Nations' target to halve the global number of deaths and injuries from road traffic crashes by 2030, death tolls from road traffic injuries (RTI) are rising in India. In the pediatric age group, falls from height add to the burden of trauma. Uncontrolled bleeding from exsanguination on scene is estimated to account for nearly 40% of RTI trauma related mortality. Stopping the bleeding in the first few minutes is crucial for meaningful survival and hence the role of training lay public who can reach the scene in minutes. Active bleeding control (ABC) pilot research project to simulation train the bystanders to stop the bleed showed promising outcomes in Hyderabad, India. This paper describes the ABC project and discusses the role of pediatricians in training the public to reduce morbidity and mortality from uncontrolled bleeding at the trauma scene.

Keywords: *Bystander training, Management, Outcome, Simulation.*

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According to the World Health Organization (WHO), road traffic injuries (RTI) are the leading cause of death for children and young adults aged 5-29 years worldwide. Approximately 1.35 million people die each year globally as a result of road traffic crashes. Between 20 and 50 million more people suffer non-fatal injuries, with many incurring a disability as a result of their injury. Around 93% of the world's fatalities on the roads occur in low- and middle-income countries. WHO warns that the price paid for mobility is too high, especially because proven measures exist, and has called for drastic action to put these measures in place, to be able to meet any future global targets to save lives [1,2]. In children, in addition to RTI, fall from heights, and skids add to the burden of trauma [3,4].

Injuries are one of the most challenging preventable problems India is facing, with very high mortality and morbidity. We continue to lose one precious life every 3-4 minutes on Indian roads just from RTI and one person is severely disabled every few seconds. National Crime Records Bureau reports that during the year 2021, India lost 1,55,622 lives due to RTIs, which is a significant rise compared to 2020 (133,201 deaths) [5,6]. An estimated 40% of RTI deaths are due to uncontrolled bleeding. Despite the worrying figures, this preventable disease has not received much attention. There is an urgent need to improve pre-hospital care, transport through well-equipped ambulance, and simultaneously improving trauma care in hospitals. Stopping the bleeding in the first few minutes is crucial for meaningful survival, considering the delays between injury and definitive trauma care. Trained first responder is the most critical, and the weakest link in the chain of survival of golden hour [7-9].

THE ACTIVE BLEEDING CONTROL PROGRAM

Active bleeding control (ABC) is a unique project initiated in Hyderabad to train, equip and empower citizens with the aim to reduce the number of road injury deaths from severe bleeding. ABC is a multi-partner collaboration pilot research project developed by Pediatric Simulation Training and Research Society (PediSTARS) India [10] and GVK Emergency Management and Research Institute (EMRI) [11], in collaboration with Children's Hospital of Philadelphia (CHOP) [12], Public Health Foundation of India (PHFI) [13], Road safety club, Hyderabad [14], and Transport department, Telangana.

Phase 1 ABC project objective was to develop and implement a lay first responder ABC program to help RTI victims along two high-risk corridors using simulation methodology. A 90-minute curriculum was designed using simple five steps of scene safety, calling ambulance, identifying life threatening bleed, and applying direct pressure and tourniquet. Five steps were taught to mastery, free of cost, using both training videos as well as repeated

practice on simulated patient with the motto "You Are the Help Until Help Arrives." ABC stop the bleed low-cost kits were created to distribute free of cost in both the phases to all those who completed training. Participants were also trained to stop the bleed utilizing available household materials such as towel, shirt, *duppatta* and shawl [15].

In Phase 2, the focus was on creating more trainers by training high school children to become "ABC- Gurus" to train family members and community. This involved needs assessment from 12 schools to understand gaps, and their willingness to train others [16]. This followed rigorous curriculum development with 2.5 hours of simulation training, sharing training materials post training, and supervising students to train four others within a week (multiplier effect) [17].

Effect on the Community

Phase 1 ABC has trained 1076 volunteers - 351 auto-rickshaw drivers, 325 police personnel; rest were shop-keepers, toll plaza staff, bus drivers, bus conductors, hospital staff and college students. These volunteers have saved greater than 163 lives of RTI victims till the last information available [15,18].

Phase 2 ABC has trained 537 students and teachers from seven government and private schools in Hyderabad to become ABC trainers (ABC gurus). These students and teachers have trained their family and neighbors under guidance, creating a pool of 2724 citizens ready to serve the community [19].

Scaling Up ABC Countrywide

ABC pilot project has developed a low-cost simple solution for the complex problem of delay in critical intervention needed at the site of life-threatening bleeding from injures. If this simple and easy training reaches most of the citizens countrywide, soon India will see a strong resilient community, saving many lives. ABC training not only empowers citizens to identify and stop the bleed, but it also trains them in activation of ambulance services and calming the victim. Empowering the community will have the additional benefit of awareness towards prevention of RTI, enhancing the community's capacity to look after each other, and stop the bleeding during non RTI bleeding such as disaster or mass casualty events, and calling ambulance early for non-injury emergencies such as cardiac arrest [15].

However, there are several challenges at the individual, organizational and national level in implementing ABC training.

Lack of understanding: Lack of awareness of the problem, understanding significance of bystander training in saving lives – at individual, organizational and government level is a major barrier.

Funding: Securing funds for ABC training, training the trainer, recruitment of volunteers, stop the bleed kits, data collection, and evaluation, needs funds and is challenging unless the importance of the program is well understood

Lack of trainers: Any program to be successful, the key is dedicated competent trainers. Currently there is no Stop the Bleed training curriculum integrated in healthcare training

Legal hassles: Worry about police case and fear of need to attend court hearings for getting involved in a RTI case.

Personal loss: Loss of wages for those volunteers during helping the victims, and pressure from passengers during stopping the vehicle to help injury victims

Fear: Fear of blood, crowd control, fear of what might happen if more harm done during helping the victim, and fear of death of victim during ABC.

Some of these barriers were studied by the authors and published previously [15].

Overcoming the Challenges

Any new program to uplift the society from a problem such as prevention of deaths on the roads needs stepwise structured approach. It needs a serious culture change and contributions from public, public health specialists, healthcare team, academicians, researchers, government and non-government agencies.

ROLE OF PEDIATRICIANS

Pediatricians have an unmatched position and unique role in the community to create that much needed change. They have the ability to reach out to children, parents, schools, organizations and policymakers to build committed relationships with compassion and trust, greater than any others in healthcare. Apart from losing parents, families and pushed to poverty from loss of GDP (Gross Domestic Product), RTI is a huge childhood endemic disease. According to UNICEF, globally road traffic injuries represent the leading cause of death in ages of 5-19 years [4]. If concerted efforts are made, thousands of lives can be saved and a even bigger impact on avoiding disability. The cause is urgent, the need is strong and the time has come for pediatricians to bring all together for this great cause.

How Can Pediatricians Make a Difference?

There are several ways pediatricians can help to spread awareness and training in ABC. **Box I** and **II** suggest some of the ways interventions can be planned. Small steps starting from home, neighborhood, recreational areas, individual hospitals and gradually creating an interest group to reach all the unreached in training ABC. The pilot

Box I Challenges and Solutions to Creating Awareness About Active Bleeding Control (ABC)

Lack of understanding the problem and role of ABC

- *Individual level*: Create awareness to all in family, neighbors, schools, shops, enroute to work, recreational areas.
- *Hospital*: ABC awareness in - outpatient and family waiting areas; hospital training times to all medical and non-medical staff; outreach hospitals; mass campaign in social media, television, newspapers.
- *Organizational*: ABC discussions in conferences. Reaching out to schools, colleges, workers and drivers association, village heads, municipalities, NGOs. ABC flash mobs, skit competitions during public celebrations.

Police harassment

- Create awareness during ABC campaign and training regarding the Supreme Court order of "Good Samaritan Law" to provide legal immunity to helpers of RTI victims [20].

Fear of blood, harm, death

- Reinforce the motto "You are the help Until the Help arrives" during awareness and training [15].
- Encourage public discussions about overcoming fear of blood, the good samaritan law and the fact that the worst thing a citizen can do is "Do Nothing."

NGOs: non-government organizations.

project has already shown how to create low cost, made in India ABC- Stop the Bleed kits. Buy-in from village heads, collectors, municipality, media, corporates, non-governmental organizations (NGOs) is crucial. Professional bodies such as Indian Academy of Pediatrics can play a vital role in this. Ultimately, transforming stop the bleed training in to a mass movement by motivating the policy makers to make ABC training mandatory for all new drivers, and integration of ABC in healthcare training could be a ray of hope for the next generation. **Fig. 1** illustrates the strategies required for dissemination of stop the bleed training.

CONCLUSION

Training the citizens to stop the bleeding during the first few minutes is crucial in the chain of trauma survival. Simple, low-cost ABC training of lay public has proven to be feasible and effective. There is an urgent need for implementation of strategies to stem the tide of trauma deaths from uncontrolled bleeding. Pediatricians have a unique role in training the public, to create that much needed culture change in the community, to build a strong resilient society saving thousands of lives. India has a great potential and no barrier is large enough if we show that the cause is strong.

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Contributors: GR: drafted and finalized the manuscript; VN: reviewed, revised and finalized the manuscript. Both the authors

Box II Challenges and Solutions Related to Pediatricians' Role in Training Public in Active Bleeding Control (ABC)

Lack of trainers

- *Individual*: Train family, neighbors, shop keepers, social contacts to create ripple effect.
- *Hospital level*: Create pool of volunteer trainers in hospital to reach out to community for multiplier training in - outreach hospitals, schools, colleges, driving schools, village heads, municipality, collectors, police, NGOs
- *Organizational level*: Certified ABC training by IAP and motivate organizations from surgeons, physicians, EMS to conduct ABC "Train the Trainer" courses. Mass training healthcare team and public during special annual events such as "World Trauma Day"
- *Government/ National*: Motivate Government to create a central body to regulate and supervise ABC training and outcomes. Reaching out to policy makers at state and national level for implementing ABC training in high schools and to all new drivers. Convincing Government to implement ABC training to medical, nursing, EMS and allied healthcare students.

Funding

- *Local*: Pooling resources from CSR funds of companies, industries, crowd funding, fund raising events such as marathon
- *National*: Persuading Government to dedicate funds specific for ABC.

Personal loss of wages

- Incentives for public who help bleeding victims.
- Rewarding life savers – Honoring in Public during special events/ festivals to recognize dedication to ABC

NGOs: non-government organizations; IAP: Indian Academy of Pediatrics; CSR: corporate social responsibility.

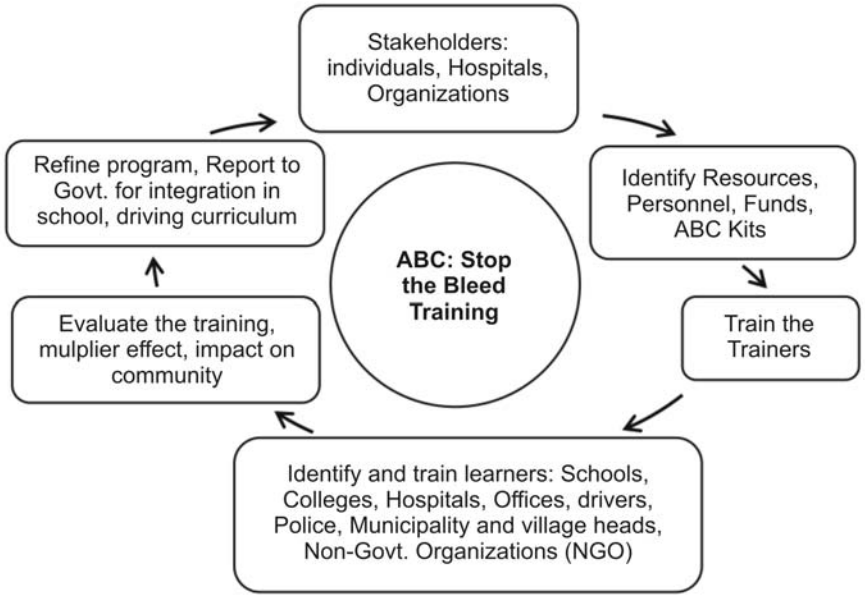

Fig. 1 A suggested strategy for dissemination of training in Active Bleeding Control (ABC) by pediatricians.

have contributed, designed and approved the manuscript.

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RESEARCH PAPER

Desmopressin Plus Tolterodine vs Desmopressin Plus Indomethacin for Refractory Pediatric Enuresis: An Open-label Randomized Controlled Trial

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Objective: To compare the efficacy of desmopressin plus tolterodine (D+T) with desmopressin plus indomethacin (D+I) for treating enuresis in children.

Design: Open-label randomized controlled trial.

Setting: Bandar Abbas Children's Hospital, a tertiary care children's hospital in Iran, from March 21, 2018, to March 21, 2019.

Participants: 40 children older than five years with monosymptomatic and non-monosymptomatic primary enuresis resistant to desmopressin monotherapy.

Intervention: Patients were randomized to receive either D+T (60 µg sublingual desmopressin and 2 mg tolterodine) or D+I (60 µg sublingual desmopressin and 50 mg indomethacin) every night before bedtime for five months.

Outcome: Reduction in the frequency of enuresis was evaluated at one, three, and five months, and response to treatment at five months. Drug reactions and complications were also noted.

Results: After adjustment for age, consistent incontinence from toilet training, and non-monosymptomatic enuresis, D+T was significantly more efficacious than D+I; mean (SD) percent in nocturnal enuresis reduction at 1 [58.86 (7.27)% vs 31.18 (3.85) %; *P*<0.001], 3 [69.78 (5.99)% vs 38.56 (3.31)%; *P*<0.000], and 5 [84.84(6.21)% vs 39.14 (3.63)%; *P*<0.001] months showing a large effect. At 5 months, complete response to treatment was only observed with D+T, while treatment failure was significantly higher with D+I (50% vs 20%; *P*=0.047). None of the patients in either group developed cutaneous drug reactions or central nervous system symptoms.

Conclusion: Desmopressin plus tolterodine appears to be superior to desmopressin plus indomethacin for treating pediatric enuresis resistant to desmopressin.

Keywords: *Adverse effect, Combination therapy, Management, Outcome.*

Trial Registration: Iranian Registry of Clinical Trials: IRCT20210613051564N1

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Enuresis, defined as bedwetting in children aged 5 years and above, is seen in around 15-20% of five-year-old children, 6.4-10.3% of seven-year-olds and 0.5-2.3% of adults, with a 15% annual spontaneous resolution rate [1,2]. Nocturnal enuresis (NE) is defined as bedwetting at night for at least three consecutive months in children aged >5 years [3]. Psychological and social issues, rather than somatic problem, are the main reasons for treating children with enuresis [3].

Desmopressin, a selective vasopressin V2 receptor agonist, is the first-line medical treatment for enuresis [4]. Generally, desmopressin is well tolerated, with hyponatremia being a rare but serious side effect [5]. The International Children's Continence Society (ICCS) recommends combination therapy when the first-line monotherapy fails [6]. Anticholinergics like tolterodine, in combination with desmopressin have been shown to be effective for treating NE [7,8]. Its side effects include dry mouth, dry eyes, constipation, urinary tract infection, hypertension, headache, blurred vision, and drowsiness [9]. Further, evidence suggests overproduction of prostaglandin E2 during the night in some children with enuresis [10]. Therefore, cyclooxygenase inhibitors such as indomethacin, which have been demonstrated to possess antidiuretic properties, have been used for treating patients with enuresis [11]. The side effects of indomethacin range from mild, such as nausea, to severe, such as increased bleeding tendency [12]. In this study, we aimed to compare the effects of desmopressin plus tolterodine with desmopressin plus indomethacin for treating children with enuresis.

METHODS

This open-label randomized controlled trial, registered at the Iranian Registry of Clinical Trials, included children over five years of age with monosymptomatic and non-monosymptomatic (simultaneous daytime lower urinary tract symptoms, such as daytime incontinence, urgency, voiding difficulties, and abnormally low or high daytime voiding frequency) primary enuresis [13]. Ethics approval was taken from the ethics committee of our university.

Monosymptomatic enuresis was diagnosed after ruling out secondary causes of enuresis, including anatomic abnormalities of the urinary tract, trauma, constipation, urinary tract infection, diabetes insipidus, excessive water intake, spinal cord disorders, hypercalciuria, diabetes mellitus, and adenoid disorders. The diagnosis was made by a pediatric nephrologist, at a tertiary care children's hospital in Iran, from March 21, 2018, to March 21, 2019. The children were included when they were resis-tant to monotherapy with desmopressin, defined as <50% reduction in the number of wet nights with incremental doses of 120 to 240 µg [14], no response to alarm therapy, and normal uroflowmetry and residual volume.

The sample size was calculated as 20 patients in each group using data from a pilot study (10 samples in each group) with mean nocturnal enuresis reduction after 15 days of 16.69% (10.91%) for the desmopressin + indomethacin (D+I) group and 28.37% (13.45%) for the desmopressin + tolterodine (D+T) group, α=0.05 and β=0.2, and by taking into account a 10% loss to follow-up.

After taking written informed consent from the parents/guardians of the patients, demographic and clinical details including history of consistent incontinence from the age of toilet training and family history of enuresis were recorded. The children were randomized into two groups using a randomization table generated by the Random Allocation software, version 1.0 [15]. Children in the D+T group received a 60 µg sublingual desmopressin tablet and a 2 mg tolterodine tablet every night before bedtime, while children in the D+I group received a 60 µg sublingual desmopressin tablet and two 25 mg (50 mg) indomethacin capsules every night before bedtime. Both groups received medications for five months. Concurrent use of other medications was noted. Compliance with the treatments was evaluated from their parents.

The primary outcome was a reduction in the frequency of nocturnal enuresis, one, three, and five months after the initiation of treatment, assessed by a 24-hour frequency chart filled in by the parents. To compare the response to medication at the end of the study period (at 5 months), we used the definition of the Standardization Committee of

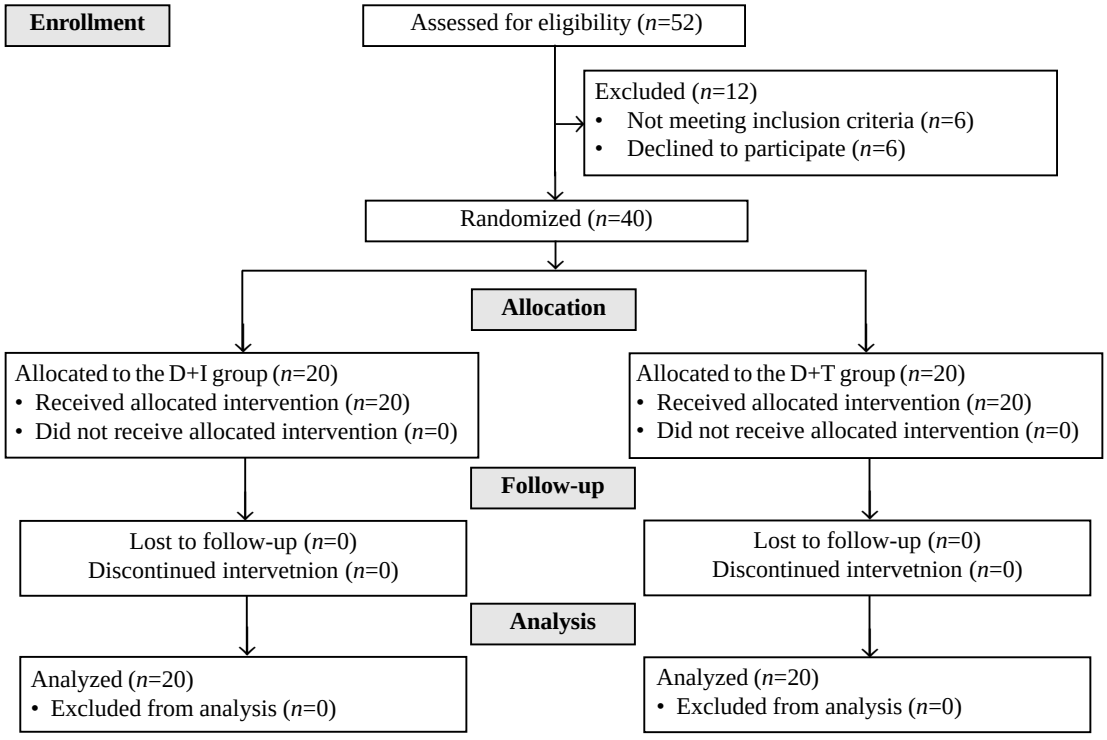

Fig. 1 CONSORT flow diagram for the study.

Table I Baseline Demographic Characteristics of Children With Nocturnal Enuresis in the Two Treatment Groups

Variables	*Desmopressin+ indomethacin (n=20)*	*Desmopressin+ tolterodine (n=20)*
Age (y)[a]	8.56 (0.98)	9.05 (2.21)
Male sex	9 (45)	9 (45)
Family history of enuresis	11 (55)	10 (50)
Incontinence since toilet training	19 (95)	15 (75)
Non-monosymptomatic enuresis	10 (50)	8 (40)

All values are no. (%) or [a]mean (SD).

Table II Response of Nocturnal Enuresis in the Two Study Groups at Various Time Points

Response	*Desmopressin+ indomethacin (n=20)*	*Desmopressin+ tolterodine (n=20)*	*P value*
Frequency of nocturnal enuresis at each month[a]			
One month	31.18 (3.85)	58.86 (7.27)	<0.001
Three month	38.56 (3.31)	69.78 (5.99)	<0.001
Five month	39.14 (3.63)	84.84 (6.21)	<0.001
Response to treatment at 5 months[b]			
Failure	10 (50)	4 (20)	0.047
Partial	10 (50)	6 (30)	0.197
Complete	0	10 (50)	<0.001

[a]Values are % nocturnal enuresis reduction in mean (SD) or [b]no. (%).

the ICCS [16] as follows: *i*) Complete response to treatment: ≥90% reduction in the frequency of enuresis per week; *ii*) Partial response to treatment: 50-89% reduction in the frequency of enuresis per week; and *iii*) Failed response: <50% reduction in the frequency of enuresis per week. The incidence of cutaneous drug reactions, and gastrointestinal or central nervous symptoms were recorded.

Statistical analysis: The Stata software (version 14.2, StataCorp LLC) was used. Due to the non-normal distribution of nocturnal enuresis reduction, a logarithmic transformation was performed for analysis, and then data were retransformed to be reported in the tables. Accordingly, the ANOVA/ANCOVA test was used to evaluate the effect of interventions on this parameter at different time points, with age as covariance, and consistent incontinence since toilet training and non-monosymptomatic enuresis as factors. Standardized mean difference (SMD) was calculated for adjusted means in each model using Glass delta. SMD interpretation was as follows: ≤0.19, trivial; 0.20-0.49, small effect; 0.50-0.79, medium effect; and ≥0.80, large effect. Eta^2 was interpreted based on the following: <0.010, trivial; 0.010-0.059, small effect; 0.060-0.139, medium effect; and ≥0.140, large effect. The chi-square test was used to compare categorical data between groups, and risk ratios were reported as effect size with the following interpretations: 0-0.81, trivial effect; 0.53-0.82, small effect; 0.32-0.54, medium effect; and ≥0.33, large effect. *P* values <0.05 were regarded as statistically significant.

RESULTS

Of the 52 children assessed for eligibility, a total of 40 patients were randomized into two groups (**Fig. 1**). **Table I** shows the baseline characteristics of the patients in both groups. None of the patients were concurrently on medications other than the study medications. D+T was significantly more efficacious than D+I in nocturnal enuresis reduction at one, three, and five months (**Table II**). At five months, complete response to treatment was only observed with D+T in 50% of children, while treatment failure was significantly higher with D+I [10 (50%) in D+I vs 4 (20%) in D+T group; *P*=0.47]. The proportion of children with partial response was not significantly different between the groups [10 (50%) in D+I vs 6 (30%) in D+T group; *P*= 0.197] (**Table II**).

After adjustment for age, consistent incontinence since toilet training, and non-monosymptomatic enuresis, D+T was still significantly more efficacious than D+I in nocturnal enuresis reduction at one, three, and five months (**Web Table I**).

None of the patients in either group developed cutaneous drug reactions or central nervous symptoms. All patients had complete compliance with the treatments.

DISCUSSION

In the current study, we found a significantly higher reduction in the frequency of nocturnal enuresis in children of the D+T group compared to those taking D+I, one month after the initiation of treatment, and at 3- and 5-month follow-ups. We also found that complete response to treatment was significantly higher with D+T, at the end of the study period. This suggests that desmopressin plus tolterodine combination therapy can be more successful than desmopressin plus indomethacin in treating pediatric patients resistant to desmopressin monotherapy. Although, there are no published trials contrasting D+T and D+I for the treatment of refractory nocturnal enuresis, these two combination therapies have both been evaluated against placebo in earlier research. Austin, et al. [8] demonstrated that a one-month combined treatment regimen of desmopressin and tolterodine reduced the mean number of wet episodes more effectively than desmopressin and placebo. However, the D+T group in our trial received a sub-

stantially lower total dosage of tolterodine (2 mg) than used by Austin, et al. [8], demonstrating that tolterodine at lower doses can still be just as effective. Likewise, Rashed, et al. [17] compared D+T with desmopressin plus placebo and showed that this combination therapy was superior in terms of treatment response. Their study's tolterodine dosage was comparable to ours. Kamperis, et al. [11] compared desmopressin plus indomethacin with desmopressin plus placebo to treat monosymptomatic nocturnal enuresis. They found that indomethacin significantly reduced nocturnal urine output compared to placebo. The number of dry nights; however, did not differ across groups [11].

Explanations for why children with nocturnal enuresis do not respond to desmopressin as the first-line treatment include patient compliance, variability in pharmacodynamics and pharmacokinetics, dietary variables, the timing of desmopressin administration, and hydration state [18,19]. Some patients who are resistant to desmopressin show bladder instability [20], and almost 70% of patients with bladder overactivity suffer from nocturnal enuresis [21], with decreased nocturnal functional bladder capacity seen commonly in refractory nocturnal enuresis [22]. These results and reports imply that desmopressin plus anticholinergic combination therapy may improve nocturnal enuresis [8,17], though additional research is required to identify the ideal anticholinergic drug and its dosage. On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) have been claimed to have antidiuretic properties, and may be used in children who do not respond to conventional therapeutic approaches. Due to the inclusion of unselected populations, studies using different NSAIDS have yielded inconsistent results [23-25].

Tolterodine is a competitive antagonist of acetylcholine at postganglionic muscarinic receptors.Therefore, by acting as a muscle relaxant, tolterodine can increase the bladder's capacity to hold urine [26]. On the other hand, indomethacin appears to exert its antidiuretic effect through anti-natriuretic properties, reduction in urea, and overall osmotic clearance. Moreover, by acting on the nervous system, tolterodine appears to have more stable effects, while indomethacin functions might be mediated under accompanying inflammatory conditions in patients with nocturnal enuresis.

