E-copy

Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 60
NUMBER 9
September 2023

www.indianpediatrics.net
ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

Supplement

Zincovit®

Tablets / Syrup / Drops

The **Trusted** No.1 **Brand**

(Awacs, for March 2023)

1) Junejo S, Lateef M, Eme PE. Life and Science. 2020; 1(suppl): 120-123.

The Tasty Treat... Meant...
for kids in Pyrexia...

P-100®
Drops
Paracetamol 100 mg/ml

P-120®
Suspension
Paracetamol 120 mg/5ml

P-250®
Susp/ Tabs
Paracetamol 250 mg

P-500®
Susp/ Tabs
Paracetamol 500 mg

P-250® MF
Suspension
Mefenamic Acid 100 mg & Paracetamol 250 mg/5ml

Offers Micronized Paracetamol

apex laboratories private limited SIDCO Garment Complex, III Floor, Guindy, Chennai - 600 032. INDIA
www.apexlab.com | Ph.No: 044-4222 5000

Indian Pediatrics

September 2023 Volume 60 Number 9

CONTENTS

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 34,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

Address for ordinary letters: **The Editor-in-Chief, Indian Pediatrics, P. Box No. 3889, New Delhi-110 049, India.**
Address for registered/speed post letters: **Dr. Devendra Mishra, Editor-in-Chief, Indian Pediatrics, 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049, India. Tel: (011) 46052593**
E-mail: *jiap@iapindia.org*; Website: *www.indianpediatrics.net*; LinkedIn: *indianpediatrics*
Facebook: *www.facebook.com/Indianpediatrics;* Twitter: *@EditorIndPed;* Instagram: *@indianpediatrics*

Impact of Climate Change on Child Health - A Cause for Concern!

UPENDRA KINJAWADEKAR
President, Indian Academy of Pediatrics, 2023
upen228@gmail.com

The science is clear – we are in the middle of a climate crisis, and if we do not act now, we will be jeopardizing the lives of our future generations. Climate change refers to the broad phenomenon of the average weather in a particular geography changing over time. As the concentration of carbon dioxide and other greenhouse gasses increase in the atmosphere, so does the amount of heat they trap, thus leading to rising temperatures across the globe. What's more, there is no one to blame for this phenomenon, except ourselves. Since the industrial revolution, human progress has grown together with technological and industrial innovation, which often relied on environmental exploitation with little regard to its consequences. According to the Intergovernmental Panel on Climate Change (IPCC), the earth's surface temperature has warmed by 0.75ºC in a century before 1980 [1], and temperatures have been rising twice as fast since then. Increases of this magnitude are expected to have widespread negative impacts on natural ecosystems, with cascading consequences for human health and livelihoods.

Although all of us are at risk, vulnerability is determined by [2]; the degree of *i*) exposure (such as geographies where floods and droughts are more common, or occupations where exposure hazards are higher); *ii*) ability to adapt, which is difficult for tribal or indigenous populations that rely on natural elements for their livelihoods, or impoverished communities that cannot afford external control measures such as purifiers; and *iii*) sensitivity, which is highest in children, pregnant women, people with pre-existing health conditions such as asthma. Children in low-income or developing countries are one of the most vulnerable to the effects of climate change, falling at the intersection of this tripartite segregation. In India alone, about 51% of children are living under the dual impacts of poverty and the climate emergency. The environment can impact child health through direct and indirect pathways, and have lasting impact through unwanted epigenetic developments. The diseases likely to be exacerbated by climate change are already leading causes of child morbidity and mortality, including vector-borne, waterborne and airborne diseases. Greater ambient heat also perpetuates adverse birth outcomes such as preterm births and still births.World over, approximately 1 billion children are at an 'extremely high risk' of the impacts of the climate crisis [2]. In fact, 88% of the global burden of disease from climate change falls on children under five, and an additional 5% of the burden falls on children between five and 14 years of age.

Climate Crisis As Child Rights Crisis

Introducing the Children's Climate Risk Index (CCRI) [1] by UNICEF is the first child-focused climate risk index, which ranks countries based on children's exposure to climate and environmental shocks, such as cyclones and heatwaves, as well as their vulnerability to those shocks, based on their access to essential services. India ranks 26th on this index, better than South Asian neighbors of Pakistan and Bangladesh, yet much worse compared to Bhutan, Nepal and Sri Lanka. A disturbing example in recent times is the finding that one in three children in Delhi suffers from asthma or airflow obstruction compared to 22.6% children in Karnataka's Mysuru and Kerala's Kottayam. Delhi is infamous for its air pollution, and its effects are being seen in the young, developing lungs of the children living and growing in the city [3]. In tribal and agrarian geographies, climate change is severely impacting crop harvest and food production. South Asian women usually eat last and eat the least in the family. Indirectly, the environment is perpetrating an intergenerational cycle of undernutrition in girls and women, and thus also in neonatal birth outcomes. South Asia has the highest burden of preterm and SGA babies. Our efforts to curb this cycle will be in vain if we do not account for the larger changes in our environment.

Systematic effort is required at the individual, community and political levels. At this year's COP 27, there was a global concurrence on the necessity of a 'loss and damage fund,' which is a tremendous win for developing countries. It is an acknowledgement of the fact that the majority of greenhouse emissions came from the developed countries over the 20th century, and the fund

can be seen as reparations for post-colonial or vulnerable nations that are now equally bearing the consequences. Our honorable union minister, in his speech at the same event, announced to the world that India has embarked on far-reaching new initiatives in renewable energy, e-mobility, ethanol blended fuels, and green hydrogen as an alternate energy source. These initiatives are truly laudable. We also need to initiate independent research in environmental health science, to wholly understand the impact of climate change, and how it can be controlled. Only then will advocacy for corrective policies be made possible. With the advent of mass production and consumerism in the last 50 years, per capita emissions have been rising. As the hon. minister said in his speech, we need a "*paradigm shift from mindless and destructive consumption to mindful and deliberate utilization*." Traditionally, Indian culture has always been respectful and grateful of nature's bounties. If we look at our 'kitchen science,' it has always incorporated root to shoot cooking with minimal wastage. Similar wisdom exists across our culture. As children, we were taught that when we borrow something, we must return it in a better condition. Without immediate action, the health of today's children and future generations is in great jeopardy. Our generation inherited this earth from our ancestors, and each of us must feel obligated to pass on a healthier, greener and cleaner planet earth to our children and grandchildren.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Dervis K. Devastating for the world's poor: climate change threatens the development gains already achieved. *In*: Green Our World! UN Chronicles. 2007;44. Accessed August 13, 2023. Available from:*https://www.un.org/en/chronicle/article/devastating-worlds-poor-climate-change-threatens-development-gains-already-achieved*
2. Press Release.Children in four South Asian countries at 'extremely high risk' of the impacts of the climate crisis – UNICEF.Unicef India, 2021. Accessed August 13, 2023. Available from:*https://www.unicef.org/rosa/press-releases/children-four-south-asian-countries-extremely-high-risk-impacts-climate-crisis*
3. Malhotra S. Air pollution impact: 1 in 3 school kids in Delhi are asthmatic, over 50% have allergies, says study. CNBC TV18, 2021. Accessed August 13, 2023. Available from:*https://www.cnbctv18.com/environment/air-pollution-impact-1-in-3-school-kids-in-delhi-are-asthmatic-over-50-have-allergies-says-study-10591481.htm*

INVITED COMMENTARY

Gastric Lavage in Neonates Born Through Meconium-Stained Amniotic Fluid – Does it Help?

SHIV SAJAN SAINI, PRAVEEN KUMAR*

Neonatal Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh.
**drpkumarpgi@gmail.com*

The management of neonates born through meconium-stained amniotic fluid (MSAF) has undergone dramatic changes over the years due to a better understanding of its pathophysiology and some high-quality clinical trials. For example, in vigorous neonates born through MSAF, routine endotracheal suctioning has been abandoned [1]. The trial by Chaudhary, et al. [2] has tried to investigate another common practice of gastric lavage in neonates born through MSAF. The primary purpose of GL in neonates born through MSAF is to decrease the incidence of gastritis and feeding intolerance caused by meconium. Secondarily, it may prevent respiratory distress related to aspiration of meconium due to vomiting. Therefore, all the previous trials had feeding intolerance as their primary outcome.

Chaudhary, et al. [2] in their trial, focused on exclusive breastfeeding (EBF) and early skin to skin (STS) contact as the primary outcomes. Prevention of gastritis and feeding intolerance may lead to increased rates of EBF as beneficial effects, but the inadvertent delayed initiation of breastfeeding due to the procedure of gastric lavage could also decrease the rates of EBF.The authors reported comparable rates of EBF at 72 hours (primary outcome) in the gastric lavage and no gastric lavage groups, amongst 110 vigorous (not requiring resuscitation beyond the initial steps) late preterm and term neonates born through MSAF. There were no differences in several secondary outcomes including the incidence of respiratory distress, feeding intolerance, and procedure-related complications between the two groups. However, on univariate analysis, the initiation of STS contact was significantly delayed, and the duration of STS contact was significantly lower in gastric lavage group.The reported results need to be interpreted in the context of the trial design, the population studied and baseline differences between the two groups. As per trial protocol, all vaginally delivered neonates in gastric lavage group were initiated on STS after the gastric lavage procedure was completed. It is a foregone conclusion that the initiation of STS will be delayed, and its duration will be lesser in the gastric lavage group. However, the statistical difference noted in the time of initiation and the duration of STS contact did not impact any clinical outcomes, specifically the EBF rates. It is to be noted that only 18% of neonates in the gastric lavage group were delivered vaginally as compared to 31% in the no gastric lavage group. As per local practice, cesarean born neonates did not undergo STS contact i.e., 82% of neonates in the gastric lavage group and 69% in no gastric lavage group did not undergo STS contact by virtue of being born by cesarean. If one were to choose EBF rate of 55% from the NFHS data as the baseline, to demonstrate a 25% relative reduction in EBF rate, we would require enrolling 394 infants. The investigators actually found EBF rates of 89% and 87% in the two groups and the enrolled sample size was sufficient to detect a 25% relative difference between the two groups. The incidence of feeding intolerance and respiratory distress requiring support were 1.8% and 9.1% in gastric lavage group vs 5.4% and 14.5% in no gastric lavage group, respectively. These differences were statistically not significant, but obviously the power to detect a significant difference was extremely low because of the very small sample size. A systematic review of six clinical trials including 1884 neonates, published in 2015, found a significant reduction in the incidence of feeding intolerance (RR 0.71, 95% CI 0.55-0.93) [3]. A subsequent systematic review of 3668 neonates from nine RCTs showed a similar statistically significant reduction in the incidence of feeding intolerance after gastric lavage (RR 0.70, 95% CI 0.58-0.85) [4]. The incidence of feeding intolerance in the control group in the systematic review was 11.8% as against 5.4% in the current trial [4]. The incidence is affected by the variations in definitions of feeding intolerance used across the studies. The incidence of meconium aspiration syndrome was too low in both the reviews to detect any significant difference. The overall quality of evidence; however, was low.

The authors' conclusion that routine gastric lavage 'appears unwarranted' in vigorous late preterm and term neonates born through MSAF is not supported by the data. The study; however, does raise a valid question about the benefits and harms of doing gastric lavage in neonates born through MSAF and indicates that the practice is based on

weak evidence. Gastric lavage may decrease feeding intolerance, need for intravenous fluids, and respiratory distress but it may have adverse effects of desaturations, bradycardia, delaying STS contact and breastfeeding. Only an adequately powered large multi-site clinical trial can provide a definitive answer.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Vain NE, Szyld EG, Prudent LM, Wiswell TE, Aguilar AM, Vivas NI. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicentre,randomised controlled trial. Lancet. 2004;364: 597-602.
2. Chaudhary RK, Chaurasia S, Singh P, et al. Impact of delivery room gastric lavage on exclusive breastfeeding rates among neonates born through meconium-stained amniotic fluid: a randomized controlled trial. Indian Pediatr. 2023 Mar 20: S097475591600515. Epub ahead of print.
3. Deshmukh M, Balasubramanian H, Rao S, Patole S. Effect of gastric lavage on feeding in neonates born through meconium-stained liquor: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2015;100:F394-9.
4. Singh P, Kumar M, Basu S. Gastric lavage for prevention of feeding intolerance in neonates delivered through meconium-stained amniotic fluid: a systematic review and meta-analysis. Indian Pediatr. 2021;58:973-7.