The strength of our study was its randomized controlled trial design. Nonetheless, including a placebo group could have added merit to this study. One limitation was that some of our patients in both groups were non-monosymptomatic. Moreover, bladder capacity can affect outcomes, especially in patients taking anticholinergic agents, and we did not compare our patients in this regard. Also, the urine output which may be an indicator of drug efficacy [11], was not assessed in our patients. Furthermore, the small sample size of this study can limit the generalizability of our findings. Finally, long-term outcomes, including relapse, continued success, and complete success [14] were not evaluated in this study.

Desmopressin plus tolterodine was superior to desmopressin plus indomethacin for the treatment of mono- and non-monosymptomatic nocturnal enuresis in this study. Further studies with a placebo arm and a larger sample size are required to confirm our findings.

Ethics clearance: IEC, Hormozgan University of Medical Sciences; No. IR.HUMS.REC.1397.070 dated May 13, 2018.
Contributors: ME: conceptualization and study validation, writing and reviewing; SEM: implementation and supervision; GZ: data analysis and interpretation. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Note: Additional material related to the study is available with the web version at *www.indianpediatrics.net*

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Web Table I Comparison of Effects on Nocturnal Enuresis Reduction Between the Groups (Adjusted Analysis)

Time	*Desmopressin + indomethacin (n=20)*	*Desmopressin + tolterodine (n=20)*	*SMD (95%CI)*	*P-value**
At one month				
Model 1	31.52 (24.78, 40.09)	58.23 (45.78, 74.30)	5.30 (3.51, 7.08)	0.001
Model 2	30.45 (23.91, 38.79)	60.27 (47.32, 76.77)	5.92 (3.94, 7.88)	<0.001
Model 3	30.33 (28.90, 38.50)	60.51 (47.67, 76.80)	6.00 (4.00, 7.98)	<0.001
At three months				
Model 1	38.66 (32.62, 45.83)	69.58 (58.70, 82.48)	6.36 (4.25, 8.45)	<0.001
Model 2	37.91 (31.90, 45.05)	70.98 (59.73, 84.36)	6.79 (4.55, 9.01)	<0.001
Model 3	37.87 (31.80, 45.09)	71.06 (59.67, 84.61)	6.81 (4.57, 9.04)	<0.001
At five months				
Model 1	39.25 (32.62, 47.22)	84.69 (73.19, 98.01)	9.47 (6.41, 12.51)	<0.001
Model 2	39.25 (32.41, 47.52)	84.69 (72.85, 98.45)	9.45 (6.40, 12.48)	<0.001
Model 3	39.45 (32.57, 47.79)	84.42 (72.61, 98.17)	9.35 (6.33, 12.36)	<0.001

SMD: standardized mean difference; All values are % nocturnal enuresis reduction, mean (confidence interval of mean). Model 1: adjusted for age; Model 2: adjusted for age and consistent incontinence since toilet training; Model 3: adjusted for age, consistent incontinence since toilet training, and non-monosymptomatic enuresis.

RESEARCH PAPER

Efficacy of *Bacillus clausii* in Pediatric Functional Constipation: A Pilot of a Randomized, Double-Blind, Placebo-Controlled Trial

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Purpose: To evaluate the efficacy of *Bacillus clausii* in the treatment of pediatric constipation.

Methods: A randomized, double-blind, placebo-controlled trial was conducted from January, 2021 to January, 2022 in children aged 1-5 years diagnosed with functional constipation according to Rome IV criteria. They were assigned to receive either *B. clausii* or placebo, once daily for four weeks. The primary out-come was treatment success (defined as ≥3 spontaneous stools per week and stool consistency grade ≥3 on Bristol stool chart). The secondary outcome was a comparison of stool frequency, consistency (defined by Bristol stool grade), and constipation-related symptoms.

Results: This trial enrolled 38 children (*B. clausii, n*=20 and placebo, *n*=18). At 4 weeks, no significant difference was noted in the treatment success between *B. clausii* and placebo groups [45% vs 56%; *P*=0.52). On within-group analyses, the mean (SD) of Bristol stool grade increased in both the *B. clausii* [1.7 (0.5) to 2.8 (1.2); *P*=0.003] and placebo [1.8 (0.5) to 2.8 (1.2); *P*=0.01] groups. Significant increases in the treatment success rate (22% to 56%, *P*=0.01) and mean stool frequency per week [3 (0.9) to 4.2 (1.7), *P*=0.01] were pronounced only in the placebo group. The frequency of painful defecation and large fecal mass were also significantly decreased in both the groups. No serious adverse events were observed.

Conclusion: A 4-week course of *B. clausii* as the sole treatment was not more effective than a placebo for the management of functional constipation in children aged 1-5 years.

Keywords: *Intestinal microbiota*, *Laxatives, Probiotics, Stool frequency*.

Trial registration: Thai Clinical Trials Registry: TCTR20210311001 **Published online:** Feb 9, 2023; **PII:** S097475591600492

Constipation is documented as a primary complaint in 3-5% of children presenting to pediatricians and 10-20% among pediatric gastroenterologists [1]. A recent study reported 78% children with functional constipation among 316 children with constipation [2]. The use of osmotic laxatives remains the first-line pharmacologic management for children presenting with fecal impaction and maintenance therapy [3]. However, a study demonstrated that more than 50% of the pediatricians felt that the caregivers of constipated children were concerned about tolerance or dependence of the five most commonly used laxatives [4]. Therefore, besides lifestyle and dietary modification, alternative non-pharmacologic management such as probiotics may be advantageous and attractive.

A previous study showed that constipation is associated with gut dysbiosis [5]. Therefore, modifying gut microbiota environment may provide a beneficial effect in patients suffering from functional constipation. Probiotics have therefore been proposed for the management of pediatric functional constipation in the past two decades [6]. Probiotics affect the gut microbiota through various mechanisms including regulating the intraluminal environment, affecting the secretion and absorption of water and electrolytes, enhancing colonic peristalsis and reducing intestinal transit time [7-10]. A recent Cochrane review [11] revealed insufficient evidence to conclude whether probiotics are beneficial in treating constipation. Even the use of probiotics as a sole treatment in this condition remains controversial [3,12].

Invited Commentaries: Pages 429-32.

Most of the *Bacillus* spp. can produce lactic and short-chain fatty acids from carbohydrate fermentation [13], resulting in a lower pH within the colonic lumen and increased peristalsis [14]. *B. clausii*, a non-pathogenic Gram-positive bacteria, has been shown to restore intestinal flora by stimulating immunomodulatory activity [15]. *B. clausii* is also considered safe and has a very low incidence of mild adverse events such as vomiting,

RESEARCH PAPER

Etiology and Outcome of Community-Acquired Acute Kidney Injury in Pediatric Inpatients

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Objective: To estimate the etiology, outcome, and risk factors for mortality in children with community-acquired acute kidney injury (CA-AKI). **Methods:** Between October, 2020 and December, 2021, consecutive hospitalized children aged 2 mo-12 years with a minimum 24 hours of stay, and at least one serum creatinine level measured at or within 24 hours of hospitalization were prospectively enrolled. CA-AKI was labelled in children with an elevated serum creatinine level at admission and subsequent fall during hospitalization. **Results**: Of 2780 children, 215 were diagnosed as CA-AKI (7.7%, 95% CI 6.7-8.6). Diarrhea with dehydration (39%) and sepsis (28%) were the most common causes of CA-AKI. 24 children (11%) died during hospitalization. Requirement of inotropes was an independent predictor of mortality. Out of 191 children discharged, 168 (88%) had complete renal recovery. At 3 months, out of 22 children without complete renal recovery, 10 progressed to chronic kidney disease (CKD), with 3 becoming dialysis dependent. **Conclusions:** CA-AKI is common in hospitalized children, and is associated with increased risk of progression to CKD, especially in those with incomplete renal recovery.

Keywords: *Chronic kidney disease, Inpatient, Outcome*.

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Acute kidney injury (AKI), characterized by an abrupt decrease in kidney function, is associated with substantial morbidity, increased risk of mortality and higher risk of progression to chronic kidney disease (CKD) [1]. Community-acquired AKI (CA-AKI), a subset of AKI, is presence of AKI at the time of hospitalization. In AKI Global Snapshot study, 47% of AKI episodes were due to CA-AKI, of which 80% occurred in low and low to medium income countries [2]. In contrast to hospital acquired AKI (HA-AKI), which has multifactorial origin and high mortality risk, CA-AKI chiefly has single etiology, mostly preventable and associated with lower risk of mortality [3]. In view of the limited prospectively collected data on CA-AKI in children, especially from India, this study was aimed to estimate the frequency, etiology, and outcome as well as risk factors for mortality in children with CA-AKI.

METHODS

This prospective study was conducted at an urban pediatric tertiary care hospital in northern India between October, 2020 and December, 2021. All consecutive hospitalized children between 2 months to 12 years of age with minimum 24 hours of stay and at least one serum creatinine value measured at or within 24 hours of hospitalization were assessed for eligibility. Children with known CKD, serum creatinine estimation <2 times during first 7 days of hospitalization, breakthrough seizure, corrosive ingestion, elective hospitalization, readmission within 2 weeks of discharge and those referred from other centers after 48 hours of hospitalization were excluded from the study.

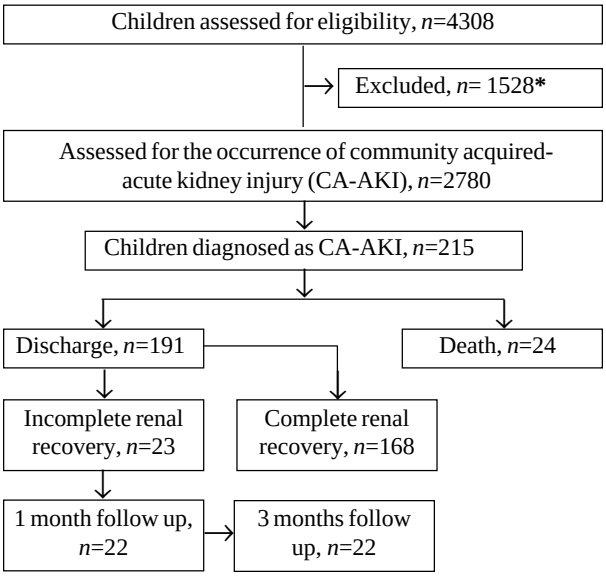
Assuming the average incidence of CA-AKI as 10% [4,5], with precision of 2% and at 95% confidence level, minimum 950 children were planned for screening, considering 10% attrition. Ethics approval was obtained from institutional ethics committee.

Invited Commentary: Pages 433-34.

Children with admission serum creatinine level of ≥1.5 times or ≥0.3 mg/dL higher than the median reference value for age [6] were presumed to have CA-AKI and enrolled for the study. A repeat serum creatinine was obtained within 24-48 hours of hospitalization. Baseline serum creatinine was defined as the lowest of any three: *i*) Serum creatinine level during last 3 months, if available; *ii*) median reference value of serum creatinine for that age; or *iii*) lowest serum creatinine value during hospitalization. Serum creatinine was estimated by modified Jaffe kinetic method traceable to IDMS using Beckman Coulter AU-680 analyzer.

Those with deranged serum creatinine level at admission were subjected to repeat blood sampling every 24-48 hours till normalization of serum creatinine value or discharge, whichever was earlier. Diagnosis and staging of CA-AKI was established by measuring subsequent fall in serum creatinine during hospitalization according to serum creatinine criterion of KDIGO classification system [7]. Final AKI stage was the maximum AKI stage achieved during hospitalization. Ultrasonography of kidney, ureter and bladder region was done where serum creatinine failed to normalize. Renal biopsy was done in cases of AKI with unknown etiology.

Outcomes were measured in terms of renal recovery at discharge, requirement of dialysis, duration of hospital stay and mortality. Renal recovery was defined as 'complete', if serum creatinine normalized to the reference range for that age, 'partial', if serum creatinine decreased to a lesser AKI stage, but still higher than the reference range and 'no recovery', if there was no change in the AKI stage. CKD was defined as eGFR <60 mL/min/1.73m^2 or eGFR >60 mL/min/1.73m^2 with structural damage or persistence of proteinuria for >3 months. Dialysis dependence was defined as persistent need of dialysis for maintaining fluid and electrolyte homeostasis. Those without complete renal recovery at discharge were further followed-up at one and three months after discharge.



**Known case of CKD/ESRD, n=24; elective hospitalization (for blood transfusion, n=165; albumin infusion, n=36; chemotherapy, n=71; IVIG infusion, n=14; pamidronate, n=21; for renal biopsy, n=36; bone marrow aspiration/biopsy, n=18; endoscopy, n=186), Breakthrough seizures, n=493; Accidental poisoning, n=87; Children with <2 serum creatinine measurement during first 7d of hospitalization, n=54; Readmission within 2 weeks after discharge, n=21; Referred from other centers after ≥48h of stay, n=302.*

Fig. 1 Study flow chart.

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24. Quantitative variables were expressed as mean or median and were analyzed by independent *t* test or Mann-Whitney *U* test, respectively. Qualitative variables were expressed as numbers/percentages and were analyzed by chi-square test or Fisher exact test. Risk factors for mortality were analyzed by logistic regression analysis.

RESULTS

Of the 4308 eligible children, 1528 were excluded and 2780 children aged 2 months to 12 years, with >24 hours of hospital stay, were assessed for CA-AKI, and 215 (7.7%, 95% CI, 6.7- 8.6) were diagnosed as CA-AKI according to KDIGO definition of AKI (**Fig. 1**).

Demographic, clinical and laboratory characteristics of children with CA-AKI are shown in **Table I**. Maximum AKI stage I, II and III were present in 11 (5%), 42 (20%) and 162 (75%) children, respectively. Diarrheal diseases with dehy-

Table I Demographic, Clinical and Laboratory Characteristics of Children With CA-AKI (*N*=215)

Characteristic	*Values*
Age group	
2-12 mo	126 (58.6)
>12 mo	89 (41.4)
Male sex	120 (55.8)
Weight (kg)[a]	7.8 (5.5,15)
Oligo-anuria	41 (19)
SBP SD score[a]	0.38 (-0.67,-0.8)
DBP SD score[a]	-0.22 (-0.8,-0.7)
Hypotension	13 (6)
PICU admission	29 (13.5)
Maximum AKI stage	
Stage I AKI	11 (5)
Stage II AKI	42 (20)
Stage III AKI	162 (75)
Dialysis	19 (9)
Peritoneal dialysis	6 (3)
Hemodialysis	13 (6)
Hemoglobin (g/dL)[b]	10.9 (3.4)
C-reactive protein (mg/L)[a]	16 (3.2,66)
Urea (mg/dL)[a]	86 (56,146)
Serum creatinine (mg/dL)[a]	
At admission	1 (0.7,1.6)
Maximum value	1.1 (0.7, 1.7)
Thrombocytopenia	42 (19.5)

Values in no. (%), [a]median (IQR) or [b]mean (SD). CA-AKI: community acquired-acute kidney injury; SBP and DBP: systolic and diastolic blood pressure; PICU: pediatric intensive care unit,

dration (*n*=85) and sepsis (*n*=61, 18 blood culture positive) were two most common causes of CA-AKI, followed by acute febrile illnesses (*n*=32) and primary renal diseases (*n*=32). Among febrile illnesses, dengue (*n*=13), pyelonephritis (*n*=5) and leptospirosis (*n*=4) were important causes of CA-AKI. Nephrotic syndrome (*n*=12) with features of hypovolemia and/or acute tubular necrosis was the most common primary renal disease associated with CA-AKI, followed by hemolytic uremic syndrome (*n*=9) and acute glomerulonephritis (*n*=10) **(Table II)**.

Out of 191 children discharged, 168 (88%) had complete renal recovery, 13 (7%) had partial renal recovery and 10 (5%) had no renal recovery. Nineteen (9%) children required dialysis (13 hemodialysis and 6 peritoneal dialysis). Median (IQR) duration of hospital stays in children with AKI stage I, II and III was 4 (3,6), 5.5 (3.7,9) and 6 (3,12.2) days, respectively. Twenty four (11%) children with CA-AKI died during hospitalization. Of 21 children who died of sepsis, 20 presented as septic shock and died even before dialysis could be started. Median SD scores of systolic and diastolic blood pressures were significantly lower in children who died in comparison to those who survived. Out of 22 children at 3 months follow-up, 10 progressed to CKD, with 3 of them becoming dialysis dependent.

On univariate analysis, sepsis, mechanical ventilation, inotropes requirement and stage III AKI were significantly associated with increased risk of mortality. On multivariate logistic regression analysis, inotropes requirement was the only independent risk factor for mortality (**Table III**).

Table II Etiological Diagnosis of Community-Acquired Acute Kidney Injury in Hospitalized Children (*N*=215)

Etiology	*No. (%)*
Diarrhea with dehydration	85 (39.5)
Sepsis	61 (28.3)
Acute febrile illnesses[a]	32 (14.9)
Dengue	13 (6.0)
Pyelonephritis	5 (2.3)
Leptospirosis	4 (1.9)
Typhoid	3 (1.4)
Primary renal diseases (*n*=32)	
Nephrotic syndrome	12 (5.6)
Hemolytic uremic syndrome	9 (4.2)
Post-infectious GN	4 (1.9)
Rapidly progressing GN[b]	6 (2.7)
Renal stones	1 (0.5)
Diabetic ketoacidosis	3 (1.4)
Dextromethorphan toxicity	1 (0.5)
MIS-C	1 (0.5)

GN: glomerulonephritis; MIS-C: multisystem inflammatory syndrome in children. [a]2 each with liver abscess, malaria and diphtheria, and 1 child with tubercular meningitis; [b]2 with lupus nephritis, and 1 each with C3 GN, anti-GBM crescentic GN, granulomatous interstitial nephritis, IgA crescentic GN.

Table III Risk Factors for Death in Children With Community-Acquired Acute Kidney Injury (*N*=215)

Variables	*OR (95% CI)*	*P value*
Requirement of inotropes	363 (26-5084)	<0.001
Sepsis	2.4 (0.4-14)	0.30
Stage III acute kidney injury	4.3 (0.16-118)	0.38
Mechanical ventilation	0.1 (0.01-1.1)	0.06

DISCUSSION

In this prospective study frequency of CA-AKI in hospitalized children was 7.7% (95% CI 6.7-8.6), with majority being in AKI stage III. Diarrheal diseases with dehydration and sepsis were predominant causes of CA-AKI. More than three fourth of cases had complete renal recovery at discharge, whereas 11% died during hospitalization. Requirement of inotropes was the only independent risk factor for mortality. Nearly half of those with incomplete renal recovery at discharge progressed to CKD at 3 months follow-up.

Frequency of CA-AKI in our study was similar to earlier studies across the globe, with incidence of CA-AKI varying between 7 to 14% [4,5,8,9]. In a meta-analysis to estimate the worldwide incidence of AKI, pooled incidence rate of CA-AKI was 8.3% [10]. Three fourth of the children in our study achieved maximum AKI stage III, similar to study by Esezobar, et al. [11], where 70% children were in 'failure' category. Majority of cases in AKI stage III in our study can be explained by predominantly infant population, which are more susceptible to infection-related AKI.

One fourth of all AKI cases in our study resulted from sepsis, similar to study from a sub-Saharan African country, where sepsis accounted for 25.7% of all AKI cases [11]. Etiological spectrum of AKI in our study was similar to other Indian studies [12,13], with infections accounting for more than half of all cases, followed by primary renal diseases.

Despite majority of our AKI cases in stage III, only 9% received dialysis, in contrast to 14.5% children requiring dialysis in a study from southern India [12]. Fewer children receiving dialysis in our study can be explained by many presenting as septic shock and succumbing within 24 hours of hospitalization even before dialysis could have been started. Mortality rate of 11% in our study was similar to pooled AKI-associated mortality rate of 13.8% in children [10]. A higher in-hospital mortality in two other Indian studies [12,13] and studies from sub-Saharan African countries [4,5] in comparison to our study can be explained by inclusion of hospital-acquired AKI cases also in their studies.

WHAT THIS STUDY ADDS?

- Majority of community-acquired acute kidney injury in hospitalized children resulted from diarrheal diseases and sepsis.

In consonance with two Indian studies [12,13], more than two-third of children in our study achieved complete renal recovery at discharge. Out of those with incomplete renal recovery, nearly half progressed to CKD at 3 months follow-up. Though, risk factors for progression to CKD were not analyzed, approximately two-thirds of surviving children who had received dialysis progressed to CKD at 3 months. In contrast to 22-35% of all AKI cases progressing to CKD at 3 months [14,15], only 5% of surviving children in our study progressed to CKD, which can be explained by majority of AKI cases due to diarrhea and fewer children requiring dialysis.

Strength of this study is prospective enrollment of cases throughout the year to include all probable CA-AKI cases with seasonal variation along with 3 months follow-up after discharge. However, the study had some limitations viz., being a single center study, results are not generalizable; urine output criterion was not used for defining AKI*;* CA-AKI in CKD cases were not assessed because of prior exclusion of known CKD cases; study not powered to assess the predictors of mortality and follow-up for children with incomplete renal recovery only, based on deranged serum creatinine at discharge, which could have missed some children showing normal creatinine but persistent proteinuria or hypertension.

To conclude, CA-AKI is common in hospitalized children, with majority resulting from diarrheal diseases and sepsis. Long-term follow-up is required in cases with incomplete renal recovery, especially those requiring dialysis because of high risk of progression to CKD.

Ethics clearance: Institutional Ethics Committee, CNBC; No F.1/IEC/CNBC/11/07/2020/78/9671, dated Sep 29, 2020.
Contributors: MK: conceptualized the study. AA: enrolled the patients, collected data, involved in patient management and prepared the initial draft; MK, KM: performed the analysis and interpretation of data. MK, AA and KM revised the draft. All the authors approved the final version of the manuscript.
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erythematous rash, and stool color change [16]. Therefore, this study aimed to demonstrate the beneficial effects of *B. clausii* on the treatment of functional constipation in young children.

METHODS

This pilot study was a randomized, double-blind, placebo-controlled trial conducted at a quaternary care teaching hospital.

Patients were recruited from both general pediatric clinics and gastroenterology clinics. Inclusion criteria included children aged 1-5 years who were diagnosed with functional constipation according to the Rome IV criteria between January, 2021 and January, 2022. Exclusion criteria were children with suspected or proven organic causes of constipation, drugs that may cause constipation (e.g., antidepressant drugs, opiates), immuno compromised host, neurological impairment, or congenital heart disease. Informed consent was taken for all participants. The study was approved by the institutional review board. The protocol for this study was registered at the Thai Clinical Trials Registry.

During the initial visit, baseline characteristics were recorded, including underlying disease, allergies, and current medication. We collected the characteristics of bowel movement including frequency, consistency defined by the Bristol stool chart on a scale of 1-7 (the scale was noted in the actual stool diary), the frequency of constipation-related symptoms including painful defecation, retentive posturing, large fecal mass (subjectively defined by the caregivers), fecal incontinence (if the child was already toilet-trained), abdominal pain, and rectal bleeding. We used a digital rectal examination for evaluating impacted feces in all children, during the initial visit, before starting the intervention. The children were then randomly assigned into two groups via a computer-generated list, either *B. clausii* or placebo. *B. clausii* (Enterogemina, Sanofi-Aventis), one vial contained *B. clausii* 2 billion spores in 5 mL, odorless, tasteless, colorless, and no refrigeration was needed. The placebo's allocation was concealed by using a vial containing the same volume of sterile water suspension in a plastic container. All caregivers were educated by a single investigator with similar advice on non-pharmacologic management including age- and weight-appropriate fiber and fluid intake, toilet training in developmentally appropriate normal children aged >2-3 years (based on the American Academy of Pediatrics recommendation) with a stool diary on a daily basis. A washout period of two weeks was applied if the child had received any prior treatments for constipation.

Caregivers were instructed to give one vial of the study product to the child once daily for 28 days, and complete a daily diary (provided by the researcher) for stool patterns based on Bristol scale, associated symptoms and adverse events. Parents were also advised to use sodium chloride enema once if the child did not defecate for three or more consecutive days (10 mL for children aged 1-2 years, and 20 mL for children aged 3-5 years). After two weeks, the caregivers sent the daily diary via an online application to the research team, who also telephoned them to ask for further explanations, if needed. Parents returned for a follow-up visit at four weeks, with the diary or via an online application, if the caregivers were unable to visit, especially during the ongoing COVID-19 pandemic. We also defined the compliance and the use of rectal enema. Children who took less than 75% of the total vials in each phase were excluded from the trial.

The primary outcome was treatment success defined as 'at least 3 defecations per week and stool consistency at least grade 3 on the Bristol stool chart' at week 2 and week 4 after the intervention. Secondary outcomes are constipation-related symptoms described above and adverse effects during the study.

Statistical analysis: Statistical analysis was performed by per protocol analysis. Descriptive statistics were performed for baseline characteristics. Continuous variables were described by mean and standard deviation (SD), or in the case of non-normal distributions, by median and interquartile range (IQR). Categorical variables were described by percentage. The significance of difference between independent samples was determined by student *t*-test or Mann-Whitney *U* test for continuous data and by Chi square test or Fisher exact test for categorical data. For paired samples, the significance of difference was determined by paired *t*-test or Wilcoxon sign-rank test for continuous data and by McNemar test for categorical data. Statistical analyses were performed with Stata software version 14.0. For all comparisons, a P value of <0.05 was considered statistically significant.

RESULTS

Caregivers of 50 children agreed to participate and were enrolled in the study. However, 11 patients were excluded during the 2-week washout period due to worsening constipation, and as some children had rectal bleeding. After randomization, 21 children were assigned to receive *B. clausii* and 18 children received a placebo (**Fig.1**). One child in the *B. clausii* group dropped out due to severe abdominal pain and rectal bleeding. Overall, the baseline characteristics of both groups were comparable (**Table I**).