INVITED COMMENTARY

Nasogastric or Orogastric Feeding in Stable Preterm Neonates?

ASHISH JAIN,* CHANDAN S

Department of Neonatology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi 110002.
**neoashish2008@gmail.com*

Aggressive early enteral nutrition is important in preterm low birth weight (LBW) infants to prevent extra-uterine growth retardation (EUGR) and to ensure better neurodevelopmental outcome. Establishment of direct oral feeding is often delayed in preterm neonate because of poor coordination of sucking and swallowing, neurological immaturity and respiratory distress. Gavage feeding via orogastric (OG) or nasogastric (NG) tube is an often-used strategy in NICUs to ensure adequate nutrition in preterm who have yet have not developmentally achieved the neuromotor and feeding mechanism maturity for a good swallow and breathe coordination. As soon as they achieve this coordination by approximately at 30-32 weeks, the cup or the *katori* spoon feeding is initiated. By 34 weeks most of the babies can be put onto breastfeeds. Even though, there is a rationale and a consensus about the choice of modality of feeds in preterm, there is lack of definitive evidence on superiority of one method over the other when it comes to gavage feeding with OG or NG [1]. Policy and practise varies widely between and within neonatal care units.

With the limited literature on the physiological changes in these modalities in human neonates, it is prudent to believe that the OG may have an advantage of patency of nares in neonates who are obligatory nose breathers. However, the pharyngeal vagal stimulation may be a concern.On the other hand, the health care providers find it easier to place and fix the NG tube and perceive the lesser migration and displacements. The daily and frequent use of this practice in the neonatal practice makes it very important to systematically investigate thisintervention.

Hence, when the researchers studied and compared these intervention, they looked into the outcomes like physiological compromise during the procedure, pain during the procedure, duration of cry and other developmental unsupportive experiences by the neonates. With regard to sustenance of the tube in place, the outcomes like quantum of displacements, time spent on the care of the tube, time to full feeds and hospital stay days were investigated. The current study also tried to look at these outcomes.

Rao, et al. [2] demonstrated mean frequency of tube displacements were 0.55/day among NG tube feeding and 1/day among orogastric tube feeding group, which was statistically significant, and there was no significant difference between the groups in time to reach full feeds and duration of hospital stay. On a closer look in the physiology, Upadhyay, et al. [3] showed mean $crSO_2$ (cerebral regional oxygen saturation) during insertion was significantly lower with NG compared to OG route. Mean PIPP-R score, heart rate variability, time to normalize crSO2 and the duration of cry were also significantly higher with NG insertion. However, this was not consistent with study by Bohnhorst, et al. [4] who suggested that route of placing the feeding tube had no significant effect on the summed rate of bradycardia and desaturation. The study could not confirm any advantage of placing tube orally in the infants, the possible explanations proposed were viz., the increase in nasal airway resistance by the 5F nasogastric tube, inserted into the smaller nostrils, is too small to have any effect on apnoea;any benefit of the oral route is neutralized by the negative effects of an enhanced vagal stimulation; the study duration was too short to detect any finding [4]. Findings similar to these were reported by Badran, et al. [5], where preterm infants who were fed via bolus NG tube achieved full enteral feeding in a signi-ficantly shorter duration compared with the infants fed via OG tube. The incidence rates of aspiration and feeding tube displacement were significantly higher in the bolus OG tube group. There was no difference in the incidence rates of apnea, NEC, bradycardia, oxygen desaturation and gastric residual in both groups [5].

However, one gap exists in these studies is that even though, this is a core developmental issue, none of the studies systematically reported the outcomes based on the gestational age. Hence, uncertainty exists with the similar findings in a spectrum of different gestation and growth categories. It would have been good if the current study looked and reported this.

As, discussed both the routes have their own benefits and disadvantages that have being reported. The perception that NG tubes may lead to partial nasal obstruction with increased

airway resistance, work of breathing and central apnea [2], was reported variably in different studies. It may be just possible that once the infants are grown up these differences may not be relevant. Hence, there was no significant differences in resistance between the two groups, which suggests that for these infants a history of NG tube feeding had no adverse effect on subsequent respiratory function. In spite of several advantages of OG tube, they are more frequently mispositioned, can loop inside the mouth, repetitive movement of tube may result in mucosal trauma and may increase the incidence of apnea and bradycardia due to vagal stimulation [7], and take more time to reach full feeds in some of the studies [5]. Given the potential for the route of enteral tube placement to affect important outcomes for preterm or low birth weight infants and the uncertainty that prevails, the researchers of the current study were very appropriate in choosing this research question for their RCT.

The present study [8] comparedtwo feeding methods of tube feeding with respect to adverse effects by evaluating the frequency of bradycardia (<100 bpm) and desaturation (<85%) episodes/hr in hemodynamically stable preterm neonates (<32 wk age) fed by NG vs OG tube placement. Each episode of insertion of a NG tube or OG tube was labelled as FTIE (Feeding Tube Insertion Episodes). FTIE lasted from the time of insertion of tube till the time tube needed to be changed. Reinsertion of the tube in same baby was taken as fresh FTIE. A total of 160 FTIEs was evaluated in this study. The episodes of bradycardia and desaturation/ hour in the NG tube group were significantly higher than OG group. The mean duration of stay was similar in both the groups, and even the tube displacements rate was similar, in contrast to many other studies.The limitation of the study was monitoring adverse effects (all apneic episodes are not picked since only pulse oximetry was used), and randomizing one baby multiple times. Pain scores and time taken to reach fullfeed was not studied in the present study, a larger study with more sample size and better methodology is required to judge the superiority of one over the other. Also, with regard to the methodology, as the displacement would be depending on the NICU practice, a detail note of the nurse – neonate ratio, the way the tube is fixed, the suction policy in NICU, the adhesive used and the experience of the unit and the training should have been elaborated by the authors.

Even though, the physiological disturbances during the NG tube placement have been reported by some of the studies and not reported by others including the current study, unless a detailed behavioral assessment and a long tern neuro-developmental evaluation is done and shown to be same, every neonatologist would still have his concerns with regard to the NG tube feeding. Also, the ways how the studies assessed the physiological disturbance varied with regard to parameters and their sensitivity being used e.g., just a change in heart rate, apnea rates that have a variable event rate to use of crSO2. Similarly, when we look at the OG tube advantage of less displacement over the NG tube, this advantage again has to be looked considering the Nurse – Neonate ratio, the way the tube is fixed, the suction policy in NICU, the adhesive used, and the experience of the unit and the training.

Hence, a Neonatologist should interpret these studies considering these facts in correct perspective. In a unit which experiences minimal adversities with OG tube feeding, the OG feeding can be continued, as this is more physiologically adaptive to the neonate as determined by many studies. When the adversities like displacement are more and effecting the smooth feeding of the babies by OG feeds, in that case than, the unit can revisit the nursing practices, fixing method of the tube, suction protocols and the nurse patient ratio; compare them with units who have minimal displacement or similar displacement to the NG feeds, and try to modify the same. In case, this is not feasible or possible, and the NG tube feeds seem to be more acceptable, the unit may adapt the same.

Understanding the above, the question still is valid for research with a better model where a sensitive and universal test with developmental attributes is used to detect the physiological instability during NG tube insertion and feeding. Also, one needs to adapt and document a detailed description of the practices followed with regard to OG tube feeding before the two groups may be compared.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Watson J, McGuire W. Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants. Cochrane Database Syst Rev. 2013;2013:CD003952.
2. Rao KR, Udaykanth S. Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants. MRIMS Journal of Health Sciences. 2015;3:190-5.
3. Upadhyay J, Kumar S, Singh P, Basu S. Cortical hemodynamic activity and pain perception during insertion of feeding tubes in preterm neonates: A randomised control cross over trial. J Perinatol.2022;42:121-5
4. Bohnhorst B etal. Oral versus nasal route for placing feeding tubes: no effect on hypoxemia and bradycardia in infants with apnea of prematurity. Neonatology, 2010;98:143-49.
5. Badran AT, Hashish M,Ali A, et al. Nasogastric versus orogastric bolus tube feeding in preterm infants: Pilot randomised clinical trial. Am J Perinatol.2021;38:1562-32.
6. Stocks J. Effect of nasogastric tubes on nasal resistance during infancy. Arch Dis Child. 1980;55:17-21.
7. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. Curr Opin Gastroent. 2007;23:178-82.
8. Gupta NP, Sahmad Z, Mittal R, Kukreja S, Jha C, Raheja K. Nasogastric vs orogastic feeding in stable preterm neonates: a randomized open label controlled trial.Indian Pediatr. 2023 Apr 20:S097475591600531. Epub ahead of print.

INVITED COMMENTARY

Considering the Family of Autistic Individuals – The Hidden Struggles of Non-Autistic Siblings

Dario Genovese,[1*] Giuseppe Quatrosi[2]

[1]*Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Via del Vespro, 133, 90127 Palermo, Italy.*

[2]*Department of Psychology, Educational Science and Human Movement, University of Palermo, 90128 Palermo, Italy.*

**dario.genovese@unipa.it*

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders characterised by difficulties in social interactions, communication, and repetitive behaviours [1]. With the global prevalence of autism on the rise, it is essential to recognise the impact the disease has on the whole family, including non-autistic siblings. While significant emphasis has been paid to the diagnosis and assistance of autistic people, the needs and experiences of their siblings are sometimes disregarded [2]. In this editorial, we highlight the necessity of considering non-autistic siblings' quality of life when diagnosing and assisting autistic individuals.

Several studies have found that non-autistic siblings of autistic people face particular obstacles and emotions [2-5]. Childhood and adolescence can be especially difficult for these siblings, as they may experience increased aggressiveness, anxiety, and stress, as well as lower perceived social support [3-5]. Growing up in a home with an autistic sibling can lead to emotions of being forgotten or receiving less parental attention due to the autistic child's demanding requirements [6]. Furthermore, non-autistic siblings may find it difficult to explain their autistic sibling's invisible condition to others, leading to feelings of isolation and difficulties sharing their experiences within the family [7].

A recent cross-sectional study published in this issue of *the journal* [8] aimed to assess the quality of life (QoL) of non-autistic siblings (aged 10-18 years) of children with ASD compared to age- and sex-matched healthy children who had typically developing younger siblings. The study, which included 40 siblings per group, employed a validated tool to assess QoL in various domains, including physical, psychological, social, and environmental. The results of the study revealed that the QoL of non-autistic siblings of children with ASD was significantly lower than that of siblings of typically developing children in each domain [8]. Among the non-autistic siblings of children with ASD, the severity of the sibling's ASD and the family's socioeconomic status were the only two factors significantly affecting one of the domains of QoL [8]. These findings align with previous studies conducted in various countries over the past 20 years, which also reported lower QoL in non-autistic siblings of children with ASD [2,6,7].

Despite these hurdles, non-autistic siblings frequently express genuine concern for the well-being and social inclusion of their autistic brothers and sisters [6]. Furthermore, they may be concerned about future responsibilities, such as taking on caregiving tasks after their parents are no longer able to support them [6]. According to research, while the link between siblings may fluctuate throughout time, it often remains steady in adulthood [9]. However, as compared to siblings of persons with other impairments, adult non-autistic siblings may have a drop in positive attitudes regarding their relationship with their autistic siblings, potentially leading to depressive and anxious symptoms [5].

Assessing the QoL of non-autistic siblings is crucial for understanding all the implications of having an autistic brother or sister [2]. However, studies in this area have been limited by a lack of consistency in evaluation methods and different tools used for QoL assessment, so it is highly recommended to develop standardized and age-specific QoL assessment tools that can capture the unique experiences of non-autistic siblings across different age groups [9].

There is also an urgent need to strengthen research and support services for non-autistic siblings of individuals with ASD [8]. Recognizing these siblings' challenges and concerns can help healthcare professionals and families give focused treatments and support [3,8]. Indeed, it is the role of healthcare practitioners to examine the impact of ASD on non-affected siblings and to advise families on how to best provide help for their children, including regular involvement of affected siblings in therapy sessions [8]. Researchers might look at both the traits that individually affect these siblings' quality of life and the remedies that could be applied

to solve those issues. Families may enhance the link between siblings and establish a nurturing environment that encourages understanding and empathy by acknowledging their challenges and fostering open communication.

Finally, it is crucial to recognize the importance of cultural context while providing complete care for ASD people and their families. Understanding the intricate variations in how people seek, obtain, and benefit from social support within different cultural settings becomes important alongside the aid provided by the health system [10]. To achieve success and inclusion in assisting non-autistic siblings of autistic people, support interventions must be tailored to different cultural settings.