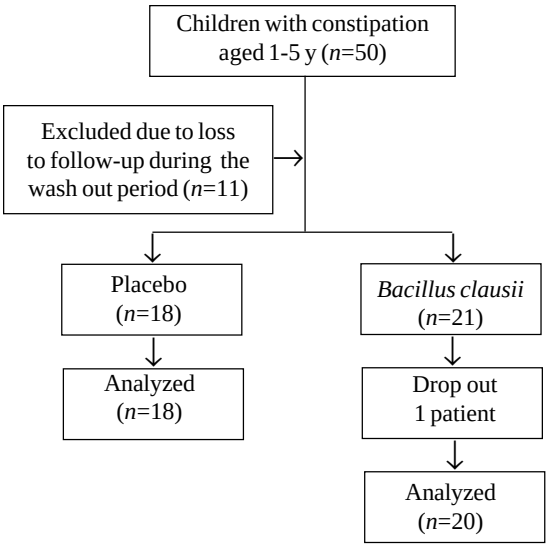


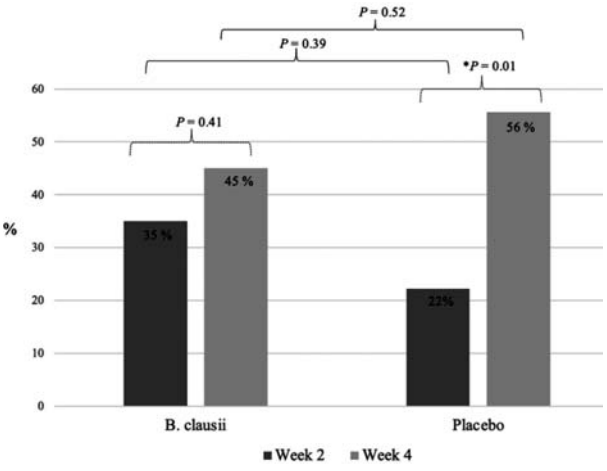
Fig. 1 Flow diagram of the study population.

Two-week follow-up: The treatment success was not significantly different when compared between the *B. clausii* and the placebo groups (35% vs 22%; *P*=0.39) (Fig. 2a). The stool consistency (Fig. 2b), rectal enema used (Fig. 2c), stool frequency (Fig. 3a), painful defecation (Fig. 3b), large fecal mass (Fig. 3c), and retentive posturing (Fig. 3d), as well as fecal incontinence and

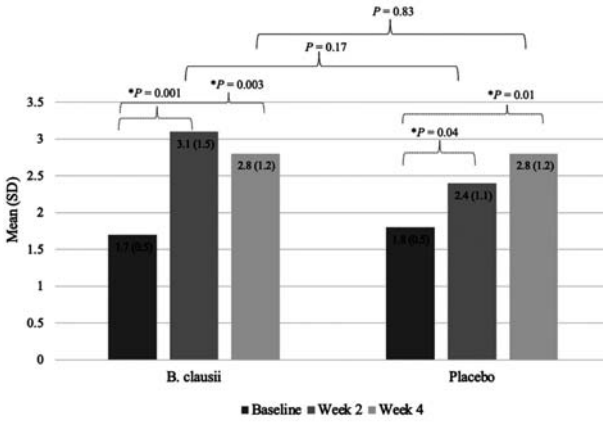
Table I Baseline Characteristics of Children With Functional Constipation Enrolled in the Study

Characteristics	*Bacillus clausii* (*n =20*)	*Placebo* (*n =18*)	*P value*
Male sex	7 (35)	10 (56)	0.21
Age (y)[a]	2.7 (1.0)	2.7 (0.9)	0.91
Body weight (kg)[a]	13.2 (3.9)	13.5 (2.6)	0.76
Duration of constipation (mo)[a]	12.1 (9.5)	12.7 (9.4)	0.69
Previous constipation treatment	15 (75)	15 (83)	0.53
Lactulose	6	12	-
Polyethylene glycol	5	3	-
Unison enema ± laxative	4	-	-
Bristol stool grade[a]	1.7 (0.5)	1.8 (0.5)	0.41
Stool frequency (per wk)[a]	4 (2.1)	3 (0.9)	0.06
Painful defecation (per wk)[b]	3 (2-3)	2 (2-3)	0.55
Large fecal mass (per wk)[b]	2 (2-3.5)	2 (2-3)	0.52
Retentive posture (per wk)[b]	1 (0-1)	1(0-1)	0.43
Fecal incontinence	5 (25)	5 (28)	0.85
Abdominal pain	5 (25)	5 (28)	0.85
Rectal bleeding	6 (30)	5 (28)	0.88
Impacted feces	4 (20)	5 (28)	0.58

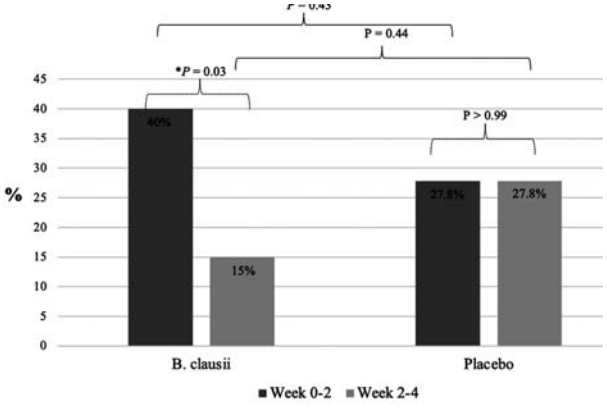
Values in no. (%),[a]mean (SD) or [b]median (IQR).



(*a*)



(*b*)



(*c*)

Fig. 2 Effect of *Bacillus clausii* and placebo on *a*) treatment success (defined by at least 3 defecations/wk and stool consistency at least grade 3 on the Bristol stool chart, *b*) Bristol stool grade, and *c*) rectal enema used during each of the 2-wk study period.

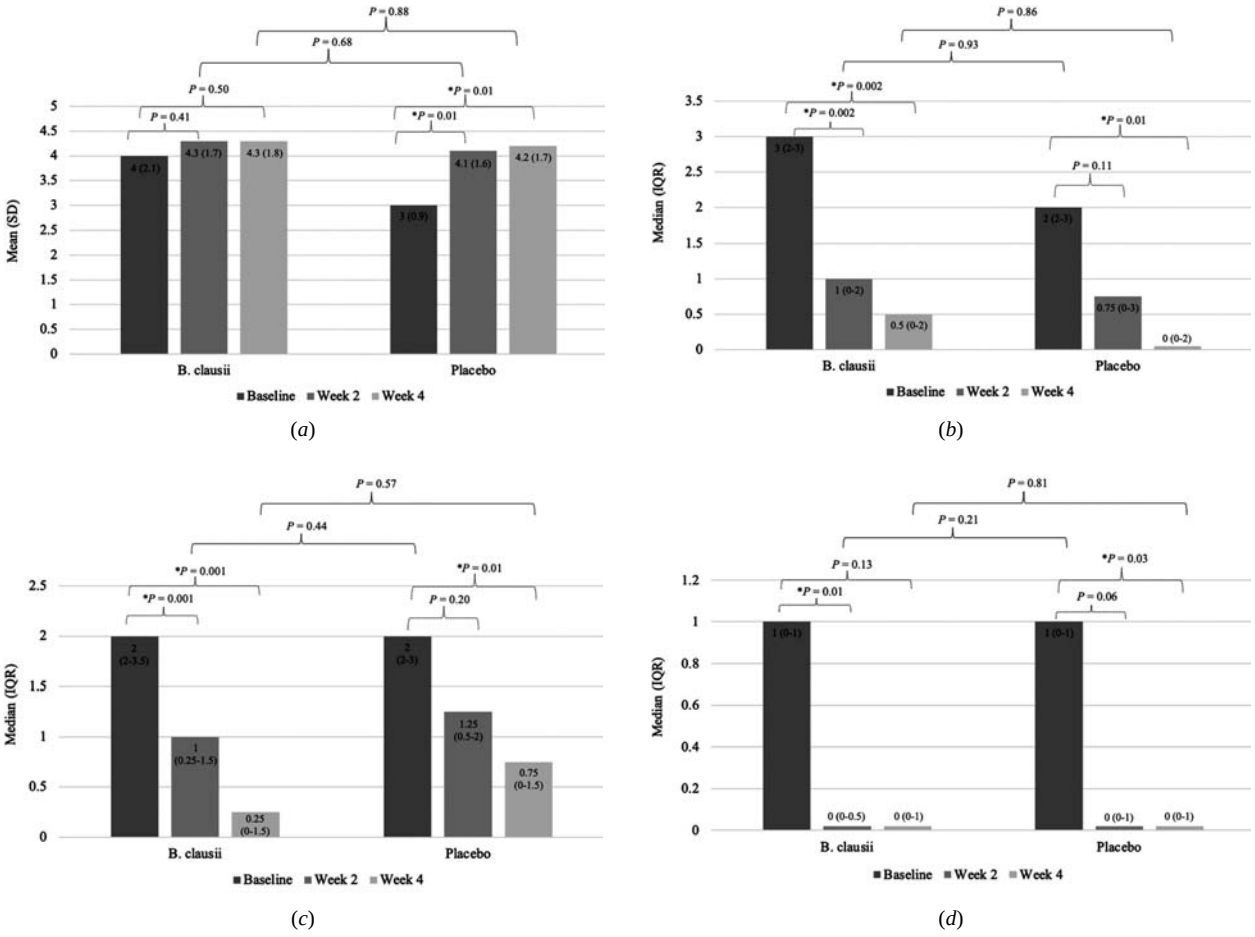


Fig. 3 Effects of *Bacillus clausii* and placebo on *a*) stool frequency, *b*) painful defecation, *c*) large fecal mass, and *d*) retentive posture.

abdominal pain, were not significantly different between groups.

The Bristol stool grade increased in both groups at week 2 as compared to baseline (P=0.001 in the *B. clausii* and P=0.04 in the placebo group) (**Fig. 2b**). Frequencies of painful defecation, large fecal mass, and retentive posture decreased in the *B. clausii* group (**Fig. 3b-d**). However, the stool frequency increased significantly only in the placebo group (**Fig. 3a**).

Four-week follow-up: Treatment success was again not significantly different when compared between the *B. clausii* and placebo groups (45% vs 56%; P=0.52). The treatment success rate of constipated children in the placebo group was even higher than the intervention. The mean stool consistency, rectal enema used, stool frequency, painful defecation, large fecal mass, and retentive posturing as well as other constipation-related symptoms were also not significantly different (all P >0.05).

The Bristol stool grade increased in both groups at week 4 as compared to baseline (P=0.003 in the *B. clausii* and P=0.01 in the placebo group) (**Fig. 2b**). Painful defecation and large fecal mass also decreased in both groups (**Fig 3b, 3c**). While rectal enema used decreased over time only in the *B. clausii* group (**Fig. 2c**), significantly increased treatment success and stool frequency were noted only in the placebo group (**Fig. 2a, 3b**). However, neither group showed any reduction in fecal incontinence nor abdominal pain (data not shown).

Adverse effects: No serious adverse effects were observed. One patient had urticaria and another had abdominal pain in the *B. clausii* group (n=2), and one patient in the placebo group had vomiting.

DISCUSSION

In this prospective randomized study, we found that the efficacy of 4-week probiotic *B. clausii* in the treatment of functional constipation in young children did not differ when compared to those who received a placebo. We also observed no significant differences in the secondary out-

WHAT IS ALREADY KNOWN?

- Besides laxatives and lifestyle modification, alternative non-pharmacologic managements such as probiotics may have a role in managing children with functional constipation.

WHAT THIS STUDY ADDS?

- A 4-week course of *B. clausii* as the sole treatment was not more effective than a placebo in constipated children aged 1-5 years.

comes or adverse effects. With regards to within-group analyses, both groups showed significant improvement in stool consistency, painful defecation, and large fecal mass after 4 weeks. However, the treatment success and stool frequency only improved in the placebo group, while the rescue use of rectal enema decreased only in the *B. clausii* group.

Clinical data support *B.clausii* use for the treatment and prevention of gut barrier impairment [17]. Trials have investigated its use in acute diarrhea [18,19] and prevention of adverse effects from *H. pylori* therapy [20]. To our knowledge, this study is the first trial investigating the efficacy of *B. clausii* as a sole treatment in pediatric functional constipation. Currently, the mainstay management of pediatric functional constipation include lifestyle modification and osmotic laxatives, while the efficacy of most probiotics strain remains in question. A previous systematic review [6] showed no significant difference between the probiotic and placebo groups in children. However, some probiotic strains showed beneficial effects on stool frequency [6].

In pediatric trials [21], four weeks of *Lactobacillus casei rhamnosus* Lcr35 revealed no additional benefit in the treatment success when compared to placebo. However, there was a significant increase in stool frequency. In another study [22], a three-week course of fermented dairy products containing *Bifidobacterium lactis* strain DN-173 010 failed to show an improvement in stool frequency when compared to placebo. The results were consistent with our trial. The lack of an effect of *B. clausii* in this trial may be contributed by an enhanced placebo effect. A high placebo response rate was observed in the earlier trials of pediatric functional constipation, which revealed a 58-70% treatment success rate [21,23]. Moreover, this may likely be a true placebo effect as the participating parents anticipate clinical improvement regardless of the intervention in a non-differential manner.

Recent data has raised concerns regarding probiotic safety. Khatri, et al. [24] reported a case of prolonged *B. clausii* bacteremia in a 17-month-old immunocompetent child, without a definite site of infection or predisposing risk factors. In another case [25], a 5-month-old child with a history of surgically corrected congenital heart disease and malnutrition developed recurrent *B. clausii* bacteremia and consequently succumbed to multidrug-resistant *Klebsiella pneumoniae* sepsis with multiorgan failure [25]. However, no serious adverse events were reported in our trial.

This trial had some limitations that could have caused biases. First, the number of subjects was rather small due to the effect of the COVID-19 pandemic that limited overall outpatient visits to our institution, which may lead to the negative finding of this trial (type 2 error). The follow-up time was also short as it may be worthwhile to wait for a longer period to observe the effect of probiotics, even after the probiotics were ceased. Nevertheless, we tried to avoid the vicious cycle of constipation going for a longer time before initiating an appropriate laxative. Most of the evaluated outcomes were based on a daily stool diary completed by the parents, which might have caused some difficulties, especially when assessing fecal soiling or incontinence and abdominal pain in toddlers. The inability to create a placebo container that was identical to the probiotics container despite the equal volume and similar physical property (clear, odorless, tasteless) of the solution may lead to a minimal bias. We did not have comprehensive data on dietary intake and toilet-related data such as toilet seat. As the gut microbiota analysis was not included in this study, hypothesis regarding the role of gut dysbiosis in children with functional constipation remained speculative. A larger trial of this probiotic strain with diet and toilet-related history, gut microbiota analysis and a longer follow-up period may confirm our finding.

A 4-week course of *B. clausii* as a sole treatment was not more effective than a placebo for the management of functional constipation in a small group of children aged 1-5 years. Larger trials with diet history and a longer follow-up may either confirm or rebut this finding.

Note: The study protocol was retrospectively registered on Feb 19, 2021 and the first patient was enrolled on Jan 5, 2021.
Ethics clearance: Institutional Review Board COA; MURA 2020/253 dated Feb 14, 2020.
Contributors: PL: preparation of the draft manuscript, conception and design, data interpretation of data, revision of the manu-

script; JP: conception and design; PT: conception and design, data interpretation of data, critical review and revision of the manuscript; SG: conception and design; CL: conception and design, revision of the manuscript; ST: conception and design, revision of the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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RESEARCH PAPER

Etiology and Outcome of Community-Acquired Acute Kidney Injury in Pediatric Inpatients

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Objective: To estimate the etiology, outcome, and risk factors for mortality in children with community-acquired acute kidney injury (CA-AKI). **Methods:** Between October, 2020 and December, 2021, consecutive hospitalized children aged 2 mo-12 years with a minimum 24 hours of stay, and at least one serum creatinine level measured at or within 24 hours of hospitalization were prospectively enrolled. CA-AKI was labelled in children with an elevated serum creatinine level at admission and subsequent fall during hospitalization. **Results**: Of 2780 children, 215 were diagnosed as CA-AKI (7.7%, 95% CI 6.7-8.6). Diarrhea with dehydration (39%) and sepsis (28%) were the most common causes of CA-AKI. 24 children (11%) died during hospitalization. Requirement of inotropes was an independent predictor of mortality. Out of 191 children discharged, 168 (88%) had complete renal recovery. At 3 months, out of 22 children without complete renal recovery, 10 progressed to chronic kidney disease (CKD), with 3 becoming dialysis dependent. **Conclusions:** CA-AKI is common in hospitalized children, and is associated with increased risk of progression to CKD, especially in those with incomplete renal recovery.

Keywords: *Chronic kidney disease, Inpatient, Outcome*.

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Acute kidney injury (AKI), characterized by an abrupt decrease in kidney function, is associated with substantial morbidity, increased risk of mortality and higher risk of progression to chronic kidney disease (CKD) [1]. Community-acquired AKI (CA-AKI), a subset of AKI, is presence of AKI at the time of hospitalization. In AKI Global Snapshot study, 47% of AKI episodes were due to CA-AKI, of which 80% occurred in low and low to medium income countries [2]. In contrast to hospital acquired AKI (HA-AKI), which has multifactorial origin and high mortality risk, CA-AKI chiefly has single etiology, mostly preventable and associated with lower risk of mortality [3]. In view of the limited prospectively collected data on CA-AKI in children, especially from India, this study was aimed to estimate the frequency, etiology, and outcome as well as risk factors for mortality in children with CA-AKI.

METHODS

This prospective study was conducted at an urban pediatric tertiary care hospital in northern India between October, 2020 and December, 2021. All consecutive hospitalized children between 2 months to 12 years of age with minimum 24 hours of stay and at least one serum creatinine value measured at or within 24 hours of hospitalization were assessed for eligibility. Children with known CKD, serum creatinine estimation <2 times during first 7 days of hospitalization, breakthrough seizure, corrosive ingestion, elective hospitalization, readmission within 2 weeks of discharge and those referred from other centers after 48 hours of hospitalization were excluded from the study.

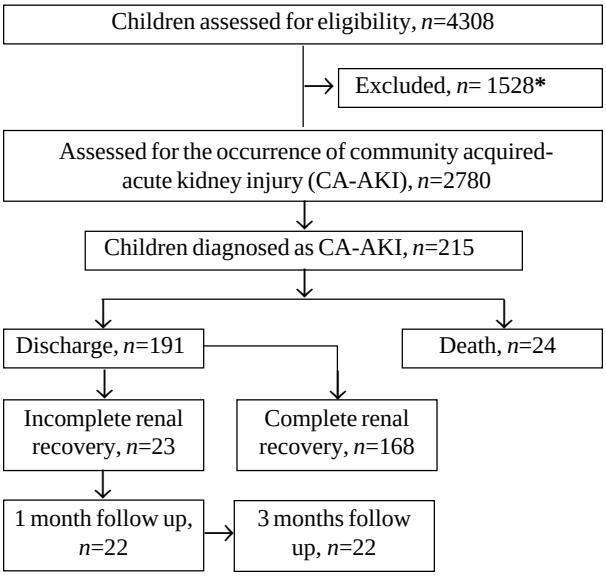
Assuming the average incidence of CA-AKI as 10% [4,5], with precision of 2% and at 95% confidence level, minimum 950 children were planned for screening, considering 10% attrition. Ethics approval was obtained from institutional ethics committee.

Invited Commentary: Pages 433-34.

Children with admission serum creatinine level of ≥1.5 times or ≥0.3 mg/dL higher than the median reference value for age [6] were presumed to have CA-AKI and enrolled for the study. A repeat serum creatinine was obtained within 24-48 hours of hospitalization. Baseline serum creatinine was defined as the lowest of any three: *i*) Serum creatinine level during last 3 months, if available; *ii*) median reference value of serum creatinine for that age; or *iii*) lowest serum creatinine value during hospitalization. Serum creatinine was estimated by modified Jaffe kinetic method traceable to IDMS using Beckman Coulter AU-680 analyzer.

Those with deranged serum creatinine level at admission were subjected to repeat blood sampling every 24-48 hours till normalization of serum creatinine value or discharge, whichever was earlier. Diagnosis and staging of CA-AKI was established by measuring subsequent fall in serum creatinine during hospitalization according to serum creatinine criterion of KDIGO classification system [7]. Final AKI stage was the maximum AKI stage achieved during hospitalization. Ultrasonography of kidney, ureter and bladder region was done where serum creatinine failed to normalize. Renal biopsy was done in cases of AKI with unknown etiology.

Outcomes were measured in terms of renal recovery at discharge, requirement of dialysis, duration of hospital stay and mortality. Renal recovery was defined as 'complete', if serum creatinine normalized to the reference range for that age, 'partial', if serum creatinine decreased to a lesser AKI stage, but still higher than the reference range and 'no recovery', if there was no change in the AKI stage. CKD was defined as eGFR <60 mL/min/1.73m^2 or eGFR >60 mL/min/1.73m^2 with structural damage or persistence of proteinuria for >3 months. Dialysis dependence was defined as persistent need of dialysis for maintaining fluid and electrolyte homeostasis. Those without complete renal recovery at discharge were further followed-up at one and three months after discharge.



**Known case of CKD/ESRD, n=24; elective hospitalization (for blood transfusion, n=165; albumin infusion, n=36; chemotherapy, n=71; IVIG infusion, n=14; pamidronate, n=21; for renal biopsy, n=36; bone marrow aspiration/biopsy, n=18; endoscopy, n=186), Breakthrough seizures, n=493; Accidental poisoning, n=87; Children with <2 serum creatinine measurement during first 7d of hospitalization, n=54; Readmission within 2 weeks after discharge, n=21; Referred from other centers after ≥48h of stay, n=302.*

Fig. 1 Study flow chart.

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24. Quantitative variables were expressed as mean or median and were analyzed by independent *t* test or Mann-Whitney *U* test, respectively. Qualitative variables were expressed as numbers/percentages and were analyzed by chi-square test or Fisher exact test. Risk factors for mortality were analyzed by logistic regression analysis.

RESULTS

Of the 4308 eligible children, 1528 were excluded and 2780 children aged 2 months to 12 years, with >24 hours of hospital stay, were assessed for CA-AKI, and 215 (7.7%, 95% CI, 6.7- 8.6) were diagnosed as CA-AKI according to KDIGO definition of AKI (**Fig. 1**).

Demographic, clinical and laboratory characteristics of children with CA-AKI are shown in **Table I**. Maximum AKI stage I, II and III were present in 11 (5%), 42 (20%) and 162 (75%) children, respectively. Diarrheal diseases with dehy-

Table I Demographic, Clinical and Laboratory Characteristics of Children With CA-AKI (*N*=215)

Characteristic	*Values*
Age group	
2-12 mo	126 (58.6)
>12 mo	89 (41.4)
Male sex	120 (55.8)
Weight (kg)[a]	7.8 (5.5,15)
Oligo-anuria	41 (19)
SBP SD score[a]	0.38 (-0.67,-0.8)
DBP SD score[a]	-0.22 (-0.8,-0.7)
Hypotension	13 (6)
PICU admission	29 (13.5)
Maximum AKI stage	
Stage I AKI	11 (5)
Stage II AKI	42 (20)
Stage III AKI	162 (75)
Dialysis	19 (9)
Peritoneal dialysis	6 (3)
Hemodialysis	13 (6)
Hemoglobin (g/dL)[b]	10.9 (3.4)
C-reactive protein (mg/L)[a]	16 (3.2,66)
Urea (mg/dL)[a]	86 (56,146)
Serum creatinine (mg/dL)[a]	
At admission	1 (0.7,1.6)
Maximum value	1.1 (0.7, 1.7)
Thrombocytopenia	42 (19.5)

Values in no. (%), [a]median (IQR) or [b]mean (SD). CA-AKI: community acquired-acute kidney injury; SBP and DBP: systolic and diastolic blood pressure; PICU: pediatric intensive care unit,

dration (*n*=85) and sepsis (*n*=61, 18 blood culture positive) were two most common causes of CA-AKI, followed by acute febrile illnesses (*n*=32) and primary renal diseases (*n*=32). Among febrile illnesses, dengue (*n*=13), pyelonephritis (*n*=5) and leptospirosis (*n*=4) were important causes of CA-AKI. Nephrotic syndrome (*n*=12) with features of hypovolemia and/or acute tubular necrosis was the most common primary renal disease associated with CA-AKI, followed by hemolytic uremic syndrome (*n*=9) and acute glomerulonephritis (*n*=10) **(Table II)**.

Out of 191 children discharged, 168 (88%) had complete renal recovery, 13 (7%) had partial renal recovery and 10 (5%) had no renal recovery. Nineteen (9%) children required dialysis (13 hemodialysis and 6 peritoneal dialysis). Median (IQR) duration of hospital stays in children with AKI stage I, II and III was 4 (3,6), 5.5 (3.7,9) and 6 (3,12.2) days, respectively. Twenty four (11%) children with CA-AKI died during hospitalization. Of 21 children who died of sepsis, 20 presented as septic shock and died even before dialysis could be started. Median SD scores of systolic and diastolic blood pressures were significantly lower in children who died in comparison to those who survived. Out of 22 children at 3 months follow-up, 10 progressed to CKD, with 3 of them becoming dialysis dependent.

On univariate analysis, sepsis, mechanical ventilation, inotropes requirement and stage III AKI were significantly associated with increased risk of mortality. On multivariate logistic regression analysis, inotropes requirement was the only independent risk factor for mortality (**Table III**).

Table II Etiological Diagnosis of Community-Acquired Acute Kidney Injury in Hospitalized Children (*N*=215)

Etiology	*No. (%)*
Diarrhea with dehydration	85 (39.5)
Sepsis	61 (28.3)
Acute febrile illnesses[a]	32 (14.9)
Dengue	13 (6.0)
Pyelonephritis	5 (2.3)
Leptospirosis	4 (1.9)
Typhoid	3 (1.4)
Primary renal diseases (*n*=32)	
Nephrotic syndrome	12 (5.6)
Hemolytic uremic syndrome	9 (4.2)
Post-infectious GN	4 (1.9)
Rapidly progressing GN[b]	6 (2.7)
Renal stones	1 (0.5)
Diabetic ketoacidosis	3 (1.4)
Dextromethorphan toxicity	1 (0.5)
MIS-C	1 (0.5)

GN: glomerulonephritis; MIS-C: multisystem inflammatory syndrome in children. [a]2 each with liver abscess, malaria and diphtheria, and 1 child with tubercular meningitis; [b]2 with lupus nephritis, and 1 each with C3 GN, anti-GBM crescentic GN, granulomatous interstitial nephritis, IgA crescentic GN.

Table III Risk Factors for Death in Children With Community-Acquired Acute Kidney Injury (*N*=215)

Variables	*OR (95% CI)*	*P value*
Requirement of inotropes	363 (26-5084)	<0.001
Sepsis	2.4 (0.4-14)	0.30
Stage III acute kidney injury	4.3 (0.16-118)	0.38
Mechanical ventilation	0.1 (0.01-1.1)	0.06

DISCUSSION

In this prospective study frequency of CA-AKI in hospitalized children was 7.7% (95% CI 6.7-8.6), with majority being in AKI stage III. Diarrheal diseases with dehydration and sepsis were predominant causes of CA-AKI. More than three fourth of cases had complete renal recovery at discharge, whereas 11% died during hospitalization. Requirement of inotropes was the only independent risk factor for mortality. Nearly half of those with incomplete renal recovery at discharge progressed to CKD at 3 months follow-up.