In summary, autism is a condition that impacts not just the diagnosed individual but also their entire family, particularly non-autistic siblings [2-5,8]. When diagnosing and supporting autistic individuals, healthcare professionals, educators, and politicians must recognize the importance of addressing the family unit [2,8]. By concentrating on the well-being of non-autistic siblings and designing tailored treatments, it should be a common mission to create a more inclusive and supportive environment for all family members who are impacted by this condition [2,8].

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Publishing, Inc.; 2013.
2. Quatrosi G, Genovese D, Amodio E, Tripi G. The quality of life among siblings of autistic individuals: a scoping review. J Clin Med. 2023;12:735.
3. Garrido D, Carballo G, Garcia-Retamero R. Siblings of children with autism spectrum disorders: social support and family quality of life. Qual Life Res. 2020;29:1193-202.
4. Koukouriki E, Soulis S-G. Self-reported health-related quality of life (HRQOL) and anxiety among Greek school-age siblings of individuals with autism spectrum disorders (ASD) in relation to parental mental health and social support. J Autism Dev Disord. 2020;50:2913-30.
5. Tomeny TS, Ellis BM, Rankin JA, Barry TD. Sibling relationship quality and psychosocial outcomes among adult siblings of individuals with autism spectrum disorder and individuals with intellectual disability without autism. Res Dev Disabil. 2017;62:104-14.
6. Ward B, Tanner BS, Mandleco B, Dyches TT, Freeborn D. Sibling experiences: Living with young persons with autism spectrum disorders. Pediatr Nurs. 2016;42:69-76.
7. Moyson T, Roeyers H. The quality of life of siblings of children with autism spectrum disorder. Except Child. 2011; 78:41-55.
8. Arya Y, Mishra D, Juneja M, Gupta A. Factors affecting quality of life in adolescent siblings of children with autism spectrum disorder. Indian Pediatr. 2023:S097475591600537. Epub ahead of print.
9. Orsmond GI, Kuo H-Y, Seltzer MM. Siblings of individuals with an autism spectrum disorder: Sibling relationships and wellbeing in adolescence and adulthood. Autism. 2009;13: 59-80.
10. Kim HS, Sherman DK, Taylor SE. Culture and social support. Am Psychol. 2008;63:518-26.

INVITED COMMENTARY

Acute Pulmonary Hypertension of Early Infancy – Is Thiamine Deficiency the Only Cause?

SATYAN LAKSHMINRUSIMHA,[1*] RAJESHWARI MADAPPA[2]

[1]*Department of Pediatrics, University of California at Davis Children's Hospital, Sacramento, California, USA.*

[2]*Department of Pediatrics, SIGMA Hospital, Mysore, Karnataka, India.*

**slakshmi@ucdavis.edu*

Acute pulmonary hypertension (aPH) is common in preterm and term infants soon after birth in both high-income countries (HIC, approximately 2/1000 live births [1]) and low- and middle-income countries (LMIC, 1.2 to 4.6 per 1000 live births in Asia [2] and 1-3 patients per month or 1-3% of admissions in most NICUs in India [3]. It is often secondary to parenchymal lung disease such as respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), pneumonia/sepsis or congenital diaphragmatic hernia (CDH). Infants with aPH have high morbidity and mortality during the neonatal period. Exacerbation of chronic pulmonary hypertension (PH) associated with conditions such as bronchopulmonary dysplasia (BPD) or CDH is common during early infancy. However, new onset aPH beyond the neonatal period during early infancy is uncommon in HIC.

In contrast, several case reports from the Indian subcontinent and case series describe aPH during early infancy in LMICs, especially among those exclusively breastfed by mothers on polished rice diet [4-8]. These cases presenting in the post-neonatal period are associated with lactic acidosis, hypoperfusion, often with severe pulmonary hypertension and hypoxemia [4]. Although, some of these infants have low thiamine levels and respond to pulmonary vasodilators and thiamine, the precise etiology of infantile aPH in the Indian subcontinent is not known.

Pulmonary vascular resistance (PVR) is high in fetal period and varies with gestational age (**Fig. 1**). During the canalicular phase of lung development, there is a paucity of pulmonary vessels resulting in high PVR. With advancing gestation, pulmonary vessels increase, decreasing PVR. Late in gestation, during the alveolar phase, pulmonary vessels become sensitive to oxygen and hypoxic pulmonary vasoconstriction increases PVR. At birth, when alveolar oxygen increases, PVR decreases and pulmonary blood flow increases, establishing lungs as the organ of gas exchange [9]. In some neonates, PVR does not decrease at birth resulting in persistent pulmonary hypertension of the newborn (PPHN).

High PVR observed in aPH of early infancy can potentially occur from two processes: *i*) chronic elevation in PVR from fetal period or birth followed by an exacerbation (acute-on-chronic PH – dotted line in **Fig. 1**), or *ii*) normal transition at birth and decrease in PVR followed by acute exacerbation (dashed line in the figure). The pathophysiology and phenotype of infantile aPH could be one of three mechanisms viz., *i*) normal pulmonary vascu-lature with acute arterial vasoconstriction, *ii*) left ventricular dysfunction with pulmonary venous hypertension, and *iii*) chronic remodeled pulmonary vasculature with superimposed arterial and venous hypertension. There is a desperate need for lung biopsy or autopsy data evaluating the morphology of pulmonary vasculature in these patients.

The exact etiology of aPH among Indian infants is not clear despite several publications; although, thiamine deficiency has been considered as a plausible explanation [5-7]. In this issue of *Indian Pediatrics,* Aroor, et al. [10] provide a large series of cases of aPH presenting in early infancy in a tertiary care institution. They provide data showing that the institution of a protocol of thiamine supplementation did not significantly alter mortality (28.6% without thiamine and 10.7% with thiamine, P=0.17). There are two major limitations to this study. No data on thiamine levels at the time of acute presentation are provided. It is possible that given the local diet that includes parboiled rice and fish, the prevalence of thiamine deficiency might be lower. Second, the sample size is small, increasing the risk of type II error. Hence, a clinically significant reduction in mortality, although not statistically significant, cannot be ignored. In addition, the authors [10] provide elegant data suggesting higher incidence of right and left ventricular dysfunction associated with higher mortality similar to that observed in infants with CDH and other causes of PPHN [10-13].

It is likely that cases of aPH in infancy are multifactorial in origin with nutritional (thiamine and other factors), infectious (viral, chlamydial, bacterial etc.) and genetic factors playing a role (**Fig. 1**). A large study that includes

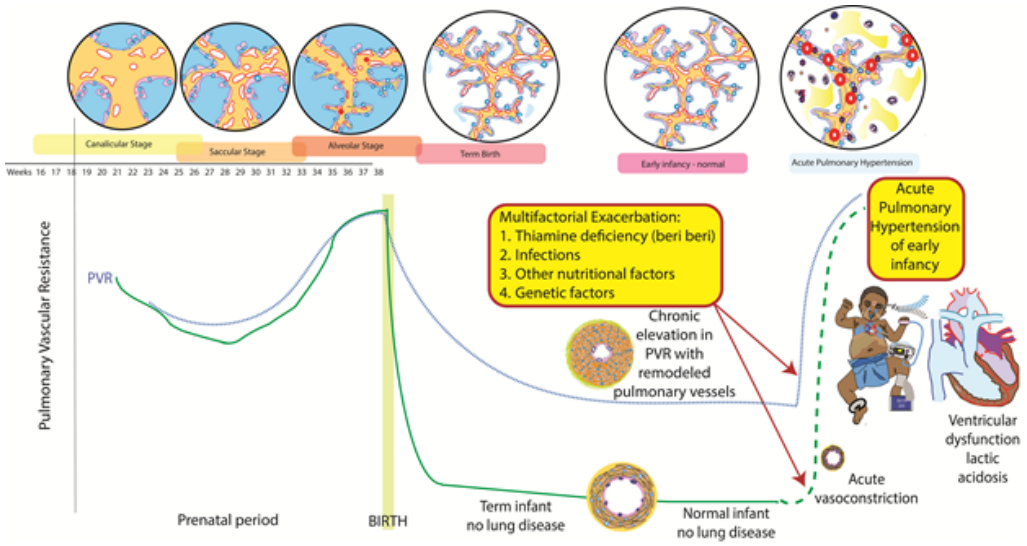


Fig. 1 Changes in pulmonary vascular resistance (PVR) during antenatal and postnatal periods. The solid line shows the variation in normal term infants. The dotted line shows the possible trajectory of PVR in chronic pulmonary hypertension with acute exacerbation. The dashed line depicts acute exacerbation in an infant with normal PVR prior to presentation.

estimation of thiamine levels in the mother and infant, lung biopsy or autopsy to evaluate pulmonary vascular morphology and if possible, a multi-center, randomized trial of thiamine infusion in aPH is warranted. Pending such studies, given the safety profile of thiamine, protocols that include supportive and pulmonary vasodilator therapy, and considering thiamine infusion (although the dose needs further evaluation) are justified in our opinion.

Funding: HD072929 (SL) – National Institutes of Health; *Competing interests*: None.

REFERENCES

1. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000;105: 14-20.
2. Nakwan N, Jain S, Kumar K, et al. An Asian multicenter retrospective study on persistent pulmonary hypertension of the newborn: incidence, etiology, diagnosis, treatment and outcome. J Mat Fetal Neonat Med. 2020;33:2032-7.
3. Singh P, Deshpande S, Nagpal R, Garegrat R, Gupta S, Suryawanshi P. Management of neonatal pulmonary hypertension-a survey of neonatal intensive care units in India. BMC Pediatr. 2023;23:149.
4. Panigrahy N, Chirla DK, Shetty R, et al. Thiamine-responsive acute pulmonary hypertension of early infancy (TRAPHEI)-a case series and clinical review. Children (Basel). 2020;7:199.
5. Sastry UMK, Kumar RK, Ghosh, S, et al. Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: a prospective observational study. Arch Dis Child. 2021;106:241-6.
6. Sindhu TG, Rajesh TV, Ajithkumar VT, Muneer K. Thiamine-responsive acute pulmonary hypertension in an exclusively breastfed infant. Indian Pediatr. 2022;59:814-5.
7. Kundana PK, Reddy N, Reddy BS, et al. Thiamine-responsive, life-threatening, pulmonary hypertensive crisis with encephalopathy in young infants: A case series. Eur J Pediatr Neurol 2022;36:93-8.
8. Samprathi M, Mohammad F, Ramachandra P, Vemgal P. Case report: fulminant infantile beriberi: a report of six cases. Am J Trop Med Hyg. 2021;104:2238-40.
9. Lakshminrusimha S, Steinhorn RH. Pulmonary vascular biology during neonatal transition. Clinics in perinatology 1999, 26, 601-619.
10. Aroor S, Handattu K, Mundkur SC, et al. Severe pulmonary arterial hypertension in healthy young infants: single center experience. Indian Pediatr. 2023:S097475591600551. Epub ahead of print.
11. Patel N, Massolo AC, Paria A, et al. Early Postnatal ventricular dysfunction is associated with disease severity in patients with congenital diaphragmatic hernia. J Pediatr. 2018;203:400-7, e401.
12. Altit G, Bhombal S, Van Meurs K, Tacy TA. Ventricular performance is associated with need for extracorporeal membrane oxygenation in newborns with congenital diaphragmatic hernia. J Pediatr. 2017;191:28-34,e21.
13. Lawrence KM, Monos S, Adams S, et al. Inhaled nitric oxide is associated with improved oxygenation in a subpopulation of infants with congenital diaphragmatic hernia and pulmonary hypertension. J Pediatr. 2020;219:167-72.

PERSPECTIVE

Infectious Causes of Acute Encephalitis Syndrome in India – Decadal Change and the Way Forward

Babasaheb V Tandale,[1] Rahul Narang,[2] G Vijay Kumar,[3] Manish Jain,[4] Shilpa J Tomar,[1] Pravin S Deshmukh[5]

[1] *Epidemiology Group, ICMR - National Institute of Virology, Pune, Maharashtra.*

[2]*Department of Microbiology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana.*

[3]*Department of Paediatrics, Kakatiya Medical College, Warangal, Telangana.*

[4]*Department of Paediatrics, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Maharashtra.*

[5]*Department of Microbiology (Project Scientist), Government Medical College, Nagpur, Maharashtra.*

Correspondence to: Dr Babasaheb V Tandale, Scientist F and Group Leader, Epidemiology Group, ICMR - National Institute of Virology, Pune, Maharashtra 411001. tandale.bv@gov.in

The diagnosis and management of encephalitis were previously largely based on clinical grounds and minimal laboratory investigations. Japanese encephalitis (JE) gets considered as the probable diagnosis in most encephalitis cases. However, reports of JE in adults and the elderly are increasing after the JE vaccine introduction among children in 2006. The Nipah virus (NiV) emerged in 2002 and continues to afflict humans in new geographic areas. Many other infections cause encephalitis, including Chandipura, chikungunya, dengue, and West Nile. Significant advances in diagnostic testing like multiplex testing panels and metagenomic approaches along with sequencing have helped in the detection of new etiologies. Recent years have witnessed an increase in climate-sensitive zoonotic diseases with encephalitis. This highlights the importance of the One Health approach in studying the impact of climate change-associated infectious diseases on human health. The government of India's efforts to develop health research infrastructure would help future responses to emerging infectious disease epidemics.

Keywords: *Diagnosis, Etiology, Management, One health, Recent advances.*

Published online: May 30, 2023; **PII**: S097475591600546

Acute encephalitis syndrome (AES) is an illness presenting with the acute onset of fever and either change in mental status with symptoms such as confusion, disorientation, coma, or inability to talk, and/or new onset seizures excluding simple febrile seizures. Encephalitis in clinical practice is considered synonymous with herpes simplex virus (HSV) encephalitis (HSE) in sporadic cases [1]. However, Japanese encephalitis (JE) is the most common cause of AES cases in endemic areas during specific seasons, and especially during outbreaks [2]. There has been a significant decline in JE contribution to AES in the last decade [3]. However, reports of JE, though still mostly reported among children, are also being reported in adults and the elderly [4], year-round beyond known seasonality [5], and outside endemic regions, including some urban areas [6].

The Nipah virus (NiV) is a zoonotic virus, with fruit bats serving as the natural host. It is transmitted through animals, contaminated food, and human-to-human. It has a case fatality rate estimated at 40-75%, which may vary in outbreak settings. Clinical presentation ranges from asymptomatic (subclinical) infection, mild acute respiratory infection to fatal encephalitis. It has no specific treatment or vaccine available. Since its emergence [7] in 2002, it continues to affect humans in new geographic areas [8], which is a concerning development. Chandipura virus (CHPV) is an arbovirus transmitted by sandflies. It was identified as the causative agent of the explosive encephalitis outbreak in Central India in 2003-2004, with a case fatality rate as high as 75%, reported within 24 hours of symptoms commencement. CHPV encephalitis outbreaks [9] and the seasonal increase in cases in early monsoon period have been reported in central, western and eastern India [10].

Trends in AES Morbidity and Mortality

In India, the National Vector Borne Disease Control Programme (NVBDCP) reports thousands of cases of AES every year [11]. JE is an endemic disease in our country and causes more than 2,500 cases and over 500 deaths annually [12]. No specific treatment exists for JE, and cases are managed with supportive care services. Currently, vaccines are the only effective preventive measure against the disease. The JENVAC (inactivated Vero cell-derived) vaccine is an indigenously developed vaccine, is safe and neutralizes genotype I-IV of JEV, with seroconversion rates of more than 90% [13]. There has been a decline in JE cases in certain geographical areas, due to increased awareness, prevention practices and vaccination uptake. The NVBDCP reports that

the mortality from AES has declined from 12.27% in the year 2015 to 3.86% in 2022.

Significant advances in diagnostic testing have happened with the availability of technologies like fully automated multiplex polymerase chain reaction (PCR) panels, where multiple pathogens can be detected simultaneously in a short duration of time. These still remain underutilized for CNS infections, although they are widely used for syndromic diagnoses like sepsis, gastrointestinal and respiratory illnesses [14]. The 'metagenomics' approach refers to the interrogation of the complete genetic material from a clinical sample [15]. It has great potential for helping clinicians in reaching a timely diagnosis. The recent advent of unbiased high-throughput sequencing (HTS) technologies to detect previously unrecognized or novel pathogens offer remarkable opportunities in undiagnosed encephalitis cases [16].

Although, there are consensus clinical guidelines provided for the diagnosis and management of encephalitis in children [17], there are new developments in the decade that require updating of the recommendations, along with the development and evaluation of diagnostic and management algorithms for different population subgroups at most risk, that could be applicable across India and also based on the regional differences [18]. An increase in climate-sensitive zoonotic diseases is getting much-needed attention recently. There is a need for prioritizing the research on climate change using the One Health approach. This article provides perspectives on infectious causes of encephalitis in India based on the changing etiological spectrum.

Before the 21st Century, the most common infectious cause of sporadic encephalitis in clinical practice among immunocompetent individuals was HSV. It was also associated with immunocompromised individuals infected with HIV-1 and AIDS in India. The testing for serodiagnosis and seroepidemiology studies were mostly done using an indirect immunofluorescence test [19]. The molecular methods of diagnosis using real-time PCR have been helpful in early and quick diagnosis along with the determination of viral load, helping clinicians in the decision on continuation or stopping of antiviral therapy.

Sporadic encephalitis cases have also been associated commonly with the pandemic influenza A (H1N1) in 2009 and rarely with Parvovirus B4, rabies, dengue and enteroviruses [20], Chikungunya [21], and West Nile [22]. Nonviral causes of encephalitis include scrub typhus [23] and leptospirosis [24], which are treatable by affordable and widely available drugs like azithromycin and doxycycline. *Neisseria meningitidis, Haemophilus influenzae*, and *Streptococcus pneumoniae* are other bacterial agents which cause AES. Also, postinfectious encephalitis in a few cases merits attention and efforts due to the additional possibility of co-infections. There are other non-infectious causes like autoimmune or antibody-mediated encephalitis along with metabolic, toxic and other encephalopathies.

The JE virus activity in India was reported first in 1952. The first human case of JE was reported from Tamil Nadu in 1955. The first epidemic of JE was reported in Bankura, West Bengal and subsequently in Uttar Pradesh in 1978. It continued to afflict human populations after the 1990s [2]. Following the epidemics in 2005 reported nationwide [25], JE vaccination was introduced as an emergency measure in 2006 as a vaccination campaign using the live-attenuated SA 14-14-2 JE vaccine among children aged 1-15 years.

Improvements in serological diagnosis and molecular assays using the RT-PCR have helped in early diagnosis. The attribution of the JE virus as the cause had been reported in 10-40% of cases of encephalitis during the largest outbreaks in Uttar Pradesh until 2005. The epidemiology of JE is changing in India following the implementation of JE vaccination in endemic districts. JE virus genotype-I was reported in India in 2011 and genotype-III recently. JE vaccination has been considered the most important tool for JE prevention and control. After the introduction of a single dose of live-attenuated SA 14-14-2 JE vaccine at 16-24 months in routine immunization schedules in 2010, an additional dose at 9-12 months was included since 2013. Many other new vaccines have been developed and introduced in India.

The changing clinical and laboratory profile of AES in Uttar Pradesh along with the association of non-JE viral and non-viral infectious agents, including enteroviruses, have highlighted the need for algorithms for clinical investigations and etiological testing. The importance of cerebrospinal fluid (CSF) for diagnostic testing has also been highlighted along with the novel developments in testing using the multiplex panels and metagenomics. This has become more important due to urban areas experiencing sporadic JE cases recently [6]. There are increasing cases and also outbreaks of JE among adults and the elderly following childhood vaccination [4]. Also, JE cases are getting reported year-round, as against peculiar seasonality in the post-monsoon period earlier, in non-endemic areas and beyond the known season [5]. However, JE may get misdiagnosed or wrongly associated with encephalitis due to issues of cross-reactivity and less specificity of serodiagnosis relying on the use of IgM ELISA assays.

Several epidemics of coma and fever in children with high case fatality rates occurred at regular intervals, in Telangana (erstwhile Andhra Pradesh) in 1997, 2002, 2003, 2005; Maharashtra and eastern districts of Gujarat in 2003, 2004 and elsewhere. These recurrent epidemics were caused by the CHPV, indicating the emergence of CHPV in the Indian subcontinent.

A recent systematic review [26] has documented that COVID-19 infection could present as encephalitis; with most frequent neurological presentations being similar to those of JE, depending upon the severity of the disease including simultaneous respiratory damage [27]. Lack of a characteristic CSF profile and a negative PCR test result may make its diagnosis less evident, though autoimmune neuropathogenesis is likely. The clinicians should consider neurological involvement in COVID-19 cases with altered mental status or behavioral changes.

There are various difficulties in pointing out the cause in most cases of encephalitis based on only clinical information. There is a need to consider clinical as well as epidemiological parameters in differential diagnosis for rationalizing testing [17]. Diagnosing encephalitis is a very costly affair. The physicians could consider rationalized testing based on clinical clues [28]. There are efforts being made recently to provide algorithms at the national level [18]. However, as studies are not reported from different geographies and endemic areas (**Table I**), there are difficulties in prescribing testing algorithms that could be applied across India [18].

Etiological Testing and Research

There are some operational issues regarding the availa-bility of appropriate and timely clinical specimens for diagnostic testing. CSF collection may not be possible in cases with clinical contraindications, lack of expertise and consent from patient relatives. Also, the non-availability of convalescent sera in the later phase of illness may be due to high mortality in the early course of illness, loss of patients to follow-up and lack of interest and motivation of patients and physicians alike**,** after recovery from an acute illness [5]. With decreasing contribution of JE in AES following JE vaccination [3], it is important to investigate other causes of encephalitis. Due to decreased burden of HIV/AIDS, and the elimination efforts for malaria and tuberculosis, it is a need to consider research on other potential causes of encephalitis.

Dengue-associated encephalitis, ranging from mild encephalopathy to severe encephalitic clinical presentation, is increasingly being recognized in tropical and subtropical countries, with a reported incidence rate varying from 0.5 to 20% [29]. A case of encephalitis or viral meningitis with normal CSF cellularity, in a dengue-endemic region, is likely to be due to dengue in 75% of the patients, followed by HSV-1 [30].

Since the year 2014, many surveillance and etiological research studies were undertaken, mostly in high-endemic regions in Uttar Pradesh, West Bengal, and Assam. The medium-endemic region in Maharashtra (Vidarbha region) and Telangana, erstwhile Andhra Pradesh (northern region) lacked such studies. These studies were undertaken for understanding the contribution of JE and other common infectious agents associated with AES. Dengue encephalopathy and rickettsial fevers were also considered for testing. Establishing enhanced hospital-based surveillance and searching for multiple infectious agents through virus research and diagnostic laboratories (VRDL) have changed the scenario in the last decade.

Clinical Management Issues

Strengthening of primary and secondary care hospitals is

Table I Infectious Causes of Acute Encephalitis Syndrome (AES) in India

Immunocompetent patients

Virus: Japanese encephalitis virus (JEV),[a] Herpes simplex virus (HSV),[b,c] Chandipura virus (CHPV),[a,b] (Telangana, Maharashtra, Gujarat, Odisha, Bihar), Nipah virus (NiV),[a,b] (West Bengal, Kerala), Enteroviruses,[b,c] Dengue,[a] Influenza A (H1N1) (H3N2),[a,c] Kyasanur forest disease (KFD), Rabies, Chikungunya,[a] West Nile (Assam, Kerala),[a] Zika

Bacteria: *Mycobacterium tuberculosis*;[b] *Orientia tsutsugamushi* (Scrub typhus);[a] Leptospira (Assam, Kerala, Others);[a] *Neisseria meningitides* (<1%)

Parasite: *Plasmodium falciparum, Naegleria fowleri* [b,c]

Immunosuppressed patients

Virus: HIV, EBV, CMV, Parvovirus B19, Human herpes virus 6

Unvaccinated children

Virus: Measles, Mumps, Rubella (clusters), Chickenpox (clusters), *Bacteria: Streptococcus pneumoniae* (~1%), *Haemophilus influenzae* (<1%)

Newer agents

Virus: SARS-CoV-2 (direct or autoimmune-mediated)[c]

[a]Outbreak potential; [b]to be considered based on clinical presentation and tested if clues or pointers are available; [c]Acute necrotizing encephalitis (ANE). Modified from: Standard Treatment Workflow (STW) for the management of Acute Encephalitis Syndrome (AES) in children, developed by the Indian Council of Medical Research (*https://stw.icmr.org.in/images/pdf/Paediatrics/Paediatrics_Acute_Encephalitis_syndrome.pdf*)

urgently needed along with preferential strengthening of tertiary care hospitals for decreasing the case fatality rate of AES. Decreased transport times to the nearest health-care settings and early management of raised intracranial pressure (ICP) and convulsions have brought significant improvements in survival.