Frequency of CA-AKI in our study was similar to earlier studies across the globe, with incidence of CA-AKI varying between 7 to 14% [4,5,8,9]. In a meta-analysis to estimate the worldwide incidence of AKI, pooled incidence rate of CA-AKI was 8.3% [10]. Three fourth of the children in our study achieved maximum AKI stage III, similar to study by Esezobar, et al. [11], where 70% children were in 'failure' category. Majority of cases in AKI stage III in our study can be explained by predominantly infant population, which are more susceptible to infection-related AKI.

One fourth of all AKI cases in our study resulted from sepsis, similar to study from a sub-Saharan African country, where sepsis accounted for 25.7% of all AKI cases [11]. Etiological spectrum of AKI in our study was similar to other Indian studies [12,13], with infections accounting for more than half of all cases, followed by primary renal diseases.

Despite majority of our AKI cases in stage III, only 9% received dialysis, in contrast to 14.5% children requiring dialysis in a study from southern India [12]. Fewer children receiving dialysis in our study can be explained by many presenting as septic shock and succumbing within 24 hours of hospitalization even before dialysis could have been started. Mortality rate of 11% in our study was similar to pooled AKI-associated mortality rate of 13.8% in children [10]. A higher in-hospital mortality in two other Indian studies [12,13] and studies from sub-Saharan African countries [4,5] in comparison to our study can be explained by inclusion of hospital-acquired AKI cases also in their studies.

WHAT THIS STUDY ADDS?

- Majority of community-acquired acute kidney injury in hospitalized children resulted from diarrheal diseases and sepsis.

In consonance with two Indian studies [12,13], more than two-third of children in our study achieved complete renal recovery at discharge. Out of those with incomplete renal recovery, nearly half progressed to CKD at 3 months follow-up. Though, risk factors for progression to CKD were not analyzed, approximately two-thirds of surviving children who had received dialysis progressed to CKD at 3 months. In contrast to 22-35% of all AKI cases progressing to CKD at 3 months [14,15], only 5% of surviving children in our study progressed to CKD, which can be explained by majority of AKI cases due to diarrhea and fewer children requiring dialysis.

Strength of this study is prospective enrollment of cases throughout the year to include all probable CA-AKI cases with seasonal variation along with 3 months follow-up after discharge. However, the study had some limitations viz., being a single center study, results are not generalizable; urine output criterion was not used for defining AKI*;* CA-AKI in CKD cases were not assessed because of prior exclusion of known CKD cases; study not powered to assess the predictors of mortality and follow-up for children with incomplete renal recovery only, based on deranged serum creatinine at discharge, which could have missed some children showing normal creatinine but persistent proteinuria or hypertension.

To conclude, CA-AKI is common in hospitalized children, with majority resulting from diarrheal diseases and sepsis. Long-term follow-up is required in cases with incomplete renal recovery, especially those requiring dialysis because of high risk of progression to CKD.

Ethics clearance: Institutional Ethics Committee, CNBC; No F.1/IEC/CNBC/11/07/2020/78/9671, dated Sep 29, 2020.
Contributors: MK: conceptualized the study. AA: enrolled the patients, collected data, involved in patient management and prepared the initial draft; MK, KM: performed the analysis and interpretation of data. MK, AA and KM revised the draft. All the authors approved the final version of the manuscript.
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RESEARCH PAPER

Gonadotropin-Dependent Precocious Puberty: Single-Center Experience From Western India

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Objective: To describe the characteristics of gonadotropin-dependent precocious puberty (GDPP) in Indian children. **Methods**: Clinical profiles of GDPP (*n*=78, 61 females) and premature thelarche (*n*=12) from a single center in Western India were retrospectively studied. **Results**: Pubertal onset was earlier in boys than girls (29 vs 75 months, respectively; *P*=0.008). The basal luteinizing hormone (LH) was ≥0.3 mIU/mL, except 18% of GDPP girls. At 60 minutes after GnRHa-stimulation, all patients (except one girl) had LH ≥5 mIU/mL. The GnRHa-stimulated LH/FSH ratio was ≥0.34 at 60 minutes in girls with GDPP unlike premature thelarche. Only one girl had an allergic reaction to long-acting GnRH agonist. Among GnRH agonist-treated girls (*n*=24), the predicted final adult height was -1.67±1.5 SDS, whereas the attained final height was -0.25±1.48 SDS. **Conclusion**: We establish the safety and efficacy of long acting GnRH agonist therapy in Indian children with GDPP. The 60-minute stimulated serum LH/FSH of ≥0.34 differentiated GDPP from premature thelarche.

Keywords: *GnRHa stimulation test, Management, Premature thelarche, Pubarche*.

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Precocious puberty is defined as the onset of secondary sexual characteristics before 8 years in girls and 9 in boys [1]. It is classified as gonadotropin-dependent (GDPP) or independent (GIPP). Most cases (>90%) of GDPP in girls are idiopathic, whereas 40-90% of boys have an identifiable central nervous sys-tem (CNS) pathology [1]. GDPP should be differentiated from premature thelarche, a normal pubertal variant. Basal serum luteinizing hormone (LH) ≥0.3 mIU/mL is indicative of pubertal onset but may not be diagnostic of GDPP and hence, necessitates the gonadotropin-releasing hormone analog (GnRHa)-stimulation test [2,3]. Magnetic resonance imaging (MRI) of the brain helps to rule out organic causes of GDPP. The goal of treatment in GDPP is to halt pubertal advancement, mitigate adverse psychosocial issues and improve final adult height (FAH). Long-acting GnRH agonists have been the gold standard of treatment in GDPP over the last few decades [1].

Only a few studies on GDPP reported from India describe this condition. However, most of these include both GDPP and GIPP [4-6]. The data on FAH outcome with GnRH agonists and the utility of the GnRHa-stimulation test to differentiate GDPP and premature thelarche are lacking in Indian cohorts. Hence, we aimed to retrospectively evaluate the clinical, biochemical, radiological, treatment, and outcome profiles of GDPP patients from a single center in Western India.

METHODS

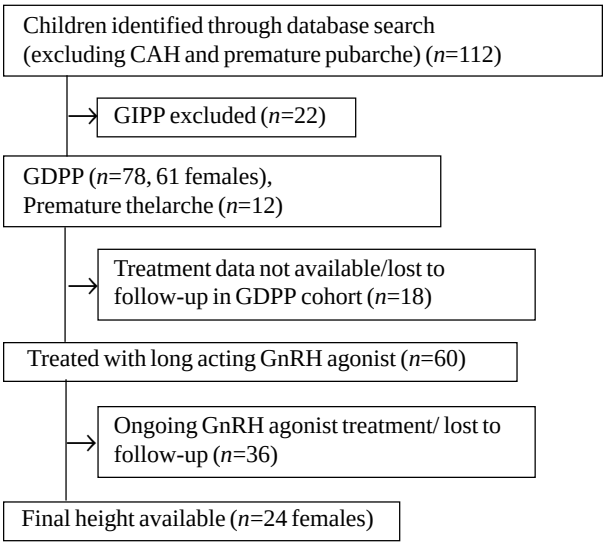
A retrospective case-record review of children with precocious puberty managed at a tertiary care center from January, 2000 to February, 2021 was done after clearance from Institutional Ethics Committee.

Clinical details and anthropometry were noted for all cases. Bone age was determined by the Tanner-Whitehouse-3 method. Predicted adult height was calculated by using Bayley and Pinneau tables [7]. Hormones [LH, follicle-stimulating hormone (FSH), testosterone (boys), and estradiol (girls)] were measured by chemiluminescence immunoassay (ADVIA Centaur XP, Siemens). Intra- and inter-assay coefficients of variation were <10% for all assays. GnRHa stimulation test was performed if basal LH was <0.3 mIU/mL. Serum LH and FSH were estimated at baseline and 30, 60, 90, 120, and 180 min after 20 µg/kg subcutaneous aqueous leuprolide. Peak-stimulated serum LH ≥5 mIU/mL with an LH/FSH ratio >0.6 was used to define GDPP [3,8]. Patients with an initial diagnosis of premature thelarche were followed up, and if pubertal

progression was noted with suggestive biochemistry, the diagnosis was revised to GDPP.

Magnetic resonance imaging (MRI) of the brain was performed in all patients with GDPP, and an ultrasonogram (USG) of the pelvis was performed in all GDPP girls. Most GDPP patients were treated with a standard dose of 11.25 or 22.5 mg depot leuprolide acetate intramuscularly every three months (140-300 µg/kg/month). Few patients were treated with triptorelin: 3.75 mg monthly or 11.25 mg every three months intramuscularly. Clinical parameters moni-tored at 3-6 months intervals included growth velocity and Tanner staging. Bone age was determined yearly. Basal serum LH <0.3 mIU/mL and/or 3 hours postleuprolide depot serum LH of <3.3 mIU/mL suggested adequate treatment response. Treatment was stopped at a bone age of ~12 years in girls and ~13 years in boys unless indicated to continue for psychosocial reasons till 10.5 and 11.5 years of chronological age in girls and boys, respectively.

Statistical analysis: Statistical analyses were performed using IBM SPSS software version 26.0 (SPSS Inc.) software. Categorical data were expressed as absolute numbers and percentages, and continuous data were expressed as mean (SD) or median and ranges as appropriate. Chi-square and Fisher exact tests were used to compare categorical variables, *t* test and Mann-Whitney *U* tests were used to compare continuous variables, as appropriate. A two-sided *P*-value <0.05 was considered statistically significant.



CAH: congenital adrenal hyperplasia; GDPP: gonadotropin-dependent precocious puberty; GIPP: gonadotropin-independent preco-cious puberty.

Fig. 1 Flow chart for case-record review of precocious puberty.

RESULTS

Fig. 1 summarizes the selection of patients for the study. The baseline characteristics of GDPP patients (*n*=78, 61 females) are summarized in **Table I**. Pubertal onset and presentation age were earlier in boys. The typical presentation was genitalia growth (76.5%) in boys and thelarche (75.4%) in females, followed by height spurt (boys: 17.6%, girls: 11.4%), pubic hair development (boys: 5.8%, girls: 6.5%) and vaginal bleeding (6.5%). Median testicular volume was 8.0 cc (range:4-20). Pubarche was present in all boys, and absent in 31.6% of girls. In girls below 6 years, 18/28 (64.3%) had pubarche. In females, the breast stage was 2, 3, 4, and 5 in 21.3%, 34.4%, 29.5%, and 14.8%, respectively, and the vaginal mucosa was dull pink in 82.1%.

Basal serum LH of ≥0.3 mIU/mL was seen in all boys but <0.3 mIU/mL in 11 girls (age: 82-99 months). All girls with GDPP except one reached a stimulated serum LH of ≥5 mIU/mL at 60 minutes. The comparison of girls with GDPP and premature thelarche who had low basal LH and under-went GnRHa-stimulation test is shown in **Table II**. When compared with premature thelarche (*n*=8), girls with GDPP (*n*=11) were significantly older, had a com-parable GnRHa-stimulated (60-minute) serum LH but a higher LH/FSH ratio. Uterine length ≥3.2 cm, corpus-to-cervix ratio >1, and endometrial echo were found in 84.2%, 80%, and 68.1% of GDPP (*n*=38) and 37.5%, 50%, and 41.6% premature thelarche (*n*=11), respectively. Median (range) ovarian

Table I Baseline Characteristics of Patients with Gonadotropin Dependent Precocious Puberty

	Boys (n=17)	*Girls (n=61)*
Age of onset of symptoms (mo)[c]	29 (0,102)	75 (0,102)
Age at presentation (mo)[c]	58 (7,114)	82 (11,123)
Height at presentation (SDS)	1.02 (-1.52,4.97)	0.75 (-1.9,3.6)
Target height (SDS)	-0.77 (-2.12, 0.09)	-0.82 (-2.6, 1.07)
Pubarche <6 y of age[a,c]	13 (100)	18 (64.3)
Pubarche >6 y of age[a]	4 (100)	24 (72.7)
BA/CA ratio at presentation	1.88 (0.87, 3.14)	1.40 (1.02, 4.61)
Basal serum LH (mIU/mL)	2.67 (0.52, 10.0)	2.2 (0, 15.8)
Basal serum FSH (mIU/mL)[b,c]	2.48 (0.42, 5.7)	5.24 (1.03, 9.8)
Basal serum LH ≥0.3 mIU/mL[a,c]	17 (100)	50 (81.9)
MRI brain abnormality[a,d]	12 (80)	12 (23.5)

Data are expressed as median (range) or [a]no. (%). BA: bone age; CA: chronological age; FSH: follicle stimulating hormone; LH: luteinizing hormone; MRI: magnetic resonance imaging; [b]n=13 in boys, n=57 in girls; [c]P<0.05; [d]P<0.001.

Table II Baseline Characteristics of Girls

	GDPP girls (n=11)	*Premature thelarche (n=8)*	*P value*
Age of onset of symptoms (mo)	83 (10,91)	14.5 (0,64.5)	0.001
Age at presentation (mo)	90 (14,99)	20.5 (15,65)	0.002
Height at presentation (SDS)	0.61 (-0.58,1.42)	-0.55 (-1.66,1.20)	0.091
Target height (SDS)	-0.67 (-2.6,0.99)	-0.385 (-3.26,0.43)	0.762
Basal serum LH (mIU/mL)	0.13 (0.05,0.29)	0.10 (0,0.25)	0.600
Basal serum FSH (mIU/mL)	3.06 (0.24,6.51)	2.8 (0.41,4.62)	0.002
GnRHa stimulated 60 min serum LH (mIU/mL)	9.64 (3.97,16.8)	7.16 (3.51,9.69)	0.129
GnRHa stimulated 60 min serum FSH (mIU/mL)	15.66 (5.7,28.3)	29.97 (13,40.75)	0.005
GnRHa stimulated 60 min serum LH/FSH	0.66 (0.34,1.62)	0.21 (0.13,0.30)	<0.001

Data expressed as median (range). Patients included with GDPP and premature thelarche with basal serum luteinizing hormone <0.3 mIU/mL who underwent gonadotropin-releasing hormone stimulation test. FSH: follicle stimulating hormone; GDPP: gonadotropin-dependent precocious puberty; GnRHa:gonadotropin-releasing hormone analogue; LH: luteinizing hormone.

volume was 2.3 (0.35-6.6) cc in GDPP and 1 (0.1-2) cc in girls with premature thelarche.

MRI brain abnormality was seen in 12/15 (80%) boys and 12/51 (23.5%) girls; 9/12 (75%) of those were newly diagnosed lesions in both groups. Hypothalamic hamartoma was the most common abnormality (*n*=7 each in boys and girls), followed by optic glioma (*n*=3), sellar suprasellar pilocytic astrocytoma (*n*=2), hypothalamic glioma, pineal cyst, Rathke cleft cyst, aqueduct stenosis with congenital hydrocephalus and healed tuberculoma (*n*=1 each). Of the three patients (2 boys) with optic glioma, both boys had a prior history of neurofibromatosis type 1. The proportion of girls with MRI brain abnormality with pubertal-onset before 6 years was significantly higher (34.6 vs 12.0%; *P*=0.038) than in those with later onset.

Fifty-five patients were treated with GnRH agonists [monthly 3.75 (*n*=2) or 7.5 mg (*n*=1), three monthly 11.25 mg (*n*=27) or 22.5 mg (*n*=25)] whereas five patients were treated with triptorelin. None had drug-related side effects, except one girl who had an allergic reaction to leuprolide and was switched to triptorelin. Except for a boy with hypothalamic hamartoma, none showed clinical pubertal progression on therapy. All tested children had adequate treatment response. The median (range) duration of treatment in those with final adult height available was 57.5 (33-120) months. The median (range) bone age to chronological-age ratio at two years, five years, and the end of treatment was 1.22 (1.18-1.27), 1.09 (0.93-1.27), and 1.1 (1-1.25), respectively. Among GnRH agonist treated girls (*n*=24), the predicted adult height was -1.67±1.5 SDS, whereas the attained final adult height was -0.25±1.48 SDS.

Four out of eight girls with premature thelarche who underwent the GnRHa-stimulation test had predicted adult height of -0.69 (-3.26 to 0) SDS, and attained final adult height of 0 (-0.88 to 0.36) SDS.

DISCUSSION

In this single centre study from a tertiary care center in western India, the pubertal onset and presentation age in GDPP were earlier in boys than girls. The stimulated serum LH/FSH ratio at 60 minutes was ≥0.34 in all girls with GDPP vs none in premature thelarche. Boys and younger girls (<6 years) more frequently had an organic etiology, hypothalamic hamartoma being the most common. Long acting GnRH agonist therapy was safe and beneficial in halting pubertal progression and improving final adult heights in children with GDPP.

Most boys presented before six years of age, unlike girls, with a higher frequency of organic etiology. Organic etiology was frequent in boys and girls with pubertal onset <6 years but not in those with later pubertal onset. Hence, routine CNS imaging may be optional in girls with pubertal onset >6 years [9]. As observed in our cohort, pubarche is reported in most boys with GDPP [10]. In contrast to the conventional belief, almost two-thirds of girls before 6 years had pubarche, probably due to ovarian androgen production despite low DHEAS [11].

The biochemical diagnosis of GDPP was based on basal LH of ≥0.3 mIU/mL in all boys and most of the girls. A basal LH >1.0 mIU/mL was considered as confirmatory of GDPP, whereas levels between 0.1-1.0 mIU/mL prompted a GnRHa-stimulation test [2]. Most of the patients in this study with basal LH between 0.3-1.0 mIU/mL had ≥2 definitive evidence of GDPP (height velocity >7 cm in the preceding year, bone age SDS >2, breast stage ≥4, uterine length ≥3.2 cm) at presentation.

The 60-minute serum LH/FSH ratio accurately discrimi-nated premature thelarche from GDPP in girls. Hence, a single sampling at 60 minutes after GnRHa stimulation may provide comparable diagnostic accuracy to

multiple conventional samplings. A recent large (*n*=1492) study also supported the diagnostic accuracy of GnRHa-stimulated LH and LH/FSH ratio at 60 minutes [8]. A GnRHa-stimulated serum LH of ≥5 mIU/mL criterion to diagnose GDPP is not applicable in early childhood. Peak serum LH may be >10 mIU/mL in ~16% girls with premature thelarche [12,13]. A discriminatory characteristic of premature thelarche in this study was a robust FSH response and 60-min LH/FSH ratio <0.34. Such observations have been reported previously [12,14,15]. Hence, serum LH levels should always be interpreted in relation to FSH response in early childhood. Uterine length of ≥3.2 cm predicted precocious puberty, which is as reported in a recent meta-analysis [16].

The rarity of allergic reactions in our study reiterates the safety of long acting GnRH agonist in GDPP [17]. Most patients had regression/stabilization of puberty despite the majority receiving three-monthly preparations, similar to the literature [18]. In patients whose final adult height was available, GnRH agonist therapy significantly improved the height outcome. However, data were inadequate to analyze the final height outcomes in boys, and girls with pubertal onset between 6 and 8 years of age. The etiological profile might have been affected by referral bias.

To conclude, this study reports the clinical and treatment outcomes of Indian children with GDPP. This study also establishes the safety and efficacy of long acting GnRH agonist therapy in improving final adult height in Indian with GDPP girls.

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RESEARCH PAPER

Cardiorespiratory Adverse Events after First Vaccination in Preterm Neonates With Gestational Age ≤30 Weeks

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Objectives: To document the adverse cardiorespiratory events following first routine immunization in preterm neonates. **Methods**: We retrieved records of neonates with gestational age ≤30 weeks, and included those who developed cardiorespiratory events after first vaccines before discharge. Our Unit's protocol is to administer Bacillus Calmette-Guerin (BCG), hepatitis B vaccine to those discharged at <8 weeks postnatal age. Hexavalent, BCG, pneumococcal vaccine and rotavirus vaccines are given at 8 weeks of age, if hospital stay is predicted to be longer. Unit compliance to vaccination administration at appropriate ages were also measured. **Results**: Data of 161 neonates ≤30 weeks (17.4% <27 week) who completed care in the unit was studied. Cardio-respiratory adverse events were reported in 21(13.7%). None of these required initiation of invasive ventilation. High flow nasal cannula therapy and caffeine restart were required for these events in 14 (9.3%) and 6 (3.9%) neonates, respectively. Lower gestational age, bronchopulmonary dysplasia and sepsis were significant risk factors on univariate analysis. On multivariate analysis, continued need for respiratory support at 4 weeks of age (*P*=aOR 14.5 (95% CI 5-59.1) was the only independent risk factor for post-vaccination cardiorespiratory adverse events. Of 38 who were not vaccinated at recommended ages by unit policy, 25 were missed opportunities, the rest were deemed unstable for vaccinations at that age by the clinical team. **Conclusion**: Adverse cardiorespiratory events were uncommon after first vaccinations in very preterm neonates. Administering vaccines in this group before discharge would allow monitoring for these events, especially for those who require long-term respiratory support.

Keywords: *AEFI, BCG vaccine, Missed opportunity for vaccination, Ventilation*.

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Vaccination is an effective intervention to reduce the morbidity and mortality due to vaccine preventable diseases (VPD). Available data supports the fact that vaccines are immunogenic and tolerated by preterm infants [1,2]. Preterm infants are susceptible to postnatal acquisition of VPD, they should ideally undergo immunization without correction of gestational age. The World Health Organization [3] and Advisory Committee on Vaccines and Immunization Practices of the Indian Academy of Pediatrics [4] recommend that all infants receive immunization regardless of any restriction based on gestational age or birth weight, with the qualified exception of hepatitis B vaccine, as the birth dose is not counted toward the full schedule due to reduced immune response. There is lack of literature about vaccination policies and actual practices from centers which care for very preterm neonates [5]. Measuring clinically significant adverse events would be the first step to design recommendations on optimal timing of the vaccines.

Our unit has a written policy towards planning vaccinations in very preterm infants in the NICU itself according to their chronological age. These infants can then be monitored for adverse events, if any. This study was planned to analyze the factors associated with cardiorespiratory adverse events following first vaccination in very preterm neonates.

METHODS

This review of hospital records was conducted in a 33-bedded Level IIIB (national Neonatology Forum India) neonatology department in Kerala. The unit has in place written policies for respiratory support of preterm neonates, caffeine therapy for apnea of prematurity, and discharge criteria [6]. Those ≤30 weeks of gestation who completed care in the unit between June, 2018 and June, 2022 were included. Relevant details were retrieved from electronic medical records (EMR).

We studied as primary outcome, proportion of very preterm neonates, who developed predefined cardiorespiratory events (CRE) after first vaccination before discharge. Our unit protocol is to administer BCG, Hepatitis B to those discharged before eight weeks

postnatal age. Since, discharge is generally not expected till beyond two weeks of life in these preterm babies, we do not administer birth dose OPV to ≤30 weeks infants [7]. Hexavalent vaccine (DTaP+IPV+Hib+Hepatitis B), BCG vaccine, pneumococcal, and rotavirus vaccine are given (staggered over 2 days) at 8 weeks postnatal age, if hospital stay is expected/predicted longer than that. Post-vaccination, these infants are monitored in the neonatal intensive care unit (NICU) with pulse oximetry for at least 48 hours. If there are ongoing supports or if CRE are noted, then multi-parameter monitoring with (ECG) and (NIBP) are also done. If the infant had been roomed-in before the eligible postnatal age for vaccinations, they were shifted back to NICU for that period of observation post-vaccination. Unit compliance to vaccine administration at appropriate ages, reasons for non-compliance, and risk factors for CRE were also measured. CRE was defined as apnea with drop in saturation below 80% and any one of: *i*) heart rate <100/min, *ii*) poor respiratory effort requiring positive pressure ventilation, *iii*) need to start/increase respiratory support for more than one hour by high flow nasal cannula/continuous positive pressure ventilation/mechanical ventilation, and *iv*) restart or increase dose of caffeine therapy due to recurrent apnea.

Presuming the incidence of adverse events following vaccination in preterm as 13% based on a previous study [8], we planned a sample size of 174, to achieve a precision of 5% and confidence level of 95%.

Statistical analysis: We used STATA ver 16.0 for analysis. Outcomes were expressed as proportions. Univariate analysis of risk factor association with CRE was done using Fisher-exact test, and logistic regression was used for multivariate analysis. Institute ethics committee clearance was obtained for retrieving de-identified data from the electronic medical records.

Table I Baseline Characteristics of Study Participants (*N*=161)

Characteristic	*Value*
Gestational age	
29-30 wk	76 (47.2)
27-29 wk	57 (35.4)
24-26 wk	28 (17.4)
Birthweight (g)[a]	1045 (875,1250)
Respiratory support	157 (97.5)
Duration of respiratory support (d)[a]	8 (4,29)
Need for support at 4 wk age	41(25.5)
Bronchopulmonary dysplasia	14 (8.7)
Culture positive sepsis	27 (16.7)
Periventricular leukomalacia (≥grade 2)	4 (2.5)
Anemia requiring transfusion	46 (28.6)

Values in no. (%) or median (IQR).

RESULTS

Data of 161 neonates with gestational age ≤30 weeks (17.4% <27 weeks) who completed care in the unit were included. The median (IQR) gestational age at birth was 28 (27-29) weeks. Most infants (97.5%) required some form of respiratory support during their NICU care; the median (IQR) duration of invasive ventilation was only 1(0,3) days (**Table I**). Important observations relevant to vaccine administration are represented in **Table II**. First vaccines were given at median postnatal age of 51(42,61) days; at postmenstrual age of 35 (35,36) weeks.

Predefined and clinically relevant cardiorespiratory adverse outcomes (CRE) were noted in 21(13.7%) of all those included. Of these, 20 infants had bradycardia, which qualified as pre-defined CRE. However, none of the CRE required re-institution of mechanical ventilation or CPAP (**Table II**). Similarly, there were no episodes of hypotension, or need for commencement of parenteral fluids after vaccination. In 11 (52.3% of those who had CRE) infants, the events were noted within 12 hours of vaccination; 10 (47.6%) occurred between 12-24 hours post-procedure; only 1 (4.7%) infant had the CRE after 24 hours. None happened during the process of injections per se. Although lower gestational age, BPD and sepsis were also significant risk factors on univariate analysis; on multivariate analysis, continued need for respiratory support at 4 weeks of age was an independent and significant risk factor for CRE post-vaccination, aOR 14.5(95% CI 5-59.1) (**Table III**). It would be prudent to monitor these high risk infants for at least 48 hours in an equipped environment for CRE after vaccines.

Table II Details of Vaccines Received by Preterm (≤30 Weeks) Neonates (*N*=61)

Detail	*Value*
Received hexavalent vaccine, PCV, Rotavirus vaccines along with BCG as first doses before discharge	99 (64.3)
Postnatal age of vaccination (d)[a]	51 (42,61)
Postmenstrual age of vaccination (wk)[a]	35 (35,36)
Cardiorespiratory adverse events (CRE) related requirements	
Mechanical ventilation or CPAP required	0
High flow nasal cannula	14 (9.3)
Caffeine restart	6 (3.9)
Combinations of more than one therapy	5 (3.5)

Values in no. (%) or [a]median (IQR). BCG: Bacille Calmette-Guerin; CPAP: continuous positive airway pressure; PCV: pneumococcal vaccine.

Table III Factors Associated With Cardiorespiratory Events Post-vaccination in Preterm (≤30 Week) Neonates (*N*=161)

Risk factor	*CRE, n=21*	*OR (95% CI)*
Gestational age <27 wk[a]	10 (35.7)	6.2 (2-18.4)
Respiratory support at 4 wk[a]	18 (44)	30.5 (7.8-169.3)
Culture positive sepsis[a]	9 (33)	5.1 (1.6-15.2)
BPD (36 wk PMA)[a]	7 (50)	9.5 (2.4-36.3)
Invasive ventilation	17 (5.5)	2.1 (0.64-9.2)

Values in no (%). CRE:cardiorespiratory events; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age. [a]P<0.001.

The unit was compliant to appropriate age for vaccinations according to the policy in 123 (76.4%) infants. Of 38 infants where the vaccinations were delayed, 25 were clearly missed opportunities. We realized that there is scope for quality improvement in this regard. A conscious decision by the clinical team to delay the vaccines based on ongoing respiratory instability was made in the remaining 13 infants.

DISCUSSION

The proportion of very preterm infants who developed CRE within 48 hours of first vaccinations before discharge was 13.7% in our study. Vaccination was done at the appropriate age as per unit policy in only 76.4% infants.

Many reports suggest adequate seroprotection after vaccines in preterm neonates [1,2,4]. Many Indian authors have expressed concern about delay in vaccination of preterm infants, mainly due to safety concerns either by healthcare professionals or parents [5,9]. Fear of adverse events in those with ongoing respiratory instability at appropriate age of vaccination seems to be evident.

In an observational study of 78 preterm infants [10], transient cardiorespiratory events (apnea, bradycardia, desaturations) were noted in 47% of infants. Schulze, et al. [8] studied preterm neonates with mean gestational age of 28 weeks. Apnea and bradycardia following immunization with hexavalent/pentavalent vaccine was found to be 13%. Older studies with small number of patients have reported adverse events in nearly one-third of preterm infants, especially when vaccinated before 70 postnatal days [11]. In our cohort, all those who had CRE had received hexavalent vaccine. Faldella, et al. [12] reported the safety of hexavalent vaccines in very preterm, concluding that these infants can be given the vaccines at 8 weeks of age with monitoring. They also reported no adverse effects on cardiac electrical activity or cerebral blood flow variations associated with first vaccination [12].

Risk of adverse events following immunization in preterm infants are better predicted by underlying cardiorespiratory instability at the time of vaccination than by gestational age or birth weight [5]. Faldella, et al. [12] noted apnea/bradycardia/desaturations in those who had chronic underlying illnesses. We too noted that continued need for respiratory support up to and beyond 4 weeks of age as a significant and independent risk factor for cardiorespiratory events. Pre-existing cardiorespiratory symptoms, those who had similar clinical manifestations in the 24 hours prior to vaccination, or those with the most severe illnesses at birth are at higher risk of adverse events post procedure [10]. Authors of a recent multicentric retrospective study reported that sepsis evaluations, need for intubations and respiratory support were higher in the 3-day post vaccination period in extreme preterm infants who received either single dose or combination vaccines [13].

Our study is limited by the retrospective study design. We had data on only 28 (17.4%) infants below 27 weeks. More research is required to make recommendations in this group, who often require longer duration of respiratory supports and have potentially higher risk of post-vaccination adverse events. Since our unit protocol includes only combination (hexavalent) vaccines at 8 weeks, there was no comparison possible between different types of vaccines. Hence, no definite conclusions on safety of hexavalent vaccines can be drawn from our findings.

Clinically relevant cardiorespiratory adverse events within 48 hours of first vaccinations given before discharge were noted in 13.7% of preterm neonates of less than 30 weeks gestation. Need for respiratory support till 4 weeks of postnatal age was a significant and independent risk factor for CRE. This data supports the recommendations that vaccinations need not be delayed for very preterm infants. Administering first vaccines based on chronological age before discharge would allow appropriate monitoring, especially in those who required long-term respiratory support.

Ethics approval: EIC, KIMS; No. KIMS/IHEC/TP030/2022 dated September, 2022.
Contributors: NJ conceived the study; HS, FP, NJ designed the study; HS collected data; FP and NJ conducted data analysis. FP drafted the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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WHAT THIS STUDY ADDS?

- Cardiorespiratory events are not common after first vaccinations in very preterm neonates, if done at recommended chronological ages.
- Neonates requiring long-term respiratory care need to be monitored post-vaccination.

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RESEARCH PAPER

Hemodynamic Responses to Recorded Maternal Voice Among Sedated Children in the Pediatric Intensive Care Unit: An Open-Label Randomized Controlled Trial

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Objective: To assess the effect of maternal audiotaped voice on clinical parameters of sedated children. **Methods:** A randomized controlled trial was conducted on 25 sedated critically ill children admitted to the pediatric intensive care unit. An audiotaped maternal voice was played to the children in the experimental group (*n*=13) via a headphone for 15 minutes, twice a day for 3 days. Children in the control group (*n*=12) received routine care without any additional auditory stimulation. Clinical and hemodynamic variables were recorded at 5 minutes interval three times. **Results:** Significant changes were observed in the mean (SD) heart rate (per minute) at 10 minutes [129.83 (19.14) vs 124.29 (14.90), *P*=0.051], respiratory rate at 5 minutes [44.38 (17.79) vs 34.65 (7.64), *P*=<0.001] and 10 minutes [42.79 (13.89) vs 35.44 (7.65) *P*=<0.001], systolic blood pressure at 5 minutes [95.24 (15.01) vs 101.02 (19.83) *P*=0.045], and mean blood pressure at 15 minutes [68.66 (13.61) vs 73.61 (17.59) *P*=0.051] mmHg between the experimental and the control group, respectively. **Conclusion:** Listening to recorded maternal voice had a positive effect on clinical parameters of sedated critically ill children.

Keywords: *Anxiety, Blood pressure, Comfort scale, Pain.*

Trial Registration: Clinical Trial Registry of India: CTRI/202/08/02378

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A critical illness subjects a child to extreme stress arising from highly invasive procedures, separation from family members, limited parental interaction, and varying intensity of light and noise levels in the pediatric intensive care unit (PICU) [1-3]. Many PICUs in India allow only brief visits by the parents and restrict visits by other family members for concerns of potential spread of infection, breach of confidentiality and privacy, undue emotional stress to the parents, and lack of space [2,3]. These restrictive policies undermine the importance of parental presence at the bedside, family-centered care and parental involvement in decision-making.

Maternal voice activates the prefrontal cortex of the child, affecting behavioral and neurological responses [4]. The effect of recorded maternal voice on anxiety and pain relief during procedures is well documented [5-7]. Recorded maternal voice has also been reported to decrease the emergence delirium in children recovering from anesthesia [8,9], but its effect on the clinical parameters of a sedated child has not been explored. This study aimed to assess the effect of audiotaped maternal voice on the clinical parameters of children admitted to the PICU. The secondary objectives were to assess its association on the duration of mechanical ventilation and length of PICU stay.

METHODS

This open-labelled randomized controlled trial was conducted at an 8-bedded PICU of a tertiary care center in northern India between September, 2020 and January, 2021. Ethical approval was obtained from the institutional ethics committee, and written informed consent was taken from the mothers.

Children from one month to 10 years of age, having a sedation score of 17-26 as per Comfort Sedation Scale (CSC) were included in the study [10]. Critically ill children with a history of hearing problems or ear discharge, children with developmental delay or neurological diseases, increased intracranial pressure, uncontrolled seizures or mental disorders, extremely sick children, children with shock, or an anticipated stay of less than 24 hours in PICU were excluded. Computer generated random number sequence was used for randomization.

Allocation concealment was ensured by the use of the sequentially numbered opaque sealed envelope (SNOSE) technique. It was done by a person not involved in the conduct of the study.

All mothers in the experimental group (EG) were assisted in the preparation and the recording of the individual script of 5-10 minutes considering the age of the child, language known to the child, and previous significant memorable events in the life of the child. After establishing rapport, she was made to listen to a sample of recorded voice of another mother. The time for the audio recording was fixed as per her convenience and done in a quiet area. The recording was checked for clarity before storing it for the use in researcher's mobile phone (Honor 7X model). The audio-recorded voice was played using a mobile phone with a wireless headphone having a wireless frequency of 2403 MHz -2480 MHz at 60 to 70 decibels. It was sweat proof and background noise-proof and had a sensitivity of 115 DB. It was played twice daily for 15 minutes in the morning (7 to 8 AM) and evening (5 to 6 PM) consecutively for 3 days.

The children in the control group (CG) did not receive any recorded auditory stimuli. Clinical parameters of including heart rate (HR), respiratory rate (RR), pulse oximetry (SpO_2) and blood pressure were recorded at baseline, intervention, at 5, 10, and 15 minutes after the intervention. After each intervention, the headphone was disinfected using a 70% alcohol swab and kept ready for the next use. Six observations were made per participant (twice a day for 3 days).

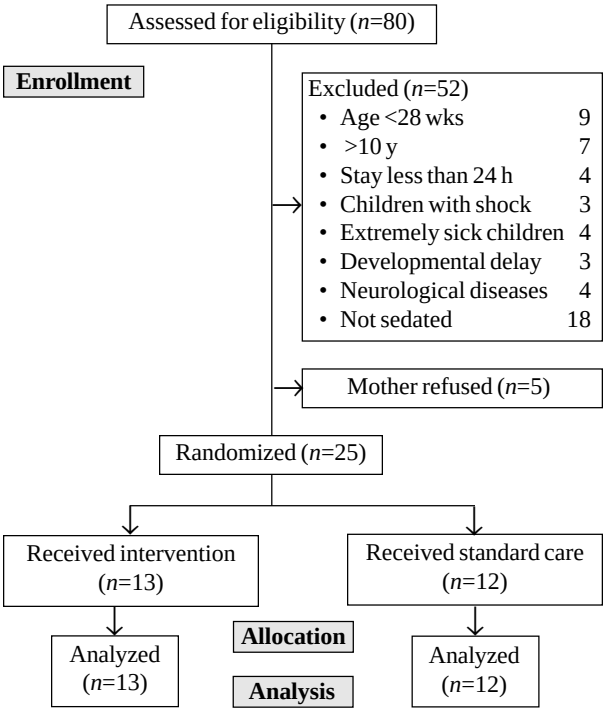

Fig. 1 Flow diagram for the study.

The tools used for data collection included the screening sheet to identify eligible children based on inclusion/exclusion criteria, demographic and clinical information sheet, pediatric Glasgow coma scale (GCS) and comfort sedation scale [10]. Patients with a comfort scale scores between 8-17 are considered over-sedated, a score between 17-26 adequately sedated, and scores between 27-40 under-sedated. The inter-rater reliability of the comfort scale ranges from 0.63-0.93 (kappa) [11].

To estimate a clinically relevant difference in the heart rate of 5 beats per minute, a pooled standard deviation of 10.2 based on previous study [5], with 80% power and 95% confidence was used to calculate a sample size of 66 in each group.

Statistical analysis: Data were entered in a Microsoft Excel spreadsheet and then imported to STATA software version 13.1 (Stata Corp). Descriptive statistics were used for the baseline characteristics. Independent sample *t* test was used to compare the means of variables between groups. Paired *t*-test was used to compare the means of related groups. Analysis of variance (ANOVA) was used to com-pare means across more than two measurement points. Non-parametric data were analyzed using the chi-square test, Fisher exact test, and Wilcoxon sign rank test. The set level of significance was 0.05.

RESULTS

A total of 80 children were assessed for eligibility; of which, 25 children were enrolled and randomized to the experimental group (EG, *n*=13) and the control group (CG, *n*=12) (**Fig. 1**). **Table I** shows the baseline characteristics of the enrolled children. All children were mechanically ventilated and also had arterial and central lines in place. None of the admitted children had COVID-19 infection.

Table I Baseline Characteristics of Hospitalized Children

Variable	*Experimental group (n=13)*	*Control group (n=12)*
Age (mo)	11 (1-96)	48 (1-120)
Girls[a]	4 (30.8)	5 (41.7)
Attending school[a]	1 (7.69)	5 (41.67)
Immunized for age[a]	8 (61.5)	9 (75)
Orotracheal tube[a]	12 (92.3)	12 (100)
Tracheostomy[a]	1 (7.69)	0
Length (cm)	64 (51-93)	97 (65.2-123)
Weight (kg)	4 (3-14)	12 (5-20)

Data expressed as median (IQR) or [a]no. (%). P>0.05 for all values.

Table II Effect of Maternal Audiotaped Voice on Primary Outcomes in the Experimental and Control Groups

Variables	*Experimental (n =13)*	*Control (n=12)*	*P value*
Heart rate (per min)			
Baseline	119.25 (19.57)	123.08 (14.71)	0.18
At 5 min	128.46 (22.12)	124.23 (15.06)	0.17
At 10 min	129.83 (19.14)	124.29 (14.90)	0.05
At 15 min	121.88 (19.63)[b]	123 (14.56)	0.69
Respiratory rate (per min)			
Baseline	37.11 (18.18)	34.36 (7.39)	0.23
At 5 min	44.38 (17.79)	34.65 (7.64)	<0.001
At 10 min	42.79 (13.89)	35.44 (7.65)	<0.001
At 15 min	38.58 (12.81)[b]	35.73 (10.38)	0.13
Oxygen saturation (%)			
Baseline	91.84 (12.88)	94.91 (12.58)	0.14
At 5 min	92.23 (14.46)	95.63 (9.74)	0.09
At 10 min	94.56 (8.72)	95.66 (9.22)	0.45
At 15 min	95.41 (10.14)	92.23 (14.46)	0.12
Glasgow coma score			
Before	8.23 (0.80)	8.19 (0.79)	0.78
After	10.10 (7.75)[b]	7.75 (0.43)	<0.001
Comfort score			
Before	18.0 (0.70)	17.92 (0.49)	0.4
After	23.37 (1.09)[b]	18.25 (0.62)[b]	<0.001
Systolic blood pressure (mm Hg)			
Baseline	104.34 (16.67)	102.13 (19.72)	0.45
At 5 min	95.24 (15.01)[a]	101.02 (19.83)	0.04
At 10 min	103.79 (18.63)	102.87 (19.33)	0.76
At 17 min	101.86 (15.16)	101.86 (19.63)	0.5
Diastolic blood pressure (mm Hg)			
Baseline	59.25 (19.22)	61.38 (19.91)	0.50
At 5 min	65.16 (18.43)	60.83 (18.71)	0.15
At 10 min	64.37 (17.53)	60.70 (19.17)	0.22
At 15 min	57.73 (14.39)[b]	59.59 (19.01)	0.49
Mean blood pressure (mm Hg)			
Baseline	68.75 (14.01)	72.68 (17.77)	0.13
At 5 min	76.57 (15.22)	74.54 (18.35)	0.45
At 10 min	75.43 (14.79)	75.80 (17.91)	0.89
At 15 min	68.66 (73.61)	73.61 (17.59)	0.05

Data expressed as mean (SD). [a]P value <0.05 or [b]P<0.001 for within group comparison.

A total of 150 observations were recorded and compared in EG *(n*=78) and CG (*n*=72) (**Table II**). No significant differences were observed in the sedation dosages, median duration of mechanical ventilation (14 vs 13 days), and the median length of PICU stay (19 vs 11 days) between the two groups.

DISCUSSION

In this trial, significant changes were observed in the heart rate, respiratory rate, systolic and mean arterial blood pressure of critically sick hospitalized children who were exposed to maternal voice. Change in vital signs is the first physiological response elicited in hospitalized patients and has a prognostic value [12]. The mother's voice is considered as non-noxious stimuli and the physiological changes induced by exposure to these familiar auditory stimuli are likely to be beneficial for the child [13].

The physical set-up of the PICU often minimizes the interaction of the child with his parents, with very little free space at the bedside. Evidence suggests that infants give more attention to their own mothers' voices as compared to unfamiliar voices present in the environment [4]. Hearing is one of the last senses to be lost in an unconscious individual [14]. Allowing frequent visits of mothers in PICU and encouraging them to talk to their sedated children, as a sensory stimulation can provide comfort to the sedated child, and can lead to improvement in their bio-physiological parameters. Several studies have reportedly shown the positive effect of maternal recorded voice on reduction in procedural pain, and anxiety, improvement in physiological parameters, and better cooperation [7,9,15].

This study observed few changes in the vital parameters of the children receiving the intervention. However, due to the small sample size, a significant improvement in the physiological parameters of children and difference in secondary outcomes could not be elicited following the intervention. The targeted sample size could not be achieved due to decreased admission rates in the PICU during the COVID-19 pandemic. The intervention could not be blinded, and that may have accounted for observer bias.

In the present study, structured, individualized and tailored communication via recorded maternal voice was used, which was safe and beneficial for the sedated children. These audios can be repeatedly played for sedated children in the PICUs in the absence of mothers, or when visitations are not practically feasible. Mothers who had agreed to the audio recordings had informally conveyed happiness and satisfaction to the researchers for playing those recordings for their children.

Therefore, healthcare providers should communicate with sedated patients during daily assignments and rounds and while giving care to them. They should also encourage the caregivers, like the mothers who play an important role for the emotional well-being and neurological development of her child. Our findings support the involvement of parents in the care of critically ill children.

Ethics clearance: EIC, All India Institute of Medical Sciences, New Delhi; No. IECPG-136, dated April 23, 2020.

WHAT THIS STUDY ADDS?

- Listening to recorded maternal voice had a positive effect on clinical hemodynamic parameters of sedated critically ill children.

Contributors: SM,PJ,LLM: conception and design, data collection, analysis and interpretation of data, drafting of manuscript, review and approval; RL: Conception and design, analysis, drafting of manuscript, review and approval.
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RESEARCH PAPER

Factors Associated With Hypertension and Cardiovascular Parameters in Children With Infrequently Relapsing Nephrotic Syndrome

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Objective: To assess the prevalence of hypertension in children with infrequently relapsing nephrotic syndrome (IRNS) and its association with dyslipidemia, and end organ damage including left ventricular hypertrophy (LVH), at relapse and after steroid induced remission. **Methods**: Prospective observational study conducted in 83 children aged 1-12 years with IRNS, presenting in relapse. Blood pressure, fundus examination, blood and urine investigations were done at relapse and then at 4 weeks of therapy. Echocardiography at 4 weeks was performed for assessment of LVH and relative wall thickness (RWT) for concentric geo-metry (CG). **Results:** 27 patients (32.5%) developed hypertension, out of which 21 patients (25.3%) had stage I hypertension. Hypertension in first episode (63.0%, *P*<0.01) and in previous relapses (87.5%, *P*<0.001) was significantly associated with hypertension in the current episode. 12 patients had a positive family history of hypertension, of which 8 (66.7%) were classified under the hypertensive group (*P*=0.016). Concentric geometry (CG) was found in 28% of hypertensive and 5.5% of non-hypertensive children (*P*=0.011). On regres-sion analysis, a lower Up:Uc at the time of relapse was found to have a protective role for development of hypertension. **Conclusion:** One third children with IRNS had hypertension at relapse and a high proportion of hypertensive patients had CG pattern on echocardiography.

Keywords: *Blood pressure, Concentric geometry, Echocardiography, End-organ damage*.

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Hypertension in children diagnosed with nephrotic syndrome is often multifactorial. It may be attributed to certain intrinsic causes (renal and non-renal) or extrinsic factors (environmental) or both [1]. While some of these contributing factors may cause acute episodic elevations in blood pressure due to fluid shifts, medications, other causes like renal fibrosis and decreased glomerular filtration rate result in a more chronic and sustained hypertension with further progression to chronic kidney disease (CKD) [2]. Childhood hypertension may eventually result in target end organ damage of which left ventricular hypertrophy (LVH) and concentric remodeling (CR) are important. However, the degree of blood pressure elevation that causes target end organ damage and increases cardiovascular risk has still not been established. Children with nephrotic syndrome also have a higher overall risk of an adverse cardiovascular outcome in adult life [3]. This may not only be due to the underlying prolonged hypertension, but also secondary to other contributory risk factors like dyslipidemia and kidney disease related risk factors.

The primary objective of this study was to assess the prevalence of hypertension in children with infrequently relapsing nephrotic syndrome (IRNS). The secondary objective was to establish the association of hypertension with dyslipidemia, end organ damage including left ventricular hypertrophy at the time of relapse and after steroid induced remission.

Invited Commentary: Pages 435-36

METHODS

We conducted a prospective cohort study at the Pediatric Nephrology Division in a tertiary care public hospital from November, 2018 to April, 2020. Institutional ethical clearance was obtained prior to the study. After taking a written informed consent, children aged 1-12 years, diagnosed with IRNS (irrespective of disease duration)

and off steroids, taking antihypertensive medications for minimum of 3 months were included in the study at the time of relapse. Children with IRNS presenting in shock, secondary causes of nephrotic syndrome, congenital heart disease and secondary causes of hypertension were excluded. A detailed clinical assessment, classification, diagnosis and management of nephrotic syndrome was done as per the standard guidelines of the Indian Society of Pediatric Nephrology [4,5].

The sample size was calculated to be 73 with an estimated prevalence of hypertension in IRNS of 25%, alpha error of 5% and acceptable absolute precision of 10% and 95% confidence interval. Assuming 10% attrition, a total of 83 patients with IRNS were recruited in the study.

Blood pressure (BP) was measured in the right arm of the child placed at the level of the heart, 90 degrees supported, after 3-5 minutes of rest in a quiet room. The Heine Gamma BP apparatus was used and BP measurements were compared with the standard tables. The correct cuff size with the bladder length of 80-100% and a width of at least 40% of the arm circumference with cuff bladder to arm width circumference ratio of 0.45 to 0.55, as recommended was followed. Childhood hypertension was defined as per the updated American Academy of Pediatrics clinical guidelines [6]. An average of three BP readings taken at each visit at a gap of 5-10 minutes was used to classify hypertension. BP was measured during the office visit before starting steroids and then again at 2 weeks and 4 weeks of steroid therapy. Treatment included lifestyle modification and dietary changes for all cases. Pharmacological therapy including angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (amlodipine) and rarely beta blockers (labetalol) was used depending upon individual cases. Diuretics were used for very few in-patients with resistant edema during albumin infusion and for a very short duration of time. As the patients enrolled were assessed at different time points to classify hypertension, effect of diuretics on the outcome was not included in the analysis. Hypertension was assessed in either one or both parents as per AHA, 2017 guidelines based on either use of antihypertensive drugs, self-reporting of hypertension or high office BP records measured after an average of three readings [7].

Dyslipidemia was diagnosed as any abnormalities in either one or more of the parameters in fasting lipid profile of both children and their parents as per the Indian Society of Pediatric Nephrology (ISPN) and American Association of Clinical Endocrinology (AACE), 2017 guidelines, respectively [8,9]. For dyslipidemia, only lifestyle modification was advised for patients as per the standard guidelines. No pharmacological therapy was initiated.

Investigations including a complete blood count, serum electrolytes, kidney function tests, total protein and albumin, complete lipid profile, urine dipstick and urinary protein to creatinine ratio (Up:Uc) were done at the time of relapse, before starting treatment and then repeated at 4 weeks of therapy. Patients were followed up during the course of treatment and blood pressure and fundus was assessed for any evidence of hypertensive changes at the onset and then at 4 weeks of drug induced remission.

For echocardiographic assessment, a specific procedure for determining the left ventricular mass and the definition of LVH by M-mode and Doppler echocardiography were performed using the Philips 11 HDXE at 4 weeks. LVH was defined as LV mass >51 g/$m^{2.7}$ or LV mass >115 g per body surface area (BSA) for boys and LV mass >95 g/BSA for girls [6]. A LV relative wall thickness >0.42 cm indicated concentric geometry/concentric remodeling and LV wall thickness >1.4 cm indicated concentric hypertrophy. This study used linear method of LV mass estimation, which uses end-diastolic linear measurements of the interventricular septum (IVSd), LV inferolateral wall thickness and LV internal diameter derived from 2D-guided M-mode or direct 2D echocardiography. This method utilizes the Devereux and Reichek cube formula [11]. Relative wall thickness (RWT) was measured as (2 x posterior wall thickness)/(LV internal diameter at the end of diastole) [13].

The LV target organ injury measures include LV structure (LV mass and the relationship of LV wall thick-ness or mass to LV cavity volume). LV structure was strati-fied into four groups on the basis of LV mass (normal or hypertrophied) and relative LV wall thickness (normal or increased): *i*) Normal geometry: Normal LV mass and wall thickness; *ii*) Concentric geometry: Normal LV mass and increased LV wall thickness; *iii*) Eccentric LVH: Increased LV mass and normal LV wall thickness; and *iv*) Concentric LVH: Both increased LV mass and increased LV wall thickness.

Statistical analysis: Categorical variables are presented in number (%) and continuous variables are presented as mean (SD) and median (IQR). Chi-square test was used to compare qualitative variables and unpaired *t* test/ Mann-Whitney *U* test for quantitative variables. Logistic regression analysis was used to identify the association with hypertension. A P value <0.05 was considered significant.

RESULTS

A total of 83 children with IRNS including 53 (69%) males with mean (SD) age of 5.52 (2.27) years, were enrolled in the study and followed up for a period of 4 weeks (**Web Table I**). Forty-six children had the BMI *z* score between

-1SD to +1SD. Two patients were lost to follow up and four became late steroid resistant, one of whom died. Echo-cardiography was done for 80 patients after 4 weeks of steroid therapy by a single cardiologist.

Out of the 83 cases enrolled, 27 (32.5%) children reported hypertension during relapse with 21 (25%) in stage I and 6 (7%) in stage II hypertension. Of these, 8.6% children persisted to have hypertension at 4 weeks of follow-up. In children who developed hypertension, a retrospective analysis of records suggested significant presence of hypertension in the first episode (63.0%, $P<0.001$) and in previous relapses (87.5%, $P<0.001$) (**Table I**). This was significantly associated with hypertension in the current episode as compared to the normotensive group. A family history of hypertension in either/both parents was found in 12 IRNS patients at the time of enrolment with 66.7% ($n=8$) ($P=0.016$) belonging to the hypertensive group (**Table I**).