Clinicians and public health authorities have started immunization against JE. However, AES is caused by many agents other than JE. Vector control, mass immunization with the JE vaccine to all below 15 years of age, and strengthening of peripheral hospitals with oxygen and mannitol, along with measures in place for decreasing transport times, could help decrease mortality and disabilities of JE, and also AES in future.

Climate Change and AES

The temperature rise, increased CO_2 levels, and changes in land use can drive extreme weather events resulting in outbreaks of JE/AES in previously naïve regions [31].Temperature is a critical factor for vector competence of JEV and mosquito survival [21]. Thus, climate change can cause the emergence of JEV in novel temperate regions. Extended warm days, and erratic rains causing flash floods and water stagnation, can contribute towards a breeding environment for the JE vector. Modelling studies have predicted that climate change can also provide opportunities for viral sharing amongst the wildlife, presently silently harboring them, and could in turn facilitate zoonotic spillover [32]. Thus, it may be postulated that novel viruses with the potential to cause AES could gain access to naïve human population in future.

Future Perspectives

Pradhan Mantri Ayushman Bharat Health Infrastructure Mission (PM-ABHIM) launched in October, 2021, is the largest Pan India scheme for public health infrastructure since 2005. It intends to fill in critical gaps in health infrastructure, surveillance and health research, spanning both urban and rural areas. It aims to make the communities *atmanirbhar* or self-reliant by establishing a strong healthcare system, which can effectively respond to epidemics across the nation, develop the core capabilities to deliver a One Health approach in the prevention of infectious diseases and build information technology (IT) enabled surveillance systems [33].

Artificial Intelligence (AI): Potential in AES Diagnosis

Machine learning (ML), the most common form of AI, is a technique of fitting models to data statistically and to 'learn' by training the models. The focus of AI, as early as the 1970s, has been on disease diagnosis and treatment [34]. 'Precision medicine' predicts what treatment and management protocols are most likely to succeed based on various patient attributes and treatment contexts. It has been applied effectively in the field of cancer [35]. AI may become an important tool in the future for the early, accurate diagnosis of AES cases, thus leading to better treatment and prognosis.

Conclusions

A significant decrease in the burden of vaccine-preventable diseases was seen after the implementation of vaccinations against measles, rubella and mumps, along with improved rabies vaccines as pre-exposure and also post-exposure prophylaxis, and with effective vaccines against Japanese encephalitis since 2006. However, many treatable causes of encephalitis such as scrub typhus, leptospirosis, malaria, tuberculosis and sepsis need guidelines for early diagnosis and proper management. The increasing endemicity and frequent outbreaks of dengue will need attention and timely efforts. The astute pediatrician will need to detect cases, seek diagnostic testing timely and engage with the health services. Awareness of possible para- and post-infectious encephalitis including SARS-CoV-2 encephalitis could help drive research for the betterment of therapies and improving the outcomes. Significant advances in diagnostic technologies have helped in the detection of novel etiological agents of infectious encephalitis. The national, state and local governments have become responsive to the health challenges. The ongoing PM-ABHIM is one such example by the Government of India. Such efforts will prove useful in the management of encephalitis to prevent mortalities and morbidities in future.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Panagariya A, Jain RS, Gupta S, et al. Herpes simplex encephalitis in North West India. Neurol India. 2001;49:360-5.
2. Kabilan L, Ramesh S, Srinivasan S, et al. Hospital- and laboratory-based investigations of hospitalized children with central nervous system-related symptoms to assess Japanese ence-phalitis virus etiology in Cuddalore District, Tamil Nadu, India. J Clin Microbiol. 2004;42:2813-5.
3. Ranjan P, Gore M, Selvaraju S, et al. Decline in Japanese encephalitis, Kushinagar District, Uttar Pradesh, India. Emerg Infect Dis. 2014;20:1406-7.
4. Jain P, Prakash S, Khan DN, et al. Aetiology of acute encephalitis syndrome in Uttar Pradesh, India from 2014 to 2016. J Vector Borne Dis. 2017;54:311-6.
5. Tandale BV, Tomar SJ, Bondre VP, et al. Infectious causes of acute encephalitis syndrome hospitalizations in Central India, 2018-20. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2022; 153:105194.
6. Adhya D, Dutta K, Basu A. Japanese encephalitis in India: risk of an epidemic in the National Capital Region. Int Health. 2013;5:166-8.
7. Chadha MS, Arankalle VA, Jadi RS, et al. An outbreak of

Chandipura virus encephalitis in the eastern districts of Gujarat state, India. Am J Trop Med Hyg. 2005;73:566-70.
8. Thomas B, Chandran P, Lilabi MP, et al. Nipah virus infection in Kozhikode, Kerala, south India, in 2018: Epidemiology of an outbreak of an emerging disease. Indian J Community Med Off Publ Indian Assoc Prev Soc Med. 2019;44:383-7.
9. Rao BL, Basu A, Wairagkar NS, et al. A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. Lancet Lond Engl. 2004;364:869-74.
10. Tandale BV, Tikute SS, Arankalle VA, et al. Chandipura virus: a major cause of acute encephalitis in children in North Telangana, Andhra Pradesh, India. J Med Virol. 2008;80: 118-24.
11. Vasanthapuram R, Shahul Hameed SK, Desai A, et al. Dengue virus is an under-recognised causative agent of acute encephalitis syndrome (AES): Results from a four year AES surveillance study of Japanese encephalitis in selected states of India. Int J Infect Dis. 2019;84:S19-24.
12. National Vector Borne Diseases Control Programme [Internet]. Ministry of Health and Family Welfare, Government of India. Accessed on 28 April 2023. Available from: *https://nvbdcp.gov.in/WriteReadData/l892s/2643699503 1670414999.pdf*
13. Singh A, Mitra M, Sampath G, et al. A Japanese encephalitis vaccine from india induces durable and cross-protective immunity against temporally and spatially wide-ranging global field strains. J Infect Dis. 2015;212:715-25.
14. Chandran S, Arjun R, Sasidharan A, et al. Clinical performance of film array meningitis/encephalitis multiplex polymerase chain reaction panel in central nervous system infections. Indian J Crit Care Med. 2022;26:67-70.
15. Ramachandran PS, Wilson MR. Metagenomics for neurological infections - expanding our imagination. Nat Rev Neurol. 2020;16:547-56.
16. Kennedy P, Quan PL, Lipkin W. Viral Encephalitis of unknown cause: Current perspective and recent advances. Viruses. 2017;9:138.
17. Sharma S, Mishra D, Aneja S, et al. Consensus guidelines on evaluation and management of suspected acute viral encephalitis in children in India. Indian Pediatr. 2012;49:897-10.
18. Ravi V, Hameed SKS, Desai A, et al. An algorithmic approach to identifying the aetiology of acute encephalitis syndrome in India: results of a 4-year enhanced surveillance study. Lancet Glob Health. 2022;10:e685-93.
19. Ratho RK, Mishra B, Hassan S. Indirect immuno-fluorescence test: role in seroepidemiology and serodiagnosis of herpes simplex viral infections. Indian J Pathol Microbiol. 2004;47:582-5.
20. Sapkal GN, Bondre VP, Fulmali PV, et al. Enteroviruses in patients with acute encephalitis, Uttar Pradesh, India. Emerg Infect Dis. 2009;15:295-8.
21. Folly AJ, Dorey-Robinson D, Hernández-Triana LM, et al. Temperate conditions restrict Japanese encephalitis virus infection to the mid-gut and prevents systemic dissemination in Culex pipiens mosquitoes. Sci Rep. 2021;11:6133.
22. Anukumar B, Sapkal GN, Tandale BV, et al. West nile encephalitis outbreak in Kerala, India, 2011. J Clin Virol. 2014; 61:152-5.
23. Jain P, Prakash S, Tripathi PK, et al. Emergence of Orientia tsutsugamushi as an important cause of acute encephalitis syndrome in India. PLoS Negl Trop Dis. 2018;12:e0006346.
24. Das BK, Mohanty S, Sahoo PK. Association of leptospirosis and scrub typhus in acute encephalitis syndrome in a tertiary care hospital in Odisha, India. Trans R Soc Trop Med Hyg. 2021;115:1088-90.
25. Chatterjee P. Japanese encephalitis outbreak in India. Lancet Neurol. 2005;4:700.
26. Islam MA, Cavestro C, Alam SS, et al. Encephalitis in patients with Covid-19: A systematic evidence-based analysis. Cells. 2022;11:2575.
27. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun. 2020;88:945-6.
28. Misra UK, Mani VE, Kalita J. A Cost-effective approach to the diagnosis and management of acute infectious encephalitis. Eur Neurol. 2017;77:66-74.
29. Li GH, Ning ZJ, Liu YM, Li XH. Neurological manifestations of dengue infection. Front Cell Infect Microbiol. 2017;7:449.
30. Soares CN, Cabral-Castro MJ, Peralta JM, et al. Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. J Neurol Sci. 2011;303:75-9.
31. Furuya-Kanamori L, Gyawali N, Mills DJ, et al. The emergence of Japanese encephalitis in Australia and the implications for a vaccination strategy. Trop Med Infect Dis. 2022; 7:85.
32. Carlson CJ, Albery GF, Merow C, et al. Climate change increases cross-species viral transmission risk. Nature. 2022; 607:555-62.
33. Operational Guidelines for PM Ayushman Bharat Health Infrastructure Mission. 2021. Ministry of Health and Family Welfare Government of India. 2021.
34. Bush J. How AI is taking the scut work out of health care. Harvard Business Review; 2018.
35. Davenport T, Kalakota R. The potential for artificial intelligence in healthcare. Future Health J. 2019;6:94-8.

PERSPECTIVE

The Health Effects of Climate Change on Children: Pediatricians Must Be Part of the Solution

RUTH A ETZEL,[1] SWATI Y BHAVE[2]

[1]*Milkin Institute School of Public Health, The George Washington University, Washington DC, USA.*
[2]*Adolescent Medicine, Department of Paediatrics, Dr. DY Patil Medical College (Dr DY Patil Vidyapeeth), Pampri, Pune, Maharashtra, India.*
Correspondence to: Dr Swati Y. Bhave, 601 Alliance Shanti, Shantisheela Co-operative society, Law College Road, Erandawane Pune 411 004, Maharashtra, India. sybhave@gmail.com

Climate change is already impacting children's health in a variety of ways. Indian children are among the most severely affected; they are experiencing respiratory illnesses from air pollution, heat-related illnesses, malnutrition, vector- and water-borne diseases; and mental health problems such as post-traumatic stress disorder from weather disasters. There is a need to increase awareness and capacity building among paediatricians for understanding the impact of climate change on the health of children and educating parents about preventive measures. Detailed environmental history taking will help to identify risk factors. To address climate change issues, professional paediatric associations should increase their advocacy with government agencies. It is essential to **ask policymakers to immediately reduce greenhouse gas emissions**. Reducing the burning of coal and other fossil fuels and moving to renewable energy sources such as solar and wind will reduce India's carbon emissions and decrease environmental illness among children. The pediatricians of India should declare that climate change is a child health emergency.

Key words: *Child, Advocacy, Heat, Flood, Air pollution.*

The Earth's climate is changing in ways that are not good for children. Burning of fossil fuels has released unprecedented amounts of carbon dioxide and other greenhouse gases into the atmosphere. Human activities worldwide have already caused approximately 1.1°C of global warming above pre-industrial levels [1]. This rise in global temperature is likely to reach 1.5°C between 2030 and 2052 if carbon dioxide emissions continue to increase at the current rate of 0.6% a year [2].

The rising global temperature impacts health, livelihoods, food security, water supply, human security and economic growth. Shifting weather patterns are expected to threaten food production and raise sea levels, thus increasing the risk of severe floods. Low- and middle-income countries are particularly affected by climate change. They are hit hardest because they are more vulnerable to the damaging effects of a hazard but have lower coping capacity. Eight out of the ten countries most affected by impacts of extreme weather events in 2019 belong to the low to lower and lower middle-income category. The global pandemic of COVID-19 has reinforced the fact that both risks and vulnerability are systemic and interconnected [3].

INDIAN SCENARIO

According to the Global Climate Risk Index [3] India is the fifth-most vulnerable country to climate change impact. The environmental, social and economic impact of climate change are already significant in India, with a population of more than 1.4 billion [4]. The lives and livelihoods of a significant proportion of the population are affected, especially those dependent on climate-sensitive sectors such as agriculture, forestry, tourism, animal husbandry and fisheries. India's economy is heavily dependent on agriculture, with about 58% of the population dependent on agriculture for livelihoods [5]. Annual agricultural incomes are predicted to decline by 15-18% and agricultural yield by as much as 2.9% due to climate change.

Soaring summer temperatures are one reason that climate change is a key area of concern for India; this was especially evident during the past several summers. In April, 2023, temperatures reached 45ºC across the northern plains of India. As a preventive measure, hundreds of schools closed [6]. Large numbers of people came to hospitals and clinics with symptoms of heat stroke in April, 2023, and 13 people died at an event in Mumbai [7].

HEALTH EFFECTS OF CLIMATE CHANGE ON CHILDREN

The climate crisis is a child health crisis [8]. Burning fossil fuels releases pollution into the air, which causes exacerbations of childhood asthma and other respiratory diseases [9]. In India, seasonal episodes of asthma increased in summer from 2.8% in 1994 to 19.8% in 2004 possibly due to

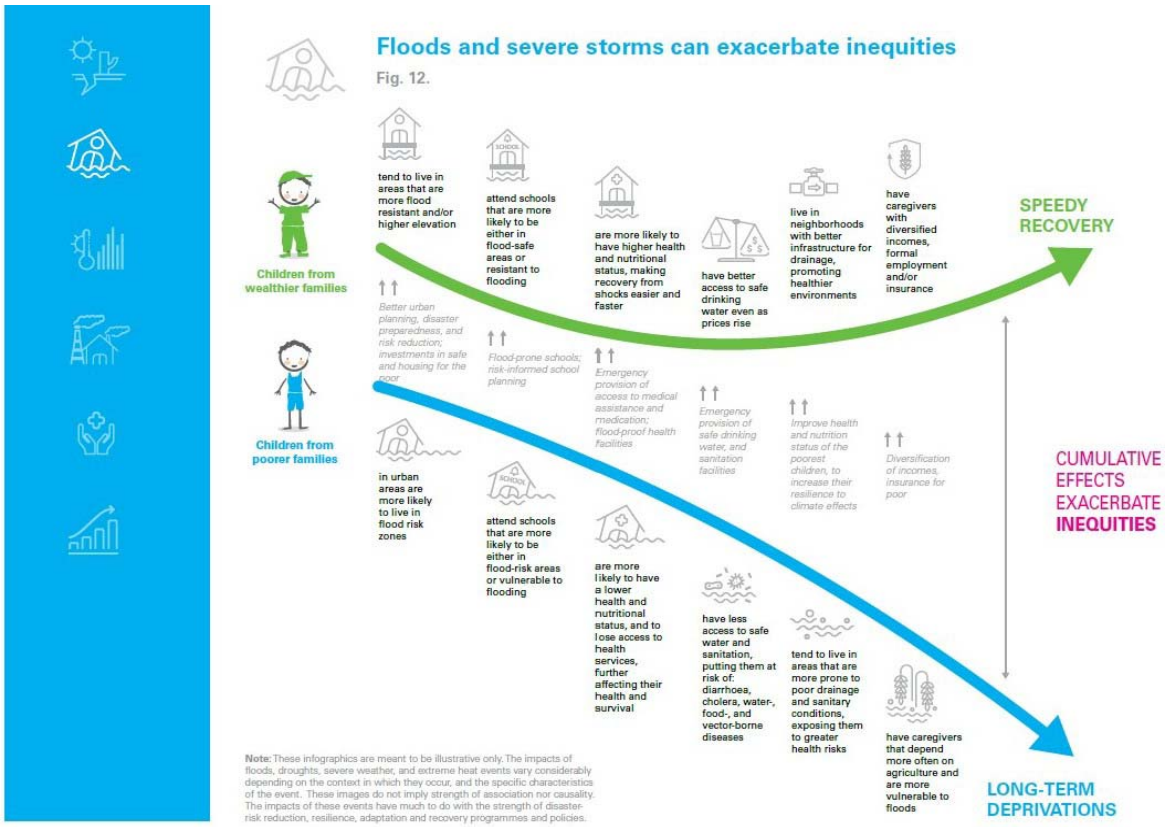
the increase in ozone production from automobile emissions [10].The risk of asthma in children has been shown to increase sequentially from 1.19 (95% CI, 1.04-1.36), 1.51 (95% CI, 1.31-1.75), and 1.51 (95% CI, 1.29-1.76) after exposure to mild, moderate and heavy traffic pollution compared with minimal traffic pollution [11].

In addition to respiratory diseases, climate change causes more heatwaves; children under one year are extremely vulnerable during heat waves. The number of heatwave days in India has increased in the last 10 years [12]. The inland regions have had, on average, more than 8 heatwave days from April to June and the affected areas have increased from 1991 to 2020, in comparison to the previous three decades starting from 1961. UNICEF reported that high heatwave duration impacts 538 million, or 23% of children globally [13]. This will rise to 1.6 billion children in 2050 at 1.7ºC warming, and 1.9 billion children at 2.4ºC warming, emphasizing the importance of urgent and dramatic emissions mitigation and adaptation measures to contain global heating.

Other health effects on children are due to extreme weather events and subsequent disasters; water scarcity and food insecurity; vector- and water-borne diseases; and mental health problems such as post-traumatic stress disorder [14]. Disadvantaged children will be most severely affected (**Fig.1**). Potential adverse consequences include orphanhood, trafficking, child labor, loss of education and development opportunities, separation from family, homelessness, poverty, trauma, and emotional disruption [15]. Children in disaster-prone areas in India are twice as likely to be living in chronic poverty as to escape poverty, and three times as likely to become impoverished [16].

GLOBAL INITIATIVES ON CLIMATE CHANGE

The Lancet Countdown on Health and Climate Change is an international, multi disciplinary collaboration, dedicated to monitoring the evolving health profile of climate change, and providing an independent assessment of the delivery of commitments made by governments worldwide under the Paris Agreement. In 2019, the Lancet Countdown on Health and Climate Change [8] declared that the worst impacts of climate change are and will continue to be felt disproportionately by children.



Source:https://www.unicef.org/reports/unless-we-act-now-impact-climate-change-children

Fig. 1 Impact of climate change in children.

For more than 25 years, the World Health Organization (WHO) has been promoting a multi-sectoral approach to dealing with the health impacts of climate change. WHO supports countries to ensure national ownership and the building of a community of practice on climate change and health at national, regional and global levels. Tools and training manuals on a wide range of topics on climate change and health are available under the WHO toolkit of climate change and health resources [17]. Furthermore, national, regional and global trainings and educational material on relevant topics are organized as part of the implementation of both overall WHO initiatives and specific projects on climate change and health.

INDIAN INITIATIVES ON CLIMATE CHANGE

India's contribution to the world's cumulative greenhouse gas emissions is less than 4% and India's annual per capita emissions are about one-third of the global average. Despite this, India aspires to enhance its 2015 commitment to reducing emissions intensity (the amount of emissions per unit of gross domestic product) by 45% from 2005 levels by 2030. At the United Nations Climate Conference in 2022, India promised to meet its 50% energy demand from renewable sources of energy and unveiled a strategy to achieve low-carbon growth, which included expanding and stabilizing the renewable electricity grid, and phasing down coal. India aims to achieve net zero emissions by 2070 [18]. India submitted its long-term low emissions growth strategy indicating low carbon transition pathways in key economic sectors. Responding to the call for increased ambition in its 2030 climate targets, India updated its Nationally Determined Contributions in August, 2022. India has embarked on new initiatives in renewable energy, e-mobility, ethanol blended fuels, and green hydrogen as an alternate energy source. India is seeking to foster strong international cooperation through action and solutions-oriented coalitions like International Solar Alliance and Coalition of Disaster Resilient Infrastructure, both of which were launched and nurtured by India.

The hot summers are causing a surge in demand for fans and air conditioning in many parts of India. This will further strain India's electric power grid. According to India's National Action Plan on Climate Change [19], only 6% of India's electricity comes from solar and wind power, while 55% is from coal. The India Cooling Action Plan [20] calls for more access to cooling for India's growing population, using greener coolants.

ROLE OF PEDIATRICIANS IN ADDRESSING CLIMATE CHANGE

Pediatricians have a key role to play in urging the government to make ambitious strides to reduce coal and other fossil fuels and move to renewable energy sources such as solar and wind. This will reduce India's carbon emissions and reduce environmental illness among children. Many pediatricians; however, learn very little in medical school about the harmful effects of burning fossil fuels, and they seldom take time to contact their policymakers or counsel parents about reducing the harms to children from climate change. The results of a multi-national survey of views of health professionals on climate change and health revealed that time constraints were the biggest factor affecting the willingness of health professionals to communicate about the impacts of climate change on health. Other factors that affected the willingness to communicate included lack of knowledge and belief that communication would not make a difference, lack of support from peers, perception of controversy, and perceived personal or professional risk [21]. It is important, therefore, to have programs for awareness and capacity building among pediatricians to increase their familiarity with the impact of climate change on the health of children and their competence in educating parents about preventive measures [22].

The International Pediatric Association (IPA) has been working on this issue for many years. An IPA environmental health advisory group was started in 2001. IPA also founded the International Pediatric Environmental Health Leadership Institute in 2005 to better prepare the world's pediatricians to address environmental health issues and climate change. IPA held one-day intensive environmental health workshops for pediatricians in 2007, 2010, 2013, 2016 and 2023. Pediatricians who successfully completed a workshop and passed an examination were accepted into the International Pediatric Environmental Health Leadership Institute. The climate crisis has been a key topic in each workshop, and pediatricians have used the knowledge gained in the workshops to provide education about climate change and child health during their national pediatric meetings. Such programs empower pediatricians to address the issues effectively, fostering interdisciplinary collaboration and creating case studies that can be used to educate communities [23].

In clinical practice, pediatricians can start using the green page, developed by the World Health Organization to guide clinicians in taking an environmental history, to discuss climate change and air pollution exposures, and counsel parents accordingly [24].This will help the pediatricians in detecting the presence or risk of environmental factors in their patient, and also guide them to counsel parents for preventive and therapeutic management.

IPA made a commitment to address the climate crisis as a child health crisis in 2021 [25]. The pediatric societies' declaration outlined the necessary actions that pediatric societies must take to achieve an equitable and just transition

to a sustainable planet for all children. It provided information about climate change and child health for national pediatric societies to use in their educational programs.

EFFORTS BY INDIAN PEDIATRICIANS

Mata Bhumihiputroohumpruthvyaha
(Earth is my mother, and I am her child)
-Atharvaveda

This statement signifies the importance of earth in Indian culture. With this in mind, in the year 2000, IAP started the Environment and Child Health Group (ECHG), a subspecialty group (currently 730 members). The ECHG mission is to create awareness among doctors and lay people about the impact of pollution on health of children and burden on the health care system, promote healthy and environmentally safe practices, promote research and entrepreneurship in environmental and child health, advocacy for safe environments and protection of child health and promote public private partnership in developing green belts, by organizing, participating and promoting activities like tree planting, water conservation and air quality. The members of this group do advocacy and capacity building for environmental issues and regularly hold webinars for both professionals and the community. Members also strive to counsel parents regarding environmental issues and suggest measures that the entire family can adopt. Recently ECHG made guidelines for conducting environmentally-friendly IAP conferences.

In 2021, the Indian Academy of Pediatrics (IAP) was one of the first national societies to endorse the pediatric societies' declaration. Pediatricians are aware that Indian parents are already concerned about this issue. A survey found that 63% of the public in India thought global warming would cause a great deal of harm to Indians. Furthermore, over half or more said global warming will cause many more disease epidemics (59%), severe heat waves (54%), severe cyclones (52%), and droughts and water shortages (50%) in India over the next 20 years, if nothing is done to address it [26]. Pediatricians are uniquely positioned to engage with other health professionals and child advocates in developing comprehensive strategies to prevent and mitigate the impact of the global climate crisis on children and youth.