Echocardiographic evaluation showed two patients in hypertensive group and none in the non-hypertensive group having LVH (**Table II**). Concentric geometry on echocardiography was seen in 7 children with hypertension at relapse and 3 without hypertension ($P=0.011$). One among them turned out to be SRNS at 4 weeks (**Table II**). Subsequently we studied the association of concentric geometry with clinical and laboratory parameters (which were measured at relapse) in 77 IRNS patients and found signi-ficant association of hypertension *(*$P=0.014$) and low serum albumin ($P=0.045$) (**Web Table II**). About 11.1 % of the hypertensive patients ($P=0.032$) had retinopathy at relapse (one each in stage 1, 2 and 3) with no new cases during the study period. Ten out of 83 children developed AKI at the time of relapse of which three children progressed to stage 3 AKI. Children in the hypertensive group also had higher risk of AKI at relapse ($P=0.010$) (**Table I**).

Table I Comparison of Characteristics of Children With Infrequently Relapsing Nephrotic Syndrome With and Without Hypertension at Relapse (*N*=83)

Characteristics	*Hypertension*		*P value*
	Present (n=27)	*Absent (n=56)*	
Age (y)[a]	5.39 (2.10)	5.59 (2.37)	0.770
Gender: Male	19	34	0.391
BMI (kg/m^2)[a]	15.83 (2.02)	16.16 (1.86)	0.333
BMI (SD)			
-3 to -2/-2 to -1/ -1 to median	2/6/5	0/9/14	0.419
Median to 1/1 to 2/ 2 to 3	7/4/3	20/7/6	
Hypertension in first episode	17	11	<0.001
Hypertension in previous relapse	14	17	<0.001
Hypertension in either/both parents	8	4	0.016
Dyslipidemia in either/both parents	6	9	0.549
Anasarca (at relapse)	20	8	<0.001
Systolic blood pressure	114 (7.21)	95.96 (6.57)	<0.001
Diastolic blood pressure	71.19 (7.99)	58.50 (5.48)	<0.001
Total protein (g/dL)[a]	3.34 (0.56)	3.87 (0.55)	<0.001
Serum albumin (g/dL)[a]	1.34 (0.30)	1.62 (0.29)	<0.001
Serum creatinine (mg/dL)[a]	0.38 (0.30)	0.28 (0.12)	0.510
Acute kidney injury	7	3	0.010
Urine protein/creatinine ratio[a]	7.18 (3.81)	4.01 (1.85)	<0.001
Total cholesterol (mg/dL)[a]	419.85 (146.75)	319.93 (90.75)	0.002
Triglycerides (mg/dL)[a]	274.89 (98.54)	211.62 (62.60)	0.002
Low density lipoprotein (mg/dL)[a]	250.93 (139.92)	167.93 (49.11)	0.001
High density lipoprotein (mg/dL)[a]	74.41 (26.70)	62.75 (17.68)	0.068
Hypertensive retinopathy	3	0	0.032

Data presented as numbers or [a]mean (SD). IFRNS:infrequently relapsing nephrotic syndrome; TG: triglyceride.

Table II Echocardiographic Parameters at Four Weeks in Children With Infrequently Relapsing Nephrotic Syndrome at Relapse (*N*=80)

Parameters	*Hypertension (AAP, 2017)*	
	Present (n=25)	*Absent (n=55)*
IVSD (mm)	6.28 (1.71)	5.70 (1.06)
LVEDD (mm)	31.58 (5.06)	32.35 (4.35)
PWd (mm)	6.00 (1.37)	5.58 (1.15)
Left ventricular mass (g)	46.76 (26.54)	42.49 (16.39)
LVMI (g/m^2)	62.40 (25.02)	57.47 (15.42)
LVH[a]	2 (8)	0
Relative wall thickness	0.37 (0.10)	0.35 (0.08)
Concentric geometry[a,b]	7 (28)	3 (5.4)

Values are mean (SD) or [a]no.(%). [b]P=0.01. IVSD: interventricular septum distance; LVEDD: left ventricular end diastolic diameter; PWd: posterior wall thickness; LVMI: left ventricular mass index; LVH: left ventricular hypertrophy. AAP: American Academy of Pediatrics [6].

Presence of persistent dyslipidemia at 4 weeks, seen in 31/77 (40.2%) children, was associated with a positive family history of dyslipidemia in either of the parents (32.3%, *P*=0.009). These children had significantly higher mean DBP (diastolic blood pressure), higher Up:Uc a lower serum albumin and higher prevalence of hypertension [15/31(48.4%)] which were measured at relapse (**Web Table III**). On regression analysis, a lower Up:Uc at the time of relapse was found to have a protective role towards development of hypertension (*P*=0.017) (**Table III**).

DISCUSSION

We found hypertension in about one-third of our patients with IRNS during relapse. Patients with nephrotic syndrome retain sodium even in a state of normovolemia with a normal plasma albumin indicating an intrinsic renal inability to excrete sodium [14]. In the study by Keshri, et al, 23% of steroid sensitive nephrotic syndrome (SSNS) reported hypertension during remission and 73.68% had a family history of hypertension [15]. Kontchou, et al. [16] reported hypertension in 65% of SSNS in the first week and 34% after 4 weeks of steroid therapy with a higher overall prevalence (88%) of essential hypertension in family members of the hypertensive nephrotic syndrome cohort. In our study, a lower proportion but persistent hyper-tension during remission was noted. This difference could be because the earlier studies used lower threshold for defining hypertension (>90th centile) and had a higher prevalence of family history of hypertension. Studies conducted on patients with minimal change disease and focal segmental glomerulosclerosis have also shown higher incidence of hypertension compared to our findings [17]. High values are known to exist among patients with steroid dependent nephrotic syndrome and steroid resistant nephrotic syndrome [18], due to the chronicity of the underlying disease, use of nephrotoxic medications and prolonged use of corticosteroids in these children.

Single center studies from India, have reported incidence between 16-23.7% of AKI in children with nephrotic syndrome [19,22]. We also saw a significant higher overall serum creatinine values from baseline in the hypertensive group during relapse.

An interesting finding in our study was the presence of concentric remodeling (CR) even in the non-hypertensive group (5.5%). We believe this may be attributed to the masked hypertension. Though, studies have documented a high triglyceride to high density lipoprotein ratio as the main predictor of concentric geometry, we noted significantly low serum albumin and hypertension at relapse in our patients with CR as demonstrated by Xu, et al. [20] and Sarkar, et al. [21], in 39.5% and 16.2% among children with primary nephrotic syndrome and FRNS, respectively. Ambulatory blood pressure monitoring (ABPM) may

Table III Univariate and Multivariate Regression Analysis for Factors Associated With Hypertension in Children With Infrequently Relapsing Nephrotic Syndrome

Factors	*OR (univariable)*	*P value*	*OR (multivariable)*	*P value*
Hypertension in parents	5.67	0.010	7.66	0.101
Total protein	0.14	0.001	0.08	0.003
Serum albumin	0.04	0.001	-	
Urine protein creatinine ratio	1.56	0.001	1.61	0.017
Total cholesterol	1.01	0.001	0.99	0.067
Triglyceride	1.01	0.002	1.02	0.019
Low density lipoprotein	1.01	0.003	1.01	0.112
Any infection	5.14	0.002	-	
Right wall thickness grading at 4wk	0.16	0.012	0.05	0.044

WHAT THIS STUDY ADDS?

- One third of children with infrequently relapsing nephrotic syndrome were hypertensive, 28% of whom had concentric geometry on echocardiography.

enable timely detection of masked hypertension to provide early treatment and avoid end organ damage. Even though no significant association between LVH and hypertension was found in our study, but the results demonstrate that hypertensive children had a greater mean LVMI and RWT as compared to normotensive children. Keshri, et al. [15] reported LVH in 10.5% patients with nephrotic syndrome despite the remission period emphasizing that organ damage in these patients is an ongoing process. As one tenth of the hypertensive children developed hypertensive retinopathy in our study, it emphasizes the role of regular ocular examinations.

Similar to the findings by Merouani, et al. [12,23], persistent dyslipidemia during remission at 4 weeks was also noted in our study in around 40% of patients with a positive family history of dyslipidemia noted in 31.5% of them. Hypertension at relapse, was significantly more seen these patients in compared to non-dyslipidemia group.

On multivariate analysis, Up: Uc ratio was found to have a significant correlation with hypertension at relapse. Previously studies have found family history of hypertension, LDL and total cholesterol to have a strong correlation with hypertension [15].

A lack of age- and sex-matched healthy control population for comparing the prevalence of hypertension, lack of association with total duration of nephrotic syndrome and a short follow up period, may limit the generalizability of findings. Moreover, the 2017 AAP classification [6] defines LV geometry using adult cut off values making it difficult to identify the expected association between left ventricular geometry and hypertension in the paediatric age group.

One third of the children with IRNS had hypertension during relapse, only one-fifth of whom had persistent hypertension after 4 weeks. A higher proportion of hypertensive patients were found to have concentric geometry pattern on echocardiography. Though, hypertension in most children with IRNS is transient, there is a need for early screening of hypertension in such children to identify those with CG.

Contributors: AS: conceptualized and designed the study, coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content; MF: acquisition of entire data, analysis and preparation of the manuscript, follow up and clinical assessment of all patients; SC: analysis and editing of manuscript and preparation of final draft; AR, DB: performed echocardiography and offered expert cardiology opinion; MY: critically reviewed the manuscript and offered expert inputs while editing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Baseline Characteristics and clinical parameters in Total Population at Relapse (*N*=83)

Baseline Characteristics	*Mean# (SD) /frequency*
Age (Years)#	5.52 (2.27)
Age (1-5)/ (5-9)/ (9-12) Y	40 /36/7
Gender (Males)	53
Weight (Kg)#	18.35 (5.27)
Height (cm)#	106.35 (15.16)
BMI (Kg/m2) #	16.05 (1.91)
BMI Z Score#	0.21 (1.23)
BMI Z Score (SD) -3 to -2 /-2 to -1/-1 to Median	2 / 15/ 19
eGFR (ml/min/1.73m2)#	176.54 (77.03)
AKI Absent / Stage 1/ Stage 2/ Stage 3	76 / 1/ 6/ 3
Urine Protein/Creatinine Ratio#	5.04 (3.02)
Total Cholesterol (mg/dL)#	352.43 (120.71)
Total Cholesterol (≥200 mg/dL)	83
Triglycerides (mg/dL)#	232.20 (81.22)
Triglycerides (≥200 mg/dL)	55
Hypertensive Retinopathy Absent/Stage 1/Stage 2/Stage 3	80 / 1 /1 /1

All parameters are represented as number except # which are represented as mean(SD)

Web Table II Association Between RWT Grading (4 Weeks) and Clinical and Laboratory Parameters at relapse in Children With IRNS (*n*=77)

Parameters	*RWT Grading (4 Weeks) Mean# (SD) /frequency*		*P* value
	Concentric Geometry (n = 9)	*Normal (n = 68)*	
Age (Years)	4.30 (2.00)	5.63 (2.30)	0.063
Male#	6	44	1.000
BMI (Kg/m2)	15.44 (2.57)	16.06 (1.77)	0.170
BMI Z Score (SD) #			0.122
(-3 to -2) / (-2 to -1) (-1 to Median)	1 / 2/ 2#	0 / 12/ 17#	
Median to 1 /(1 to 2)/ (2 to 3)	1 / 2/ 1	25 / 7/ 7	
S. Albumin (g/dL)	1.36 (0.30)	1.58 (0.31)	0.045
S. Creatinine (mg/dL)	0.33 (0.23)	0.29 (0.14)	0.994
Urine Protein/Creatinine Ratio	5.89 (3.75)	4.62 (2.67)	0.441
Total Cholesterol (mg/dL)	402.22 (108.69)	333.49 (114.77)	0.060
Triglycerides (mg/dL)	226.89 (69.40)	230.24(83.57)	0.787
LDL (mg/dL)	168.78 (44.31)	191.28 (101.66)	0.800
HDL (mg/dL)	58.78 (10.13)	66.43 (23.03)	0.475
SBP (mmHg)	109.33 (14.90)	99.94 (9.28)	0.072
DBP (mmHg)	67.11 (10.73)	61.29 (7.94)	0.152
Hypertension#	6	16	0.014
BP Grading (cenile) # (50th-90th) / (90th-95 th) / (>95th) / (>95th +12)	2 /1/4/2	48 /4/14/2	0.008

[RWT, relative wall thickness] Significant at p<0.05, 1 are represented as mean (SD), except which are represented as number (%). Among 80 patients whose echo was done at 4 weeks,3 patients turned out to be SRNS at 4 weeks, hence association of clinical parameters with RWT grading was done in 77 IRNS patients.

Web Table III Association between Persistent Dyslipidemia (4 Weeks) and Laboratory Parameters at relapse in IRNS (*n*=77)

Parameters (n=77)	*Persistent Dyslipidemia (4 Weeks) Mean# (SD) /frequency*		*P value*
	Present (n = 31)	*Absent (n = 46)*	
Total Protein (g/dL)	3.63 (0.64)	3.82 (0.55)	0.138
S. Albumin (g/dL)	1.42 (0.31)	1.64 (0.28)	0.004
S. Creatinine (mg/dL) mean	0.33(0.17)	0.27 (0.13)	0.110
Dyslipidemia in Parent	10	4	0.009
Urine protein/creatinine ratio	6.34(3.67)	3.71 (1.25)	<0.001
Total Cholesterol (mg/dL)	438.74 (114.14)	276.00 (54.44)	<0.001
Triglycerides (mg/dL) mean	285.39 (83.89)	192.41 (54.84)	<0.001
LDL (mg/dL) mean	240.23 (130.15)	153.89 (38.26)	<0.001
HDL (mg/dL)	67.87 (24.61)	63.96 (20.21)	0.633
SBP (mmHg)	103.87 (12.50)	99.13 (8.35)	0.119
DBP (mmHg)	64.77 (10.08)	60.09 (6.60)	0.036
Hypertension	15	7	0.002

. All parameters are represented as mean (SD) except which are represented as number (%).

UPDATE

New WHO Recommendations for the Care of Preterm and Low Birth Weight Infants – A Potential Strategy to Transform the Current Healthcare Needs of Neonates

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Despite major advances in the field of maternal and child health, preterm and lowbirth neonates still carry a substantial burden of both mortality and morbidity, especially in low and middle-income countries. In view of accumulating new evidence, there was a felt need for updating and expanding the previous World Health Organization recommendations of 2015. The new evidence-based recommendations for care of the preterm or low birthweight infant consist of 25 recommendations and one good practice statement and were published on 15 November, 2022. We herein provide the key recommendations for the benefit of the readers.

Keywords: *Management, Small vulnerable newborns.*

The overall needs of preterm and low birth weight neonates with respect to their requirement of resuscitation, respiratory support, nutrition, and long-term neurodevelopmental follow-up are remarkably different from term born neonates [1-3]. Taking into consideration the burden of global mortality, preterm account for 36.1% of total neonatal deaths and 17.7% of death under 5 years of age [4].

The WHO Departments of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA) and Sexual and Reproductive Health and Research (SRH) had developed various guidelines based on the available evidence in 2011, 2012 and 2015 [5-7]. Since the last guidelines, significant evidence has emerged in numerous areas of neonatal health that could potentially serve to simplify and improve the complexities associated with the care of small and sick neonates. In 2020, a group of experts comprising 25 Guideline Development Group (GDG) members from six WHO regions examined and interpreted the evidence, formulated the final recommendations, and provided the related comments at multiple virtual meetings between November, 2021 and January, 2022. On November 15, 2022, WHO published the outcomes of this process in the 'WHO Recommendations for Care of the Preterm or Low Birthweight Infant [8].'

The guidelines provide insight into the implementation aspect of these recommendations in the care of small and sick neonates along with addressing other associated applicability issues. A detailed description of the need for focusing on future implications has also been included. Lastly, the monitoring and evaluation of the impact of these guidelines to inform and update the future guidelines has also been taken into account.

Target audience: Prioritizing neonatal health with the aim to end preventable deaths, the guidelines intended to update the recommendations that would immensely impact the areas with high clinical or public health burden. For fulfilling the objective, the guidelines focused to inform the national and subnational public health policy-makers, implementers and managers of maternal, newborn and child health programs, supervisors for in-service training, health workers, NGOs, professional societies, researchers, and those involved in the education of parents.

Guideline development methods: The Grading of Recommendation Assessment, Development and Evalua-tion (GRADE) approach was used to define the quality of evidence and strength of quantitative evidence, whereas the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) tool was used for qualitative evidence. The DECIDE approach (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence), an evidence-to-decision tool, was used to formulate the recommendations by the GDG members.

The Concept of Family Values and Preferences

Being cognizant of the interventions to improve the survival of vulnerable preemies and taking into consideration

the growing awareness among parents about the care of small and sick neonates, the WHO committee reviewed 203 studies from Low- and middle-income countries (LMICs) about 'what matters' to families with regard to the care of preterm and LBW neonates. The committee reported that families aspire for the best possible positive outcome for their babies, urge to be involved as an active care provider and have the desire to participate in decision making related to interventions provided to their babies. The domains covered under family values and preferences include- positive outcomes, active involvement in care, coping at home, emotional support for the family, health-care environment, information needs met, logistic support and positive relationships with staff.

RECOMMENDATIONS

The recommendations were based not only on the concept of the 'assessment of effects' that includes benefits and harms of the interventions and preterm and LBW infant health outcomes, but has also taken into consideration the values and preferences of the families and health workers, acceptability, resource requirements, feasibility and equity. Seventeen new systematic reviews were commissioned and 21 additional existing systematic reviews and meta-analyses were assessed. The guidelines comprising 25 recommendations and one good practice statement (**Table I**) were published on November 15, 2022. Of the recommendations, 11 are new and 14 are updated and the

Table I WHO Recommendations for the Care of the Preterm or Low Birth Weight Infant

Recommendations	*Status*	*Strength*
Preventive and Promotive Care		
Any kangaroo mother care (KMC): KMC is recommended as routine care for all preterm or low birth weight (LBW) infants. KMC can be initiated in the health-care facility or at home and should be given for 8-24 h per day.	Updated	Strong
Immediate KMC: KMC for preterm or LBW infants should be started as soon as possible after birth.	New	Strong
Mother's own milk: MOM is recommended for feeding of preterm or LBW infants, including very preterm (< 32 wk gestation) or very LBW (< 1.5 kg) infants.	Updated	Strong
Donor human milk: When MOM is not available, donor human milk may be considered for feeding of preterm or LBW infants, including very preterm or very LBW infants.	Updated	Conditional
Multi-component fortification of human milk: Multi-component fortification of human milk is not routinely recommended for all preterm or LBW infants but may be considered for very preterm or very LBW infants who are fed mother's own milk or donor human milk.	Updated	Conditional
Preterm formula: When mother's own milk and donor human milk are not available, nutrient-enriched preterm formula may be considered for very preterm or very LBW infants.	Updated	Conditional
Early initiation of enteral feeding: Preterm and LBW infants, including very preterm (< 32 wk gestation) and very LBW (< 1.5 kg) infants, should be fed as early as possible from the first day after birth. Infants who are able to breastfeed should be put to the breast as soon as possible after birth. Infants who are unable to breastfeed should be given expressed mother's own milk as soon as it becomes available. If mother's own milk is not available, donor human milk should be given wherever possible.	Updated	Strong
Responsive and scheduled feeding: In health-care facilities, scheduled feeding may be considered rather than responsive feeding for preterm infants born before 34 weeks' gestation, until the infant is discharged.	Updated	Conditional
Fast and slow advancement of feeding: In preterm or LBW infants, including very preterm (< 32 wk gestation) or very LBW (< 1.5 kg) infants, who need to be fed by an alternative feeding method to breast-feeding (e.g. gastric tube feeding or cup feeding), feed volumes can be increased by up to 30 mL/kg per day.	Updated	Conditional
Duration of exclusive breastfeeding: Preterm or LBW infants should be exclusively breastfed until 6 mo of age.	Updated	Strong
Iron supplementation: Enteral iron supplementation is recommended for human milk fed preterm or LBW infants who are not receiving iron from another source.	Updated	Strong
Zinc supplementation: Enteral zinc supplementation may be considered for human milk-fed preterm or LBW infants who are not receiving zinc from another source.	Updated	Conditional
Vitamin D supplementation: Enteral vitamin D supplementation may be considered for human milk-fed preterm or LBW infants who are not receiving vitamin D from another source.	Updated	Conditional
Vitamin A supplementation: Enteral vitamin A supplementation may be considered for human milk-fed	Updated	Conditional

contd....

Table I *continued from pre-page*

Area of interest	*Recommendations*	*Status*	*Strength*
	very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants who are not receiving vitamin A from another source.		
	Probiotics: May be considered for human-milk-fed very preterm infants (< 32 wk gestation).	New	Conditional
	Emollients: Application of topical oil to the body of preterm or LBW infants may be considered.	New	Conditional
	Care of Complications		
	CPAP for respiratory distress syndrome: Continuous positive airway pressure (CPAP) therapy is recommended in preterm infants with clinical signs of respiratory distress syndrome.	Updated	Strong
	CPAP immediately after birth: CPAP therapy may be considered immediately after birth for very preterm infants, with or without respiratory distress.	New	Conditional
	CPAP Pressure sources: For preterm infants who need CPAP therapy, bubble CPAP may be considered rather than other pressure sources.	New	Conditional
	Methylxanthines for treatment of apnea: Caffeine is recommended for the treatment of apnea in preterm infants.	New	Strong
	Methylxanthines for extubation: Caffeine is recommended for the extubation of preterm infants born before 34 wk gestation.	New	Strong
	Methylxanthines for prevention of apnea: Caffeine may be considered for the prevention of apnea in preterm infants born before 34 wk gestation.	New	Conditional
	Family Involvement and Support		
	Family involvement: Family involvement in the routine care of preterm or LBW infants in health-care facilities is recommended.	New	Strong
	Family support: Families of preterm or LBW infants should be given extra support to care for their infants, starting in healthcare facilities from birth and continued during follow-up post-discharge. The support may include education, counselling and discharge preparation from health workers, and peer support.	New	Conditional
	Home visits: Home visits by trained health workers are recommended to support families to care for their preterm or LBW infant.	New	Strong
	Parental leave and entitlements: Parental leave and entitlements should address the special needs of mothers, fathers and other primary caregivers of preterm or LBW infants.	New	Good practice statement

good practice statement is a new addition. Some of the newer recommendations include the concept of Immediate KMC, the use of caffeine for the prevention of apnea and extubation, use of CPAP immediately after birth, emphasizing the importance of family involvement and home visits, the use of probiotics and emollients and the need for education and counselling, peer support and discharge preparedness. They were sub-categorized into three categories viz., preventive and promotive care (16 recommendations), care of complications (6 recommendations), and family involvement and support (3 recommendations)

A good practice statement was made for parental leave and entitlements, as although the evidence favoring this is limited but there is an obvious associated benefit.

THE WAY FORWARD

The panel also identified the knowledge gaps and listed the priority research questions that need further evaluation, some of which are provided in **Box I**. The GDG also proposed implementation considerations for each recommendation and reflected on the principle of adopting, adapting, and implementing, to ensure quality care in accordance with a human rights-based approach. The members emphasized to focus strategically on a phased approach for facilitating the implementation and for overcoming the barriers. The implications demand innovative policies, the building of infrastructure, adequate manpower, apt finances and safe service delivery. The impact of these guidelines is planned to be monitored at the various health services including at national and subnational levels on clearly pre-defined criteria and indicators that are associated with locally agreed targets.

Integrating the new WHO guidelines to provide the best services in favor of small and sick neonates requires enthusiasm and commitment by the policymakers both in terms of financial help and for structured framework. This

Box I Some Suggested Research Areas in Preterm and Low Birthweight Care

- What is the effectiveness of KMC on longer-term (i.e., up to 2 years of age, school-age, adolescence) growth, neurodevelopment, behavior, mental health and disability outcomes?
- What is the effectiveness of immediate KMC in critically ill preterm or LBW infants?
- How can immediate KMC be scaled up in routine health systems?
- How can exclusive breastfeeding be promoted, supported and scaled up for preterm or LBW infants, especially those who are very preterm or very LBW?
- What are the most effective early feeding strategies for very preterm or very LBW infants, infants with illnesses (e.g. post-surgery), and infants with other conditions (e.g. doppler abnormalities, severe growth restriction)?
- What is the effectiveness, safety and feasibility of human milk banks in LMICs?
- What is the effectiveness and safety of probiotics in human-milk-fed infants?
- What is the effect of probiotics on immune function and gut microbiome in preterm or LBW infants?
- What are the most optimal probiotic compositions for preterm or LBW infants – that is, the optimal combination of genera, species and strains?
- What is the optimal probiotics regimen (dosage and duration) for preterm or LBW infants?
- What is the effectiveness of probiotics alone compared with a combination of probiotics and prebiotics for preterm or LBW infants?
- What is the role of probiotics in the prevention and management of postnatal growth restriction in preterm infants?
- What is the effect of emollients on mortality, invasive infection, sepsis, growth and longer-term neurodevelopment in preterm or LBW infants?
- What is the effect of emollients on thermoprotection and the microbiome in preterm or LBW infants?
- Which emollients (which oils, which composition) are most effective and safe for preterm or LBW infants?
- What is the optimal regime (dose, frequency, duration) and mode of application (e.g. non touch applications) for very or extremely preterm infants?
- What is the effectiveness of CPAP compared with humidified high-flow nasal cannula and other forms of non-invasive ventilation in preterm or LBW infants with respiratory distress syndrome?
- What strategies can be used to increase family participation in the care of their preterm or LBW infants in intensive and special care units, and in settings without dedicated newborn units?
- What is the most effective type of family support (including education, counselling, discharge preparation, peer support) for families of preterm or LBW infants?
- What is the effectiveness of standard in-person home visits compared with digital home visits (e.g. online video, mobile application [app], mHealth) for post-discharge follow-up of preterm or LBW infants?
- What is the feasibility of digital home visits in low-, middle- and high-income countries?

also demands the active participation of healthcare professionals who would serve as the frontline workers involved in the actual implementation of these policies to transform the recommendations into actions, so as to make the frame shift change in maternal and neonatal health.

Country level initiatives need to be taken for implementation of the various evidence-based guidelines for ensuring quality care of preterm and LBW infants at facility and community level. There is scope for adopting these *in toto*, or adapting some or all based on country needs and equity considerations.