Additional Actions That Pediatricians Can Take

Although much progress has been achieved, there are additional ways that pediatricians can elevate the issue of the climate crisis and its impact on child health. For example, pediatricians can advocate with policymakers for greater use of renewable energy to reduce air pollution and climate change caused by burning of fossil fuels. Pediatricians can advocate that city leaders take steps to develop city-level climate change response policies [27] by promoting the air quality index, substituting clean and renewable energy in place of polluting coal, and promote adaptation to warming through reflective cool roofs that can reduce cooling energy demand in buildings. In Ahmedabad, these have been documented to achieve substantial air quality and health co-benefits [28]. As malnutrition is likely to increase, pediatricians should advocate that food systems be strengthened to withstand hazards and ensure continued access to healthy diets. Increased investments must be made in the early prevention, detection and treatment of severe malnutrition in children. Children need climate change education, disaster risk reduction education, green skills training and opportunities to meaningfully participate and influence climate policy making. Pediatricians should partner with children and work to build youth capacity.

CONCLUSION

Now is the time for pediatricians to raise their voices to prevent a climate catastrophe for children [29]. Pediatricians are respected by policymakers and government leaders and they should ask those leaders to reduce greenhouse gas emissions. The pediatricians of India should declare that climate change is a child health emergency and urge the government to immediately revisit its national climate plan and policies to increase action.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Intergovernmental Panel on Climate Change, 2023: Summary for Policymakers. *In*: Lee H, Romero J, editors. Climate Change 2023: Synthesis Report. A Report of the Intergovernmental Panel on Climate Change. Contribution of Working Groups I, II and III to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. IPCC, 2023. Accessed June 8, 2023. Available from:*https://www.ipcc.ch/report/ar6/syr/downloads/report/IPCC_AR6_SYR_SPM.pdf*
2. Friedlingstein, P, Jones MW, O'Sullivan M, et al. Global Carbon Budget 2019, Earth.SystSci Data. 2019;11:1783–1838.
3. Eckstein D, Künzel V,Schäfer L,Winges M. Global Climate Risk Index 2020. Who Suffers Most from Extreme Weather Events? Weather-Related Loss Events in 2018 and 1999 to 2018. 2019. Accessed 9 June, 2023. Available from:*https://germanwatch.org/sites/default/files/20-2-01e%20Global%20Climate%20Risk%20Index%202020_13.pdf*
4. United Nations Department of Economic and Social Affairs, Population Division [2022]. World Population Prospects 2022: Summary of Results. UN DESA/POP/2022/TR/NO. 3. Accessed on 8 June, 2023. Available from: *https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf*
5. Government of India. The Economic Survey 2018.Accessed 8 June 2023. Available from: *https://www.indiabudget.gov.in/budget2019-20/economicsurvey/doc/echapter.pdf*
6. Heatwave in India: Schools closed, school timings changed in these states.India Today, April 18, 2023. Accessed on 8 June, 2023. Available from:*https://www.indiatoday.in/education-to-*

day/news/story/heatwave-in-india-schools-closed-school-timings-changed-in-these-states-2361471-2023-04-18

7. Deaths due to heat stroke at Maharashtra event rise to 13.NDTV April 17, 2023. Accessed on 8 June, 2023.Available from:*https://www.ndtv.com/india-news/deaths-due-to-heat-stroke-at-maharashtra-event-rise-to-12-3954760*
8. Watts N, Amann M, Arnell N, et al. The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. Lancet. 2019;394:1836-78.
9. Pawankar R, Wang JY, Wang IJ, et al. Asia Pacific Association of Allergy Asthma and Clinical Immunology White Paper 2020 on Climate Change, Air Pollution, and Biodiversity in Asia-Pacific and Impact on Allergic Diseases. Asia Pac Allergy. 2020;10:e11.
10. Paramesh H. Asthma in children: Seasonal variations. Int J Environment and Health 2008;2: 10.1504/IJENVH.2008.020932.
11. Singh S, Sharma BB, Sharma SK, Sabir M, Singh VISAAC collaborating investigators. Prevalence and severity of asthma among Indian school children aged between 6 and 14 years: associations with parental smoking and traffic pollution. J Asthma. 2016;53:238-44.
12. Jocob S. How heatwaves and climate change impact children. Accessed on May 3, 2023. Available from: *https://www.theweek.in/news/sci-tech/2022/06/05/how-heatwaves-and-climate-change-impact-children.html*
13. UNICEF warns urgent action is needed to increase funding for adaptation to protect children and vulnerable communities from worsening heatwaves and other climate shocks. Accessed June 4, 2023. Available from:*https://www.unicef.org/press-releases/heatwaves-report*
14. Office of the United Nations High Commissioner for Human Rights. Analytical study on the relationship between climate change and the full and effective enjoyment of the rights of the child - Report of the Office of the United Nations High Commissioner for Human Rights. OHCHR, 2017. Accessed May 2, 2023. Available from: *https://www.ohchr.org/en/documents/reports/analytical-study-relationship-between-climate-change-and-full-and-effective*
15. Faustini P. The Challenges of Climate Change: Children on the Front Line. Innocenti Insights, 2014. Accessed May 3, 2023. Available from: *https://www.unicef-irc.org/publications/716-the-challenges-of-climate-change-children-on-the-front-line.html*
16. Diwakar V, Lovel E, Opitz-Stapleton S, Shepherd A,Twigg J. Children poverty disasters and climate change: Investigation relationships and implications over the life course of children. Chronic Poverty Advisory Network, March 2019. Accessed April 2, 2023. Available from: *https://cdn.odi.org/ media/ documents/12616.pdf*
17. World Health Organization.Toolkit of climate change and health resources.Accessed 8 June, 2023. Available from: *https://www.who.int/teams/environment-climate-change-and-health/climate-change-and-health/capacity-building*
18. Ministry of Environment, Forest and Climate Change, Government of India. National statement of India delivered at COP27 posted on 15.11.2022 by PIB Delhi. Accessed 8 June, 2023. Available from: *https://pib.gov.in/Press ReleasePage.aspx?PRID=1876119*
19. Ministry of Environment, Forest and Climate Change, Government of India. National Action Plan on Climate Change. 2018. Accessed 8 June, 2023. Available from: *https://moef.gov.in/wp-content/uploads/2018/04/Pg01-52_2.pdf*
20. Ministry of Environment, Forest and Climate Change, Government of India. India Cooling Action Plan.Accessed 8 June, 2023. Available from:*https://moef.gov.in/en/india-cooling-action-plan/*
21. Kotcher J, Maibach E, Miller J, et al. Views of health professionals on climate change and health: a multinational survey study. Lancet Planet Health. 2021;5:316-23.
22. Health workers training.The Hindu.Accessed June 5, 2023. Available from: *https://www.thehindu.com/news/national/karnataka/two-day-training-programme-on-climate-change-and-its-impact-on-health/article66440105*
23. Parmesh H, Sankam J.Health in a changing climate: empowering health professionals meeting report.Curr Sc. 2023;124: 1027-8.
24. World Health Organization. Children's environmental record green page.Accessed 9 June, 2023. Available from:*https://www.who.int/publications/m/item/children-s-environmental-record–green-page*
25. Etzel RA, Ding J, Gil SM, et al. Pediatric societies' declaration on responding to the impact of climate change on children. Journal of Climate Change and Health. 2021;4:10038.
26. Leiserowitz A, Thaker J, Carmen J, et al. Climate Change in the Indian Mind, 2022. Accessed 10 Feb, 2023. Available from*https://climatecommunication.yale.edu/publications/climate-change-in-the-indian-mind-2022/*
27. Limaye VS, Knowlton K, Sarkar S, et al. Development of Ahmedabad's Air Information and Response (AIR) Plan to Protect Public Health. Int J Environ Res Public Health. 2018; 15:1460.
28. Limaye VS, Magal A, Joshi J, et al. Air quality and health cobenefits of climate change mitigation and adaptation actions by 2030: an interdisciplinary modeling study in Ahmedabad, India. Environ Res Health 2023;1:021003.
29. UNICEF. Over the Tipping Point.UNICEF East Asia and Pacific Regional Office. 2023. Accessed 8 June, 2023. Available from:*https://www.unicef.org/eap/media/13501/file/Over%20the%20tipping%20point_report.pdf*

RESEARCH PAPER

Impact of Delivery Room Gastric Lavage on Exclusive Breastfeeding Rates Among Neonates Born Through Meconium-Stained Amniotic Fluid: A Randomized Controlled Trial

RAHUL KUMAR CHAUDHARY,[1,2] SUMAN CHAURASIA,[1] POONAM SINGH,[1] MAYANK PRIYADARSHI,[1] NOWNEET KUMAR BHAT,[2] JAYA CHATURVEDI,[3] SRIPARNA BASU[1]

[1]*Department of Neonatology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand.*
[2]*Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand.*
[3]*Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand.*
Correspondence to: Prof Sriparna Basu, Department of Neonatology, All India Institute of Medical Sciences, Rishikesh,Uttarakhand. sriparna.neonat@aiimsrishikesh .edu.in
Received: December 26, 2022; Initial review: January 23, 2023; Accepted: March 4, 2023.

Background: Delivery-room gastric lavage reduces feeding intolerance and respiratory distress in neonates born through meconium-stained amniotic fluid (MSAF).

Objectives: To evaluate the effects of gastric lavage on exclusive breastfeeding and skin-to-skin contact in neonates delivered through MSAF.

Design: Randomized controlled trial.

Participants: 110 late preterm and term neonates delivered through MSAF not requiring resuscitation beyond initial steps.

Methods: Participants randomized into gastric lavage (GL) (*n*=55) and no-GL (*n*=55) groups. The primary outcome was the rate of exclusive breastfeeding at 72±12 hours of life. Secondary outcomes were time to initiate breastfeeding and establish exclusive breastfeeding, rate of exclusive breastfeeding at discharge, time to initiate skin-to-skin contact and its duration, rates of respiratory distress, feeding intolerance, and the procedure-related complications of gastric lavage monitored by pulse oximetry and videography.

Results: Both the groups were similar in baseline characteristics. 49 (89.1%) neonates in GL group could achieve exclusive breast-feeding at 72 hours compared to 48 (87.3%) in no-GL group [RR (95% CI) 1.02 (0.89-1.17); *P*=0.768]. Initiation of skin-to-skin contact was significantly delayed and the total duration was significantly less in GL group compared to no-GL group. No difference in respiratory distress and feeding intolerance was observed. Procedure-related complications included retching, vomiting, and mild desaturation.

Conclusions: Gastric lavage did not help to establish exclusive breastfeeding, delayed the initiation of skin-to-skin contact in delivery room and reduced its total duration. Moreover, the procedure of gastric lavage was associated with neonatal discomfort.

Keywords: *Feeding intolerance, Outcome, Respiratory distress, Skin-to-skin contact.*

Trial registration: Clinical Trial Registry of India: CTRI/2021/03/031727

Published online: March 20, 2023; **PII**: S097475591600515

In utero passage of meconium complicates 9-12% of deliveries [1], exposing these neonates to the risk of developing various respiratory as well as non-respiratory complications. Over two decades back, Narchi, et al. [2], for the first time, reported the beneficial role of gastric lavage in neonates delivered through meconium-stained amniotic fluid (MSAF). Subsequently, multiple randomized controlled trials [3-6] and meta-analyses [7,8] documented similar benefits of prophylactic gastric lavage in the delivery room, particularly for the reduction in the incidence of feeding intolerance. The rationale cited by the authors for performing gastric lavage included prevention of meconium-induced gastritis, reported to be almost three times more common in this group [9], and a reduction in the risk of meconium aspiration syndrome (MAS) caused by the secondary aspiration of meconium-stained stomach contents during vomiting [6]. Based on this evidence, many neonatal units continue to perform prophylactic gastric lavage on the basis of treating unit's protocols.

However, the trials advocating gastric lavage did not assess its effect on clinically more relevant outcomes such as the rate of early establishment of exclusive breast-feeding and initiation of skin-to-skin contact [8], which may be delayed by the intervention. Initiation of breast-feeding within one hour of birth is associated with decreased

Invited Commentary: Pages 701-02

neonatal mortality and improved childhood survival [10-12]. Similarly, immediate skin-to-skin contact has enormous benefits to the mother and the infant in the form of better temperature maintenance, promotion of early breastfeeding

initiation and exclusive breastfeeding rate, and improvement of mother-infant bonding [13]. The resuscitation guidelines endorse the practice of skin-to-skin contact and early breastfeeding at birth [14].

Although, gastric lavage is apparently an innocuous procedure, but it may be associated with several short- and long-term adverse effects such as feeding tube malposition [15], oxygen desaturation, bradycardia [16], gastrointestinal perforations [17], retching, disruption of pre-feeding behavior [18], and development of functional gastrointestinal disorders later in life [19]. These adverse effects have not been rigorously assessed in previous trials.