India as a country has been the torch bearer for facility based newborn care (Special care newborn units, Newborn stabilization units and Newborn care corners) and the country's experiential learning has paved way for development of global framework for care of small & sick newborn. We are well poised to adopt all the components of these guidelines in the clinical care of our neonates both in the public and private sector. Challenges anticipated in ensuring uniformity in implementation should be predicted and addressed at the inception to reap full benefits. Research areas spelled out for different domains should be explored both at the individual clinical and at systems level.

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Reye Syndrome- An Enigma That Remains

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Reye syndrome was first reported sixty years back by Ralph Douglas Kenneth Reye, Graeme Morgan and Jim Baral in Australia as a non-inflammatory encephalopathy with fatty degeneration of multiple visceral organs with 80% of their patients succumbing to the illness [1]. Gradually it started being reported all over the world. Chandrasekaran, et al. [2] reported a series of nine children (from 1971 to 1973) from Chandigarh who were diagnosed clinically as Reye syndrome. They were the first to report survival of patients suffering from Reye syndrome in India [2]. As time passed, Reye syndrome was managed better and the case fatality rate dropped to 10-20% [3].The exact etiology of Reye syndrome is yet to be understood. However, a strong association with the use of aspirin in the setting of a viral illness was identified. A prompt action in the form of widespread warning against the use of aspirin in febrile viral illness laterled to the disease becoming almost non-existent. It is worthwhile to review the last fifty years as this rapidly progressive fatal disease was made almost non-existent by timely intervention.

THE PAST

Although, reports of illness similar to that of Reye syndrome existed in the literature from 1929, it was first described as a distinct entity by Reye, et al. [1] in 1963. Following this report, small cluster of cases were being reported initially. This clinical entity gained significant attention once an association with aspirin use became evident. The Centre for Disease Control (CDC) established a surveillance system for Reye syndrome in 1968 [4]. Thereafter, 11 to 83 cases were reported annually till 1973. As the disease gained more attention and reporting became better, a peak of 555 cases were reported in 1979-80. The incidence gradually declined with no more than two cases being reported annually from 1994-97 [4]. Similarly, in India, 242 cases of Reye syndrome were reported till 1991 [5].

Reye syndrome is a disorder of the pediatric age group and commonly affects 5-14 years age group [4,5]. The etiology and pathogenesis is not clearly established. Viral infections such as influenza and varicella, toxins such as aflatoxin, pesticides or drugs such as aspirin and valproate have all been implicated. By far the greatest association is with the use of aspirin during viral prodrome. Infection with patho-genic viruses results in an altered immune response with release of various inflammatory mediators that results in damage to the mitochondria. This results in metabolic failure, an arrest in gluconeogenesis and release of toxic metabolites such as ammonia and fatty acids responsible for the clinical presentation. This metabolic failure is accentuated by drugs such as aspirin or other toxins [6]. The controversy regarding aspirin as a causative agent stemmed from the fact that aspirin was being used for a long time before Reye syndrome started being reported. Also, a subgroup of patients of Reye syndrome has no exposure to aspirin. Almost no patient reported from India had exposure to aspirin. Moreover, less than 0.5% of the patients who used aspirin developed Reye syndrome. However, multiple epidemiological studies were carried out and a consistent link with aspirin exposure and development of Reye syndrome was established. We also cannot ignore the fact that reducing the use of aspirin during a viral illness has almost made Reye syndrome disappear [7,8].

Reye syndrome typically presents as a biphasic illness. It begins with a viral illness such as chicken pox, influenza or acute viral gastroenteritis, and several days later there is sudden onset projectile vomiting and altered sensorium that rapidly deteriorates to lethargy, stupor, convulsions and coma. Reye syndrome is a clinical diagnosis and requires fulfilment of the following criteria: presentation as a biphasic illness, cerebrospinal fluid analysis showing less than 10 cell/mm^3, elevated serum transaminases by

200% and serum ammonia by 150%, and exclusion of other causes of encephalopathy and hepatocellular dysfunction [3]. Liver biopsy is diagnostic and helps to differentiate from inborn errors of metabolism (IEM), which mimic presentation like Reye syndrome. It has to be done early in illness to identify the characteristic changes. Light microscopy reveals microvesicular steatosis and absence of necrosis and inflammation. Mitochondrial pleomor-phism and matrical swelling, proliferation of endoplasmic reticulum, a great increase in microbodies and more or less depletion of glycogen can be identified on electron microscopy. In contrast, IEM will have a normally appearing mitochondria [9]. Correction of hypoglycemia with a higher glucose infusion rate and adequate measures to tackle the raised intracranial pressure must be initiated immediately [3].

THE PRESENT

The classical Reye syndrome, which occurs with a prodromal viral illness and an associated aspirin use has almost disappeared, with only a few sporadic cases continuing to be reported. However, IEM such as fatty acid oxidation defects, urea cycle disorders, organic acidurias can masquerade as Reye syndrome. One study reported that 12% of the patients initially diagnosed as Reye syndrome were later found to be having an underlying IEM [6]. Presentation in infancy or toddler age group, as recurrent episodes or an associated family history must raise the suspicion of an underlying IEM.

The larger question that needs to be answered by us is whether the benefits of aspirin withdrawal outweigh the benefits of aspirin use. Aspirin has largely been replaced by acetaminophen. Acetaminophen differs from aspirin in that it does not have anti-inflammatory properties at antipyretic doses. Also, over dosage results in toxic liver injury. Acetaminophen poisoning is the most common cause of acute liver failure in USA. With aspirin over-dosage, toxic liver injury rarely occurs. Aspirin use is still very beneficial in inflammatory conditions such as Kawasaki disease (KD) and acute rheumatic fever (ARF). Reye syndrome has almost never been reported in the setting of these inflammatory conditions (incidence < 0.005%) [6]. By highlighting the risk of Reye syndrome too much, we may be forced to use other non-steroidal anti-inflammatory drugs, which may not be as well tolerated.

Another concern is the increase in the prevalence of childhood asthma. There may be a correlation of early life exposure to acetaminophen and increased incidence of childhood asthma. This has yet to be proven. Likely, changing over from aspirin to acetaminophen has brought about this new dynamic [10].

CONCLUSIONS

In times of coronavirus pandemic, we must be careful in the use of aspirin as prior clustering of cases occurred during epidemics of influenza. One case of multisystem inflammatory syndrome complicated by Reye syndrome has been reported. Care must be taken to utilize aspirin only when absolutely needed. Fear of Reye syndrome should not stop us from using aspirin in conditions such as KD or ARF where its benefits significantly outweigh the risks. The new British guidelines on the management of KD do not mention Reye syndrome as a potential adverse event anywhere in the guidelines as they recognize that the beneficial effect of aspirin outweighs the risk in these conditions.

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Is Expectant Management Noninferior to Early Ibuprofen for Patent Ductus Arteriosus?

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SUMMARY

In this multicentre non-inferiority trial, 273 infants with echocardiographically confirmed PDA (diameter >1.5 mm) who were extremely preterm (<28 weeks gestational age) underwent randomization to receive either expectant management or early ibuprofen treatment. The composite primary outcome included necrotizing enterocolitis (Bell's stage IIa or higher), moderate to severe bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age. The median gestational age was 26 weeks, with a median birth weight of 845 g. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 (63.5%) in the early-ibuprofen group (absolute risk difference, -17.2 percentage points; upper boundary of the one-sided 95% confidence interval [CI], -7.4; P<0.001 for noninferiority). Necrotizing enterocolitis occurred in 24 of 136 infants (17.6%) in the expectant-management group and in 21 of 137 (15.3%) in the early-ibuprofen group (absolute risk difference, 2.3 percentage points; two-sided 95% CI, -6.5 to 11.1); bronchopulmonary dysplasia occurred in 39 of 117 infants (33.3%) and in 57 of 112 (50.9%), respectively (absolute risk difference, -17.6 percentage points; two-sided 95% CI, -30.2 to -5.0). Death occurred in 19 of 136 infants (14.0%) and in 25 of 137 (18.2%), respectively (absolute risk difference, -4.3 percentage points; two-sided 95% CI, -13.0 to 4.4). The authors concluded that expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age.

COMMENTARIES

Evidence-based Medicine Viewpoint

Critical Appraisal

The classical presentation of hemodynamically significant (hs) patent ductus arteriosus (PDA) in extreme preterm neonates comprises of increase in pulmonary blood flow leading to pulmonary oedema, respiratory deterioration, and sometimes bronchopulmonary dysplasia (BPD). The alteration in blood flow due to hsPDA may also cause necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), and even death [1].

The incidence of PDA beyond the first 3 postnatal days exceeds 50% in infants less than 28 weeks gestation. Historical practice has led to medical or surgical therapy in 60% to 70% of such infants [2,3]. The available pharmacological modalities include cyclooxygenase inhibitors and surgical ligation for non-responders. These therapies have their own risk, and the metanalyses evaluating the outcomes of pharmacotherapy lack robustness to refute the role of expectant management [4,5].

Over the years the evidence has moved from intervention to expectant management of PDA in preterm. Observational evidence suggests that conservative management using supportive therapy alone in preterm infants with PDA may be a reasonable option with ongoing assessment and intervention if needed [6]. In a network meta-analysis that compared all pharmacological methods versus placebo or no treatment, the latter had the poorest rate of PDA closure. However, all treatment options (including placebo and no therapy) had similar outcomes of patient-centred outcomes, such as mortality, NEC, or IVH [7].

The BeNeductus trial [8] compared expectant management vs early Ibuprofen therapy for PDA in pre-term neonates <28 weeks who had echocardiographically confirmed PDA, ductal diameter >1.5 mm and left-to-right shunt detected at 24-72 hours of age. The *a priori* non-inferiority margin was an absolute risk difference of +10%. The primary outcome was a composite of NEC, moderate-to-severe BPD or death at a postmenstrual age of 36 weeks. The authors were able to achieve only 48.4% of the calculated sample size. Despite the inadequate sample size, the results showed that expectant management was non-inferior to early ibuprofen therapy vis à vis the composite outcome, and sepa-

rately BPD and death. In fact, the results suggest a significantly higher incidence of BPD in the ibuprofen group.

Conclusion

This trial adds to the growing evidence that non-pharmacological conservative treatment is effective in most preterm neonates. There is a need to find the subset of preterm who would need PDA closure. The trial throws up the interesting possibility that ibuprofen may worsen pulmonary outcomes through mechanisms that need further elucidation.

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Neonatologist's Viewpoint

Patent Ductus Arteriosus (PDA) occurs commonly among preterm infants with incidence being as high as 50-80% among extreme preterm infants (<28 weeks) [1, 2]. Closing PDA early in the course would possibly prevent PDA associated mortality and various morbidities including bronchopulmonary dysplasia (BPD), pulmonary haemorrhage, intra-ventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC). However, there is a controversy about the optimal management of PDA with recent trend shifting towards 'expectant' management.

Traditionally neonatologists have followed four different kinds of approaches for treating PDA. These are 1) Prophylactic treatment (within 24 hours of birth) 2) Pre-symptomatic/early treatment (usually 3-7 days after birth) 3) Symptomatic treatment (after 1st week of life) 4) Expectant management. All these approaches have their own pros and cons with the 'prophylactic' strategy being out at present as large proportion of infants get exposed to potential serious side effects of drug treatment, when their PDA would have been closed spontaneously. Moreover, it has not shown any significant advantage on the mortality or long-term neurodevelopmental outcome [3]. Though, the trials assessing the effectiveness of 'early treatment' versus 'expectant' management for hemodynamic significant PDA (hs PDA) did not find any significant difference in any of the morbidity or all-cause mortality however, critical analysis of these trials revealed that a significant proportion of infants (20-85%) in the 'expectant' management group received 'open-label' treatment thus contaminating the overall results [4]. Thus, there is a research gap where 'expectant' management has been compared with 'early treatment' strategy in extreme preterm infants with minimal to no contamination.

Hundscheid, et al, in this multicentric, non-inferiority trial randomized extreme preterm infants with echocardiographically confirmed PDA (>1.5 mm with left-to-right shunting) within first 72 hours of life to receive either 'expectant' management (intervention) or 'early-ibuprofen' treatment (active control). The primary outcome was the composite of definite NEC, moderate-to-severe BPD or death at 36 weeks' of postmenstrual age with a non-inferiority margin of 10% [5]. The trial was stopped prematurely due to slower-than-anticipated recruitment and could enroll only half of the expected sample size. The 'expectant' management was found to be non-inferior to 'early-ibuprofen' treatment with absolute risk difference of the composite primary outcome being -17.2% (63/136 [46.3%] in 'expectant management' group versus 87/137 [63.5%] in 'early-ibuprofen' group) with upper boundary of one-sided 95% confidence interval being -7.4%. The results were largely driven by higher incidence of BPD in 'early-ibuprofen' group than in the 'expectant' group [57/137 (50.9%) vs 39/136 (33.3%)].

Though, the results of this trial are significant however, half of the infants received diuretics and 25% received paracetamol in the 'expectant' group, thus contaminating the results. This is despite of the fact that the protocol explicitly highlighted to have avoidance of such co-interventions to

get the true difference. No information is available about the daily fluid intake. It is important to know the same as fluid restriction is one of the early intervention done in preterm infants with hs-PDA. Moreover, the results in this open-label trial are primarily driven by the difference in the incidence of BPD and excess fluid has been directly implicated in the patho-physiology of BPD. Also, there is no information about the number of infants receiving 'open-label' treatment. It is worth noting that one-third of the infant deaths (6/19) occurred beyond first 28 days of life in 'expectant' group unlike 'early-ibuprofen' group where no more deaths occurred beyond this time period. This difference may also reflect performance bias in this open-label trial with more care being given to infants in the 'expectant' group especially in first few days of life when hs-PDA is active requiring treatment.

Though the results of this trial are encouraging and reassures that the 'expectant' group is noninferior to 'early-ibuprofen' group in short-term, however, being underpowered with above-mentioned limitations, one need more evidence in this direction to change the current practice. Another similar trial named 'baby-OSCAR' addressing the similar research question has finished the enrolment and the results are awaited soon [6].

Thus, both strategies i.e., 'expectant' management and 'early/late treatment' have their own role to play however; there is a need to identify the subgroup of infants who would benefit maximum with minimal adverse events with each of these two strategies. Till we have more evidence it's appropriate to conclude what Evan's said *"It is the clinical approach that is most widely used but we do not have any evidence to support it"* [7].

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Pediatrician's Viewpoint

Patent Ductus Arteriosus (PDA) is one of the most common congenital heart defects seen in neonates. Its incidence is inversely related to the gestational age and degree of prematurity. Failure of closure of ductus is seen in 64% neonates born at 27-28 weeks of gestation at 7 days of life in 80% of those between 24-28 weeks and 90% in those born less than 24 weeks of gestation [1]. Prolonged rupture of membranes, sepsis, respiratory distress syndrome, are some risk factors reported with increased incidence of PDA. Use of antenatal steroids is reported to be beneficial specially when administered at least 24 hours before delivery, thereby reducing the incidence of PDA [2].

Management of PDA in preterm neonates has been a topic of debate with a shift in management strategy in the last 30 years. With increasing use of antenatal steroids, exogenous surfactant and advances in ventilation strategy has shifted management strategy from aggressive early closure to Wait and Watch policy [3]. Numerous studies are available documenting an association between necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) and PDA. Prolonged shunt exposure and high left to right shunt volume across the ductus are some factors suggested [4]. However, there are multiple randomized controlled trials (RCT) that have failed to show any improvement in these morbidities even after early closure of PDA and prophylactic surgical ligation no longer recommended due to reported associated significant morbidities [5,6]. Even in this study, expectant management of PDA is extremely premature infants was found to be no inferior to early ibuprofen therapy with respect to NEC, BPD or death at 36 weeks' postmenstrual age. Similar findings have been reported in the past in meta-analysis and placebo controlled RCT [7,8]. Therefore, management of PDA continues to be a challenge with pharmacogenetics seeming to be the next management strategy in premature infants with the ongoing debate as to who needs intervention minimising the morbidity and mortality.

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Change in Apo B100/A1 Ratio in Children With Epilepsy on Monotherapy With Sodium Valproate, Oxcarbazepine or Levetiracetam

A prospective longitudinal study was conducted to assess the Apo B100/A1 ratio as a marker of cardiovascular risk in children with epilepsy aged 5-14 years on long-term anti-seizure medication monotherapy with either sodium valproate, oxcarbazepine, or levetiracetam. Apo B100/A1 ratio showed an increase after six months of monotherapy with oxcarbazepine (*P*=0.05).

Keywords: Adverse effect, *Cardiovascular risk, Lipid profile, Outcome.*

Epilepsy in children often require long term anti-seizure medications. Studies have demonstrated that anti-seizure medications including phenobarbitone, carbamazepine, valproate and phenytoin might affect the serum lipid profile including levels of high density lipo-protein (HDL-C), low density lipoprotein (LDL-C) and total cholesterol to HDL (TC/HDL-C) ratio [1,2]. Apo B is a prominent risk factor for atherosclerosis and coronary heart disease (CHD); whereas Apo A manifests anti-atherogenic effects. Studies have shown that the Apo B/A1 ratio is a more reliable and effective predictor of coronary disease than others [3].

The effect of anti-seizure medications on lipid profile may not directly translate into increased risk for cardiovascular morbidity as there is a paucity of literature on Apo B/A1 ratio as a cardiovascular risk for children with epilepsy. Hence, the present study was planned to assess the Apo B100/A1 ratio including lipid profile as a marker of cardiovascular risk in children with epilepsy (CWE) on long-term anti-epileptic monotherapy.

This prospective cohort study was conducted in the department of biochemistry and pediatrics at our tertiary care teaching hospital. An institutional ethics committee approval was sought, and written informed consent was obtained from the caregivers of all participants. Children with epilepsy aged 5-14 years who were planned to be started on monotherapy with either sodium valproate, oxcarbazepine, or levetiracetam were enrolled consecutively. Children with a body mass index of more than the 95th percentile were also excluded. Children with known chronic renal disease, chronic liver disease, progressive neurological disorder, or congenital heart disease were excluded from the study. Children who were receiving any drug that could affect lipid metabolism were also excluded. A convenience sample size of 15 children each planned for sodium valproate, oxcarbazepine and levetiracetam were chosen. The eligible participants were enrolled consecutively till a desired sample size of 15 was achieved for each anti-seizure medication. Baseline demographic and clinical details of the enrolled participants were recorded. Their treatment records were retrieved.

A blood sample (4 mL) was collected twice, once at baseline when AED was commenced and at a six-month follow-up. The serum was separated by centrifugation and was preserved at -20^0C. Baseline hemogram, liver function test, renal function test, random blood sugar and fasting lipid profile were estimated. Serum apolipoprotein B100 and apolipoprotein A1 were analysed by the enzyme-linked immunosorbent assay (ELISA) method [6]. ApoB100/ApoA1 ratio was computed and compared between the baseline and six months in all three groups.

Statistical analysis was performed using the Statistical package for social sciences (SPSS version 21.0). All data were entered in Microsoft Excel (MS Excel).

Table I Demographic and Clinical Profile of Children With Epilepsy

	VPA (n=15)	*OXC (n=15)*	*LEV (n=15)*
Age (y)[a]	10.2 (2.24)	10.3 (2.98)	10.2 (3.02)
Male gender	9 (60)	8 (53.33)	11 (73.33)
BMI (kg/m^2)[a]	16.8 (1.31)	17.0 (2.25)	16.7 (1.95)
Seizure type			
Focal	11 (24.4)	9 (20)	8 (17.8)
Generalized	3 (6.67)	4 (8.89)	6 (13.3)
Unknown	1 (2.22)	2 (4.44)	1 (2.2)
Diagnosis			
Neurocysticercosis	7 (15.6)	5 (11.1)	9 (20)
Post-meningitic sequaelae	1 (2.22)	0	1 (2.2)
Encephalitis sequalae	1 (2.2)	0	0
Tubercular meningitis	3 (6.7)	2 (4.4)	3 (6.7)
Febrile seizures	1 (2.2)	0	1 (2.2)
Idiopathic epilepsy	2 (4.4)	8 (17.8)	1 (2.2)
Abnormal EEG record	1 (2.2)	2 (4.4)	1 (2.2)
Abnormal neuroimaging	4 (8.9)	2 (4.4)	2 (4.4)

All values in no. (%) or [a]mean (SD). VPA: sodium valproate; OXC: oxcarbazepine; LEV:levetiracetam.

Table II Apolipoproteins and Apo B/100/A1 Ratio of Children With Epilepsy (*N*=45)

	At baseline	*At 6-mo follow-up*
Valproate group, n=15		
Apo A1 (ng/mL)[a]	234.5 (137.0)	154.7 (69.37)
Apo B100 (ng/mL)	193.3 (137.73)	152.0 (133.57)
Apo B100/A1 ratio	0.9 (0.89)	1.1 (1.1)
Oxcarbazepine group, *n*=15		
Apo A1 (ng/mL)	182.7 (71.81)	171.1 (70.20)
Apo B100 (ng/mL)[a]	140.8 (89.59)	295.3 (246.47)
Apo B100/A1 ratio	0.9 (0.63)	1.8 (1.11)
Levetiracetam group, n=15		
Apo A1 (ng/mL)	170.0 (64.24)	147.0 (58.12)
Apo B100 (ng/mL)[b]	211.0 (163.15)	218.6 (103.00)
Apo B100/A1 ratio	1.2 (0.87)	2.0 (1.71)

Values in mean (SD). [a]*P<0.05;* [b]*P=0.05.*

Categorical variables were expressed as numbers (percentage) and continuous variables as median (IQR). The ApoB100/ApoA ratio and other continuous variables were compared between the groups and within the group using Wilcoxon signed rank test and paired student *t* test or Kruskal Wallis test. Values of ApoB100 and ApoA were correlated among the three groups using the Spearman correction coefficient. *P* value equal to or less than 0.05 was considered significant.

In the present study, out of the 45 children, 15 children each on monotherapy with valproate, oxcarbazepine, and levetiracetam were enrolled. The baseline demographic profile and disease characteristics were comparable between the groups (**Table I**). Only one child on oxcarbazepine required increase in the dose after one month and was then well controlled on same dose till 6-month follow-up period. No child required addition of new anti-seizure medication or change of medication in the 6-month follow-up period.

The mean serum ApoA1 level decreased significantly after six months of valproate therapy, whereas serum ApoB100 levels had a significant increase in the oxcarbazepine group (**Table II**). Apo B100/A1 ratio increased significantly in oxcarbazepine group. (*P*=0.05) (**Table II**). There was a signi-ficant positive correlation between ApoB100 and ApoA levels among those who received OXC therapy (r=0.74; *P*=0.01). However, the correlation was not significant in the VPA (r=0.17; *P*=0.54) and LEV (r=-0.45; *P*=0.09) groups (**Fig. 1a-c**). There was a significant fall in the HDL levels and a rise in the VLDL level in the valproate group. The rest of the biochemical laboratory parameters did not reveal any significant change before and after the drug administration and were also comparable between the three groups (**Web Table I**).

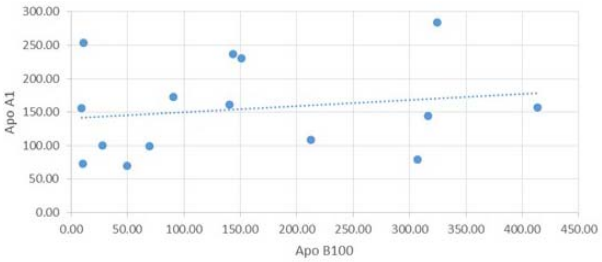

Fig. 1a Correlation of Apo B100 & A1 among group A after six months of VPA monotherapy.

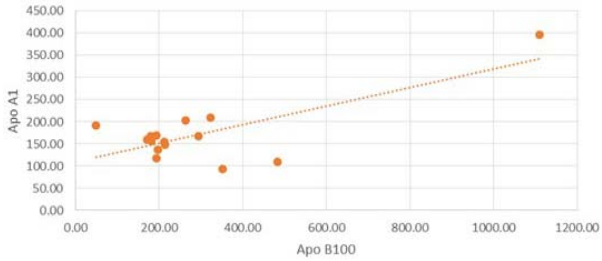

Fig. 1b Correlation of Apo B100 & A1 among group B after six months of OXC monotherapy.

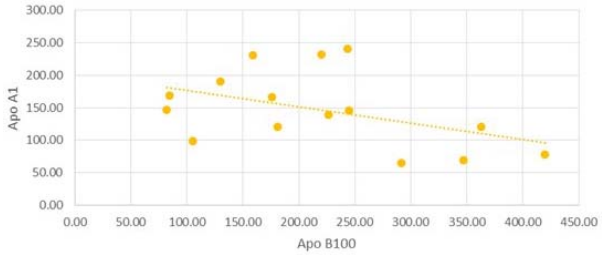

Fig. 1c Correlation of Apo B100 & A1 among group C after six months of LEV monotherapy.

Apo B100/A1 ratio has been reported as a sensitive measure of atherogenicity. Literature reveals that higher the value of Apo B100/A1 ratio, the higher is the risk of future cardiovascular and cerebrovascular disease [3, 5]. The ratio of Apo B100/A1 is considered a better indicator for the new cardiovascular events than the lipid profile [5]. The present study with a limited sample size found a statistically significant increase in Apo B100/A1 ratio among children receiving oxcar-bazepine monotherapy for six months.

The lipid-raising effect of AEDs may be due to the induction of cytochrome enzymes. Cyt p450 enzyme system is involved in the synthesis and metabolism of cholesterol and enzyme-inducing drugs also stimulate the endogenous hepatic synthesis of cholesterol. However, adverse lipid profile has been reported with both enzyme-inducing and enzyme-non-inducing anti-seizure medications [6].

Our findings are consistent with the findings of other authors who have also revealed deranged lipid profiles with the use of oxcarbazepine, even after 3 months of therapy [7]. These findings are in congruence with others, who have demonstrated a neutral effect on Apo B100/A1 in those who were on mono-therapy with levetiracetam [8]. Kim, et al. [9] reported a significant increase in LDL-C, apo B, and Apo B/A1 ratio after six months of monotherapy with levetiracetam, oxcarbazepine and topira-mate. There was no significant increase in Apo ratio in the valproate group, which was consistent with previous literature. Increased total cholesterol, triglyceride, LDL-C and apo B100 have been reported with VPA in epileptic children [10].

The limitations include a small sample size in each group, and limited follow-up till 6 months. The enrolled participants have a wide heterogenicity thus limiting the generalizability of the study results. In addition, dietary pattern of fat intake during the six-month follow-up period was not documented, which could confound the results in all the three groups. Further studies could be planned with a sufficient sample size and a follow-up period of 1-2 years. In the future studies, children with family history of premature cardiac deaths may also be excluded considering its association with mortality related to cardiovascular diseases.

The findings of the present study raise a concern about potential cardiovascular risk in terms of the ApoB100/ApoA level ratio among children receiving oxcarbazepine mono-therapy. Confirmation of these findings from larger, multicentric studies with dietary data will quite further policy regarding monitoring and follow up of children on oxcarbazepine monotherapy.

Ethics clearance; IEC, Pt. BD Sharma PGIMS; No. BREC/Th/19/Bio/02, dated Dec 26, 2019.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Laboratory Parameters of Enrolled Children With Epilepsy

Characteristics	*Sodium Valproate group*		*Oxcarbazepine group*		*At baseline At 6-mo follow-up*	
Hemoglobin (g/dL)	11.55 (0.73)	11.49 (1.14)	11.68 (0.76)	11.39 (0.84)	11.9 (0.90)	11.58 (0.77)
Total leukocyte count (cu mm)	9.09 (1.40)	8.77 (1.65)	9.77 (1.93)	9.41 (0.85)	9.14 (1.83)	8.97 (1.54)
(creatinine (mg/dL)	0.71 (0.1)	0.68 (0.07)	0.61 (0.16)	0.70 (0.13)	0.76 (0.20)	0.75 (0.12)
AST (U/L)	29.13 (8.77)	26.33 (8.03)	35.60 (14.39)	30.80 (23.49)	35.53 (24.12)	27.67 (23.92)
ALP (U/L)	213.07 (51.16)	234.73 (90.50)	226.07 (43.16)	263.80 (140.90)	187.40 (69.46)	225.53 (55.53)
Albumin (gm/dL)	3.25 (0.86)	3.04 (1.06)	3.28 (1.14)	3.13 (1.12)	3.52 (1.17)	3.46 (1.01)
Amylase (mg/dL)	73.8 (28.13)	75.67 (24.22)	78.40 (30.52)	81.13 (23.52)	89.47 (28.68)	80.60 (10.62)
Blood glucose (mg/dL)[a]	92.93 (14.45)	92.67 (13.10)	86.93 (11.11)	88.0 (10.92)	101.73 (23.77)	87.53 (8.77)
Triglycerides (mg/dL)	99.53 (42.63)	100.60 (40.61)	132 (98.48)	136.93 (49.84)	117.33 (59.17)	123.87 (49.87)
Cholesterol (mg/dL)	149.67 (24.27)	159 (41.43)	142.07 (34.34)	159.07 (24.11)	150.27 (26.31)	163 (48.16)
HDL (mg/dL)[b]	57.47 (11.92)	54.13 (11.27)	50.20 (10.29)	44.60 (17.55)	56.83 (13.06)	53.20 (18.57)
LDL (mg/dL)	71.67 (21.76)	84.93 (38.90)	69.33 (25.20)	82.20 (20.80)	70.80 (28.81)	86.27 (32.47)
VLDL (mg/dL)[c]	19.93 (8.45)	20.53 (8.05)	26.67 (19.74)	28.13 (10.58)	23.53 (11.84)	24.67 (9.88)

All values in mean (SD). All between group (VPA-OXC-LEV) P> 0.05; All within group comparison (before-after) P values>0.05 in all groups except in Lev group=0.01; [b]VPA group=0.02; [c]VPA group=0.01$ HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein

Neurological Manifestations in Rotavirus Gastroenteritis in Children Under two Years of Age

Rotavirus infection is usually localized to the intestine but involvement of central nervous system (CNS) has been reported along with norovirus and adenovirus. The pre-valence of neurological manifestations is 2-5% in children with rotavirus gastroenteritis, which includes encephalitis, encephalopathy and epileptic seizure [1,2]. In addition, rotavirus is known to cause mild encephalopathy/encephalitis with a reversible splenial lesion (MERS), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) and acute necrotizing encephalopathy (ANE) in children [3]. Convulsions associated with gastro-enteritis are yet to be recognized as an epilepsy syndrome or situation-related seizures by the International League Against Epilepsy (ILAE) [4]. In spite of high incidence of rotavirus gastroenteritis, there are very few reports on child-ren presenting with acute gastroenteritis (AGE) and neuro-logical symptoms, its etiology and clinical outcome from our country [5].

A total of 57 children with acute gastroenteritis and neurological manifestations were screened for rotavirus between October, 2013-May, 2016 and 12 were found to have rotavirus in stools. Of these, we report four children in whom rotavirus RNA was detected both in stool and (CSF) samples. The four children had history of convulsion and passage of loose watery stool 8-10 times in a day with no dehydration, but had (single/multiple) episodes of febrile/afebrile convulsions. Seizure semiology was sequential progression from non-motor (behavioral arrest) to motor (multi focal clonic) seizures. Sleep EEG showed genera-lized rhythmic high amplitude theta activity over a normal background. Three children under 6 months of age were exclusively breastfed; one child under 6 months of age had similar history of diarrheal episode in her family. All three children had normal anthropometric measures. Serum electrolytes were within the normal range in all the patients (**Table I**).

CSF was collected by lumbar puncture and examined for routine biochemistry, cell type, cell count and was also tested for rotavirus by nucleic acid based molecular assays (RT-PCR) for VP7 gene (G type). We collected stool samples in McCartney bottles using sterile catheters and examined the samples within 2 hours for enteric pathogens comprising bacterial, viral and parasitic pathogens using conventional, immunological and molecular methods. Stool samples were tested for bacteria (salmonella, shigella, aeromonas, vibrio, campylobacter, *E. coli*) parasites (Giardia and entameba) and viruses (group A and adenovirus 40/41). The samples negative for bacterial and parasitic pathogens were tested for viral pathogens. Both stool and CSF samples were screened by immune-chromatography for the presence of enteric adenovirus and group A rotavirus VP6 antigen. The presence of viral genome was confirmed by amplification of rotavirus VP7 gene (G genotype) by conventional RT-PCR method in both stool and CSF samples. Rotavirus RNA was present in stool and CSF of all four children.

All the patients were receiving oral rehydration solution at home, before admission, and did not have dehydration at presentation. Oral antibiotic was prescribed at primary health care level. Antipyretic and anti-emetic was given for fever and vomiting. Adequate hydration was maintained, the course was benign and longterm anti-seizure medicine was not required. All the patients improved within 5-7 days and no fatality was reported.

We also observed that 66.7% (8/12) children with rotavirus infection with negative rotavirus RNA in CSF did not have seizure during the second episode of fever. In this aspect an important hypothesis is the pathomechanism of low-grade inflammation (encephalopathy) by the Rotavirus itself. Minami, et al. [6] measured the elevation of serum IL-6 and TNF-α, CSF IL-6 and IL-8 levels and suggested encephalopathy as a consequence to systemic immune response to cytotoxicity. Another possible explanation is increased concentration of carnitine in CSF reported in some cases, which may damage blood brain barrier. Alternatively, shared peptide hormones between the brain and the gastrointestinal tract, associated with spontaneous electrical epileptogenic activity and lowered seizure threshold seen in some adults, could be a contributing factor to the occurrence of afebrile convulsions during gastroenteritis [7]. More studies are needed to understand the pathophysiology of afebrile seizures in gastroenteritis. Moreover, concomitance of febrile and afebrile convulsions to rotavirus gastroenteritis are reported as 1.2-6.4% [8]. Thus, it is important to identify other probable causes for convulsions, other than electrolyte imbalances, destruction of blood-brain barrier by fever or encephalopathy and encephalitis [8].

Further evaluation may be needed to understand the pathogenesis in our case, which could possibly be because of some inflammation due to systemic immune response to cytotoxicity. Rotavirus encephalitis is a complication that is not

Table I Clinical Characteristics of Children With Rotavirus Diarrhea and Neurological Manifestation With Detection of Group A Rotavirus (GARV) Gene in Stool and Cerebrospinal Fluid (CSF)

Case	*Age/sex*	*Presenting history*	*Fever*	*Biochemical test*	*Cerebrospinal fluid (CSF) analysis*	*Rotavirus VP7 (G type)*	
						Stool virology	*CSF*
1	4 mo/F	Diarrhea,vomiting, drowsiness	Afebrile	Na - 136 mmol/L K-3.8 mmol/L Ca- 9.2 mg/dL Glucose- 96 mg/dL	Glucose-64 mg/dL Protein-86 mg/dL Cells-10/µL	Positive G9	Positive (G Typing NT)
2	3 mo/F	Diarrhea, convulsion	Febrile	Na -142 mmol/L K-4.1 mmol/L Ca-9.5 mg/dL Glucose- 120 mg/dL	Glucose-80 mg/dL Protein-75 mg/ dL Cells-8/µL	Positive G1	Positive G1
3	5 mo/F	Diarrhea, convulsion	Febrile	Na -139 mmol/L K-4 mmol/L Ca-9.3 mg/dL Glucose-80 mg/dL	Glucose- 55 mg/dL Protein- 60 mg/dL Cells- 12/µL	Positive G1	Positive (G Typing NT)
4	14 mo/M	Diarrhea, convulsion	Febrile	Na-140 mmol/L K- 4.2 mmol/L Ca-9.6 mg/dL Glucose-95 mg/dL	Glucose-65 mg/dL Protein- 100 mg/dL Cells-20/ µL	Positive G1	Positive G1

M: male; F: female; Na: sodium; K: potassium; Ca: calcium; NT: non typable.

so rare as is evidenced from reports. We recommend that rotavirus etiology should be investigated for in children having seizures during episodes of gastroenteritis.

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Early Onset Refractory Anti-NMDAR Encephalitis in a 13-Month-Old Infant

Anti-N-methyl-D-aspartate (anti-NMDAR) encephalitis is a common cause of encephalitis in children. Previous studies on toddlers with NMDAR encephalitis have shown that the earliest presentation in this age group is behavioral changes [1,2]. Nevertheless, distinguishing anti-NMDAR encephalitis in infants and toddlers on initial presentation may be quite challenging as initial symptoms could be non-specific. We report the clinical picture of an infant with anti-NMDAR encephalitis.

A 13-month-old girl presented with a history of cough and cold followed one week later by irritability and intermittent brief episodes of staring look. After 4-5 days, she developed sleep disturbances, sleeplessness, excessive crying, right focal seizure and brief intermittent twitching movement of right face, lasting 5-15 seconds. She had no significant birth history, past history or family history. Her developmental milestones were normal for age. On examination, she was irritable and had oromotor and limb dyskinesia. She had received a course of oral antibiotics before being referred to our center. Her hemogram, C-reactive protein (CRP), serum electrolytes, and liver and renal function tests were within normal range. At this stage, acute encephalitis syndrome/ herpes simplex viral (HSV) encephalitis was suspected and magnetic resonance imaging (MRI) brain was done, which was normal. EEG showed left hemispheric seizure onset with background slowing. Her cerebrospinal fluid (CSF) cell count was 23/mm^3 (100% lymphocytes) with normal protein and glucose. Her CSF HSV-DNA polymerase chain reaction (PCR) was negative. Based on clinical presentation of seizure/ abnormal movements and altered sleep pattern, anti-NMDAR encephalitis was suspected. Her CSF was sent for anti-NMDAR antibody levels, and treatment with intravenous methylprednisolone was started. Her CSF anti-NMDAR IgM antibody was reported positive.

After 4 days of hospitalization, she developed loose stools, gaseous abdominal distension with raised CRP. She had intermittent episodes of moderate to high grade fever, which went on for about a month. Her blood, urine, stool and CSF cultures had no growth. Due to fever, loose stools and high CRP, treatment with intravenous antibiotics (piperacillin, metronidazole) was started empirically. Repeat MRI brain after one week showed right cerebellar and left hippocampus T2W/FLAIR hyperintensity without diffusion restriction. Her stool frequency reduced over the next three weeks. Her ultrasound (USG) whole abdomen and pelvis was normal. She had ongoing dystonia /dyskinesia during awake state. She was given tetrabenazine, trihexphenidyl and clonidine for involuntary movements, to which she responded partially. After methylprednisolone, she also received two days of intravenous immunoglobulin (zg/kg). But due to partial response to these immunosuppressive therapy, she was started on weekly doses of rituximab after one month after the onset of illness.

After one month of hospitalization, child was followed-up for weekly rituximab for total of three doses and maintenance dose of IVIG every three weeks. After 3 doses of rituximab, her CD19 count was 0 cells. At 3 month follow-up, she was afebrile with significant reduction of involuntary movements and improvement in alertness. Her follow-up EEG at 3 months showed low amplitude background with poorly formed age appropriate sleep background. Due to persistent clinical symptoms and CSF antibodies, treatment was started with cyclophosphamide dose every 3 weeks for total of five doses. As repeat CSF anti-NMDAR antibody was negative at 6 months from disease onset, she was not given long-term immune therapy. Follow-up MRI at one year showed diffuse cortical atrophy. At one year follow-up, she had some clinical improvement in developmental milestones with minimal dyskinesia. She could achieve head control, sitting balance with support, and could reach out for objects using hands, but was non-verbal.

The clinical symptoms of anti-NMDAR encephalitis are complex, especially in younger pediatric patients, and many clinicians cannot promptly distinguish them from those of other diseases such as viral encephalitis or psychological conditions. Patients typically present with psychiatric symptoms, behavioral dysfunction, seizures, speech and cognitive impairment, movement disorders, decreased consciousness, autonomic instability, and central hypoventilation [1,2]. In children, most commonly, the first presentation may be nonpsychiatric, including seizures [2]. Although paroxysmal events may appear as intractable epileptic seizures, recording of these events often discloses no epileptic discharge and these events prove not to be epileptic [3].

Fever and diarrhea in this girl was probably due to autonomic dysfunction, which are well described in anti-NMDAR encephalitis [2,4]. Cardiac arrhythmias, hypotension, hypertension, hypoventilation, and hyper-or hypothermia have all been described. Although, the initial symptoms in our patient were seizures, movement disorder and altered sleep pattern, the presence of a fever and gastroenteritis posed an initial management challenge. Children with NMDAR encephalitis commonly experience prodromal symptoms such as fever and vomiting [4]. The spectrum of symptoms usually progresses to include seizures and sleep disturbances [5]. The dystonia, involuntary movements and orofacial dyskinesia noted in our patient are

the most commonly reported motor manifestation in toddlers [6]. In a case series from India [7], among 11 patients of pediatric anti-NMDAR encephalitis (age 2.5 to 18 years, mean 9 years) common presentations were progressive extrapyramidal syndrome with neuroregression, seizure (generalized: 64%, focal:36%), sleep disturbances, psychiatric manifestations and autonomic instability [7].

Investigations are usually necessary to exclude other pathologies that may mimic NMDAR encephalitis, notably other types of encephalitis. Currently, commonly used first line immune-therapies include high-dose corticosteroids, IVIG and plasmapheresis. Second-line therapies include rituximab and cyclophosphamide [8,9]. Earlier treatment of anti-NMDAR encephalitis is associated with better outcomes [10]. Children have been reported to recover faster than adults, usually within six months [11]. Toddlers have a good prognosis, with full recovery in 67% of patients and no reports of mortality [1]. Cases in children and adults reported generalized/fronto-temporal and potentially reversible cortical atrophy as sequelae of anti-NMDAR encephalitis leading to changes in behavior, learning, and memory. NMDAR is present in high density in the fronto-temporal area, suggesting an immunological cause of the brain atrophy of these area [12].

In conclusion, we believe that Anti-NMDAR encephalitis is probably underreported in infants and young children due to its varied clinical presentation. Its early diagnosis can hasten initiating proper management and early recovery.

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Calcified Neurocysticercosis- Are We Missing Something?

We read the recent article by Shanmugavel, et al. [1] with interest. Out of 30 patients with active neurocysticer-cosis (NCC), 8 patients had vesicular lesions and 16 had colloidal lesions. However, the stage of the lesion was not mentioned for the remaining 6 (20%) patients, which we presume to be nodular, considering that calcified or partly calcified lesions were excluded from the study. Authors mention that 10 of them had more than one lesion but number of lesions among each subject was not described.

It is known that the rate of calcification is higher among children with multiple lesions compared to that of single lesion [2]. Moreover, authors have represented the proportion of those with calcification as number of individuals who developed calcified NCC instead of number of lesions that calcified. In a previous study, the proportion of calcification was demonstrated as 37.8% among 147 patients (188 cysts developed calcification out of 497 cysts) [3]. Timing of the repeat imaging will also determine the rates of calcification. Studies have demonstrated 32.5-37.8% rate of calcification when the neuroimaging was performed at one-year follow-up instead of 6-month follow-up [3,4].

It is possible that higher rates of calcification observed by the authors could have been because the number of patients instead of number of lesions was considered as the denominator for calculating the rate of calcification. In addition, it was interesting to see the severity of perilesio-nal edema being described in the methodology but the same was not considered for estimating the predictors of calcifi-cation. Calcified lesions are associated with perilesional edema and recurrence of seizures [5]. It would have been interesting to know whether the extent of perilesional edema is a predictor for calcification. Similarly, authors could also consider mentioning how many of the calcified lesions had perilesional edema at follow-up image, and whether the patients had any recurrence of seizures.

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REPLY

We thank the readers for their interest in the study [1]. Our clarifications follow:

As deduced by the readers, the rest of the cases were nodular lesions. As we knew neurocysticercosis most commonly presents as single lesion, we took single lesion as one group and more than one lesion as another group.

Follow-up imaging has been done in previous studies from 3 month to one year [2-4]. So, we did follow-up imaging at 6 months. It is possible that by doing neuro-imaging later, calcification rate might change.

We used perilesional edema based on severity as a possible predictor, with mild, moderate and severe being the three groups. However, in our study group of 30 children, no case of severe perilesional edema was found. Sixteen out of 30 lesions were calcified in our research, and only one case of recurrent seizure occurred on follow-up. This child with recurrent seizures had calcified lesion.

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LATCH Score: Bridging the Gap in the Observational Study

We read with interest the study on LATCH score in the recent issue of the journal [1]. We wish to raise a few issues related to this study.

The paper fails to define clearly the target population under study. They could have included the geographical and socioeconomic description of population under study.

Follow-up may have been ensured in the study as many neonate-mother dyads encounter various problems regarding breastfeeding later on in the infancy. A six months follow-up regarding adherence to exclusive breastfeeding may have led to a better assessment of the impact of breastfeeding training imparted to the mothers.

Many neonatal conditions which could have interfered with breastfeeding and hence, outcome of the study, like cleft lip/palate, facial nerve palsy, low birth weight, traumatic delivery, nose block, choanal atresia and other congenital malformations could have been excluded from the study population.

Separate research staff could have been used as trainers of breastfeeding and observers of final outcome. Blinding of final outcome observer could have been done for eliminating the observer bias.

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AUTHORS' REPLY

We thank the authors for their interest in our work [1]. All the neonates who did not require neonatal intensive care unit (NICU) admission were included in the study. We agree that geographical and socioeconomic factors are more likely to influence breast feeding after discharge in the home setting, but our study was focussed on early breast feeding problems in the immediate postnatal period. Thus, follow-up of mother-infant dyads was not in the scope of the study; though, it would have definitely added more information on the long-term effects of training in the immediate postnatal period. All neonates weighing less than 2.2 kg were excluded from the study, which is the admission criteria for our nursery, and none of the included neonates had congenital abnormalities, which interfere with breast feeding. Having two different groups of nurses with one set of nurses providing training to mothers and the other set of nurses making LATCH assessment would have eliminated the observer bias. However, due to the availability of a small pool of nurses, it was not possible to utilize this strategy.

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NEWS IN BRIEF

ChatGPT for Psychotherapy

Telehealth exploded in the COVID pandemic. As did mental health problems. Psychiatrists were quick to adapt to the new paradigm. Online psychotherapy became common and there is even evidence to show its equivalence to in-person therapy. A large meta-analysis from University of Memphis found no difference in the efficacy of in-person clinical interventions versus that using video-conferencing by psychia-trists. This is a game changer considering that there are only 4 psychiatrists per 100,000 population worldwide.

But a recent report of the use of the artificial intelligence (AI) chatbot Chat GPT for psychotherapy has raised questions about ethics and long term consequences of technology that is not perfectly understood. The first chatbot called Eliza was invented in MIT in the 1960s by Joseph Weisenbaum. He trained the program to respond to human speech using various rules such as pattern matching and substitution methodology. It was an unexpected success with human beings attributing unwarranted feelings like empathy to this crude program based on Rogerian therapy techniques.

A recent tweet by Rob Morris, founder of the mobile mental health app- Koko has created a storm. Koko essentially provides support for people labouring under mental stress via replies which are crowd sourced. However, in October, 2022, the app started providing some suggestions on how to interact with the person under stress. These suggestions were written up by the chatbot GPT-3.

The concerns which people have regarding AI-based psychotherapy include safety, privacy and legal liability. There are reports of personal data being sold or leaked. Further, evidence of its efficacy has not been studied.

But it appears that AI-based health care interventions are here to stay. What we need to do is to strengthen the check and balances of this nascent technology. (*Nature 3 May,2023*)

The Loneliness Epidemic

The Surgeon General of America has released an advisory bringing attention to the problem of widespread social disconnectedness in the US and possible strategies to mitigate it. More than 50% of adults in the US struggle with loneliness, and it appearto be equally common in childhood. It has been seen that the mean time spent with friends among 15-24-year-olds has decreased by 70% from 150 minutes/day in 2003 to 40 minutes per day in 2020. Single person households have increased from 13% in 1960 to 29% in 2022.

The consequences are significant. Data across 148 studies with an average of 7.5 years follow-up has revealed that social connection increases the odds of survival by 50%. Social isolation increases the risk of heart disease by 29%, stroke by 32% and dementia by 50%. Even childhood social isolation is associated with higher risks of obesity, hypertension and high blood glucose levels in adulthood.

How does social connection affect our health? They do so by changing biological processes like stress hormones, by changing behaviors like time spent on exercise and by changing by mood.The surgeon general has suggested a framework along which national policies can be decided to mitigate the widespread epidemic of loneliness. The first is to design environments which promote connection such as parks, libraries and community halls. The second is to enact policies which support connection such as good public transport and paid family leave. The third is to sensitize healthcare professionals to identify and advise risk factors for social disconnectedness. The fourth is to critically monitor our interaction with digital technology. The fifth is to encourage further research into the causes and consequences of socialization. And the last is to foster a culture of social interaction. (*https://www.hhs.gov/about/news/2023/05/03/new-surgeon-general-advisory-raises-alarm-about-devastating-impact-epidemic-loneliness-isolation-united-states.html*)

WHO Advisory on Valproate Use in Girls

The WHO has announced a safety statement regarding the use of valproate in women and girls with child bearing potential. Because of the enhanced risk of birth defect and developmental disorders associated with valproate exposure in utero, it is suggested that valproate is avoided in women and girls after puberty. The recommended drugs for both focal and generalized seizures are either lamotrigine or levetiracetam.

Those who are already on sodium valproate must be advised regarding contraception use if there is chance of pregnancy. One must make effort to switch to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the risks of valproic acid (sodium valproate) for the unborn child to support her informed decision-making. A specialist should periodically review whether valproic acid (sodium valproate) is the most suitable treatment for the person. (*https://www.who.int/news/item/02-05-2023-use-of-valproic-acid-in-women-and-girls-of-childbearing-potential)*

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CLIPPINGS

EULAR/PRES Recommendations for vaccination of pediatric patients with autoimmune inflammatory rheumatic diseases: update 2021 (Ann Rheum Dis. 2023; 82:35-47)

The paper outlines recommendations for vaccinating pediatric patients with autoimmune and inflammatory rheumatic diseases (AIIRD). The principles emphasize the importance of vaccination, alignment with national immunization programs, administering vaccines before starting immunosuppressive drugs, following specific recommendations for each vaccine, using non-live vaccines for patients on glucocorticosteroids or disease-modifying antirheumatic drugs (DMARDs), and avoiding live-attenuated vaccines for immunosuppressed patients. The specific recommendations include strongly consi-dering non-live seasonal influenza vaccination for patients on glucocorticosteroids or DMARDs, providing pneumococcal vaccination (PCV10 or PCV13) to non-vaccinated patients, following general guidelines for tetanus vaccination with additional precautions for patients on B-cell depleting therapy, recommending HPV vaccination for all AIIRD patients, avoiding yellow fever vaccination for immunocompromized patients, and limiting live attenuated vaccines except for MMR booster and varicella vaccination under specific conditions. These principles and recommendations serve as guidance for healthcare professionals when making vaccination decisions for pediatric AIIRD patients, considering factors such as the disease, treatment, and individual characteristics.

Favorable outcomes with reduced steroid use in juvenile dermatomyositis (Pediatr Rheumatol Online J. 2021; 19:127).

This retrospective analysis of 31 juvenile dermatomyositis (JDM) patients explored the use of reduced doses and durations of glucocorticoids with early steroid-sparing agents. The study revealed that this approach yields comparable outcomes to the conventional high-dose, long-duration steroid therapy for JDM. The median initial gluco-corticoid dose was 0.85 mg/kg/day, and patients achieved control of myositis and cutaneous disease within median durations of 7.1 and 16.7 months, respectively. These findings support the effectiveness of reduced glucocorticoid dosing and duration in combination with early steroid-sparing agents for positive outcomes in JDM, suggesting that high-dose gluco-corticoids may not be necessary. However, to definitively determine whether lower-dose steroid regimens are sufficient or if higher doses are still needed in JDM, further investigation through a randomized controlled trial is necessary. Apart from glucocorticoid therapy, alternative treatment options for JDM include methotrexate, rituximab, hydroxychloroquine, and mycopheno-late mofetil. Encouragingly, emerging therapies like Janus kinase inhibition with baricitinib show promise in managing refractory cases of JDM.

Intravenous immunoglobulin for the treatment of Kawasaki disease (Cochrane Database Syst Rev. 2003; 2003:CD004000)

In a Cochrane systematic review of 31 studies involving 4,609 participants, the efficacy of intravenous immunoglobulin (IVIG) for Kawasaki disease was assessed. The review showed that high-dose IVIG regimens may reduce the occurrence of coronary artery abnormalities (CAA), duration of fever and need for additional treatment compared to medium- or low-dose regimens, while showing little difference in hospital stay or mortality rates. IVIG is likely more effective than acetyl-salicylic acid (ASA) in lowering CAA incidence, with a probable shorter duration of fever, but uncertain impact on additional treatment compared to prednisolone. Regarding secondary treatment options, the review did not find a clear distinction in CAA incidence between IVIG and infliximab, after resistance to initial IVIG treatment. However, there may be reduced need for further tertiary treatment in the infliximab group. Similarly, no definitive difference in CAA incidence was observed between IVIG and prednisolone, after resistance to initial IVIG treatment. These findings provide valuable insights into IVIG and alter-native treatments for Kawasaki disease, particularly regarding CAA incidence, fever duration, and additional treatment needs.

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