Standard guidelines do not discuss about the role of gastric lavage in neonates born through MSAF and there is a paucity of studies that have been conducted with meticulous monitoring of the procedure. The present study was planned to evaluate the effects of gastric lavage on the establishment of exclusive breastfeeding and skin-to-skin contact, incidence of in-hospital morbidities including respiratory distress, feeding intolerance, and procedure-related complications among late preterm and term neonates delivered through MSAF.

METHODS

This parallel-group randomized controlled trial was conducted over 17 months (March, 2021 to August, 2022) after obtaining approval from the institutional ethics committee. The trial was prospectively registered with Clinical Trial Registry of India. Written informed consent in the local language was taken from the parents before enrollment.

Settings and study population: The study was conducted in a level III tertiary care hospital with a 24-bedded neonatal intensive care unit (NICU) serving as a referral center in the state. Our unit policy adheres to baby friendly hospital initiatives (BFHI), and we have a policy of initiating and aggressively promoting exclusive breastfeeding unless justified.

The study population comprised of inborn neonates of gestational age (GA) ≥34 weeks delivered through MSAF not requiring resuscitation beyond 'initial steps' [14]. Exclusion criteria included presence of major congenital anomalies, known contraindications to breast-feeding, and failure to obtain parental consent.

The primary outcome was the rate of exclusive breastfeeding at 72±12 hours of life, defined as the proportion of neonates on breastfeeding as exclusive mode of feeding in previous 24 hours. Secondary outcomes included time to initiate breastfeeding, proportion of neonates in whom breastfeeding could be started within one hour after delivery, time to establish exclusive breastfeeding, rates of exclusive breastfeeding at discharge, time to initiate skin-to-skin contact in vaginal deliveries and its duration, rates of feeding intolerance (defined as >2 vomiting in any 4 hour period or >3 in 24 hour; or abdominal distension i.e., increase in abdominal girth of >2 cm from baseline) [3], incidence of respiratory distress, need and duration of respiratory support, other morbidities, final outcome, duration of hospital stay, and the incidence of procedure- related complications of gastric lavage monitored by pulse oximetry and videography.

Randomization, group allocation and blinding: Randomization was done by computer-based variable-block random sequence (*http://www.sealedenvelope.com*) stratified to two gestational age-based subgroups, late preterm (34-36 weeks) and term (≥37 weeks), generated by an independent statistician, not involved in the study. Eligible neonates were randomly allocated soon after delivery to either gastric lavage (GL) or no-GL group. Gastric lavage was performed by designated nursing officers attending delivery, particularly trained for this purpose prior to the commencement of the trial. Allocation concealment was ensured using sequentially numbered sealed and opaque envelopes. Though the procedure was open-label due to the nature of the intervention, outcome assessors and the statistician were blinded regarding the group allocation.

Intervention: Neonates allocated to GL group were shifted to pre-warmed radiant warmer after delivery. All necessary equipment for gastric lavage were kept ready before delivery. After thoroughly drying and covering the neonate with dry warm linen, a Masimo Rad-97 pulse oximeter probe was attached to the right wrist. An 8-Fr feeding tube was inserted orally with length equal to the distance from the bridge of the nose to the earlobe and from the earlobe to a point halfway between the xiphoid process and the umbilicus. After confirming the position of the orogastric tube by aspiration of stomach contents and pushing of air, lavage was done with 20 mL of normal saline. The whole procedure was done under strict asepsis and the entire procedure was videotaped. Neonates in no-GL group were managed as per the standard resuscitation guidelines [14].

Delayed cord clamping was done in both groups except in non-vigorous newborns, where early cord clamping was done, and the neonate was shifted to pre-warmed radiant warmer for initial steps. All neonates delivered vaginally were subjected to skin-to-skin contact accord-ing to Early Essential Newborn Care package policy of World Health Organization (WHO) [20], immediately after delivery in no-GL group, and after the procedure in those who underwent gastric lavage. The time to start as well as the duration for skin-to-skin contact were recorded by a digital stopwatch.

All infants were monitored for the development of complications, if any. Stable neonates were roomed in and

nursed with their mothers in postnatal ward. Those who developed respiratory distress or any other complication were admitted to the NICU and were managed as per our unit policy. The mothers of both the groups were counseled and helped to establish exclusive breastfeeding by lactational counselors. Enrolled neonates were monitored and followed up till discharge. Video-clips were scrutinized to note the clinical as well as pulse oximetry details, heart rate and peripheral oxygen saturation (SpO_2).

Previous studies have not assessed the outcome of exclusive breastfeeding at 72±12 hours of life. Thus, we based our sample size on the surrogate of exclusive breastfeeding at 0-6 months from the national data published in the National Family Health Survey (NFHS)-4. It showed exclusive breastfeeding rates of around 55% amongst children aged 0-6 months [21]. Assuming a similar exclu-sive breastfeeding rate in our population, to detect a diffe-rence of 25% at an alpha level of 0.05 and a power of 80%, a sample size of 52 neonates per arm was calculated (*https://sealed envelope.com/*). Considering an attrition rate of 5%, the total sample size was calculated to be 110 (55 in each group).

Statistical analysis: Data were recorded in Microsoft Excel 2019 and analyzed in SPSS version 25.0 (IBM Corp) on intention-to-treat basis. Categorical measurements are presented as number (%) while continuous variables are presented as mean (SD) or median (IQR). Fisher exact test or the Chi-square test was used to compare categorical variables while Student *t* test or Mann-Whitney *U* test were used to compare continuous variables. Relative risk (95% CI) was calculated, where relevant.

Analysis of the primary outcome was planned a priori for the sub-groups viz., late preterm vs term, vaginally born vs cesarean section delivered, and thick vs thin MSAF. Time to achieve exclusive breastfeeding was evaluated by Kaplan-Meier survival plot analysis. A *P*-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 163 mothers with MSAF were assessed for eligibility, out of which 53 were excluded for various reasons. Moreover, the study had to be stopped for three months (April to June, 2021), coinciding with the second wave of COVID pandemic wherein the institute policies mandatorily separated all neonates from their mothers, compromising breastfeeding initiation and maintenance. Finally, 110 neonates were randomized into GL (*n*=55) and no-GL (*n*=55) groups. All neonates received allocated intervention and were analyzed. The flow of participants is depicted in **Fig. 1**.

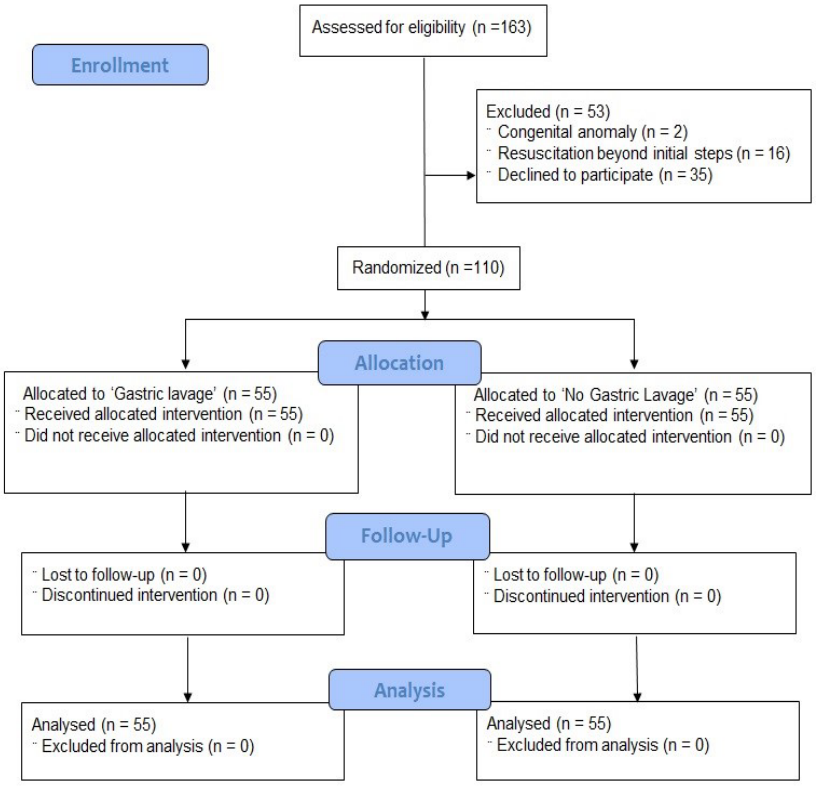


Fig. 1 Study flow diagram.

Both the groups were comparable with respect to maternal variables, intrauterine growth status, consistency of meconium, mode of delivery, birth weight (BW), GA, gender, vigorous cry at birth, and Apgar score. The mean (SD) GA of GL and no-GL groups were 38.5 (1.7) and 38.7 (2.1) weeks, respectively (*P*=0.586) **(Table I)**.

The rate of exclusive breastfeeding at 72±12 hours of life and other feeding outcomes are shown in **Table II**. A total of 49 (89.1%) neonates achieved exclusive breastfeeding at 72 hours compared to 48 (87.3%) in no-GL group [RR (95% CI) 1.02 (0.89-1.17); *P*=0.768]. There was no significant difference in the time to achieve exclusive breastfeeding between the two groups [Hazard Ratio (HR) (95% CI), 0.94 (0.63-1.40); *P*=0.771] **(Fig. 2).** The median age of first breastfeeding was 2 hours in both the groups (*P*=0.160). There were no differences in time to initiate breastfeeding, initiation of breastfeeding within first hour of birth, time to establish exclusive breastfeeding, and the rates of exclusive breastfeeding at discharge. Analyses in the pre-planned subgroups for the primary outcome did not reveal any significant difference (**Web Table I**). Overall, initiation of breastfeeding within first hour was possible in 25/27 (93%) of neonates delivered vaginally compared to 15/83 (18%) among LSCS (*P*<0.001).

In vaginally-delivered neonates, skin-to-skin contact could be initiated in 9/10 in GL and 16/17 in no-GL group **(Table III)**. One neonate in each group developed respiratory distress soon after birth and were shifted to the NICU. Initiation was significantly delayed in GL group [median (IQR) 0.3 (0.2,0.3) min in no-GL vs 16 (14,18) min in GL group; *P*<0.001]. Similarly, the total duration or dose of skin-to-skin contact was significantly longer in no-GL compared to GL group [62 (60,64) vs 50 (50,55) min; *P*<0.001)].

No differences were observed in other morbidities including the incidence of respiratory distress, duration of respiratory support, neonatal hyperbilirubinemia, hypoglycemia, polycythemia, and the duration of hospital stay. Feeding intolerance was observed in 1 (1.8%) neonate in GL group compared to 3 (5.4%) in no-GL group (*P*=0.308). There was no mortality in either group. Procedure related complications in GL group included retching (*n*=32; 58.2%), vomiting (*n*=5; 9%), and mild desaturation (SpO_2 <85%) (*n*=10; 18.2%). None of the neonates developed apnea, significant desaturation (SpO_2<80%) or brady-cardia (heart rate <100/min).

Table I Baseline Maternal and Neonatal Characteristics of Neonates Born Through Meconium Stained Amniotic Fluid Enrolled in the Study

Characteristics	*Gastric lavage (n=55)*	*No gastric lavage (n = 55)*
Maternal characteristics		
Age (y)[a]	27.1 (4.8)	26.6 (4.0)
Gravida[b]	2 (1,3)	2 (1,3)
Complete antenatal care	29 (52.7)	23 (41.8)
Oligohydraminos	6 (10.9)	9 (16.4)
PV leak >18 h	7 (12.7)	7 (12.7)
PIH	8 (14.5)	7 (12.7)
Anemia	15 (27.3)	16 (29.1)
Hypothyroidism	3 (5.5)	7 (12.7)
Fetal distress	20 (36.4)	15 (27.3)
Vaginal delivery	10 (18)	17 (31)
Thick meconium	31 (56.4)	30 (54.5)
Neonatal characteristics		
Birth weight (g)[a]	2695 (494)	2813 (476)
Gestational age (wk)[a]	38.5 (1.7)	38.7 (2.1)
Small for gestational age	21 (38)	16 (29)
Male	30 (54.5)	34 (61.8)
Vigorous baby	53 (96)	52 (95)
Apgar score [b]		
1 min	8 (8,9)	8 (8,9)
5 min	9 (9,9)	9 (9,9)
Received initial steps	2 (3.6)	3 (5.4)

Values in no. (%), [a]mean (SD) or [b]median (IQR); P>0.05 for all comparisons. PIH: pregnancy induced hypertension.

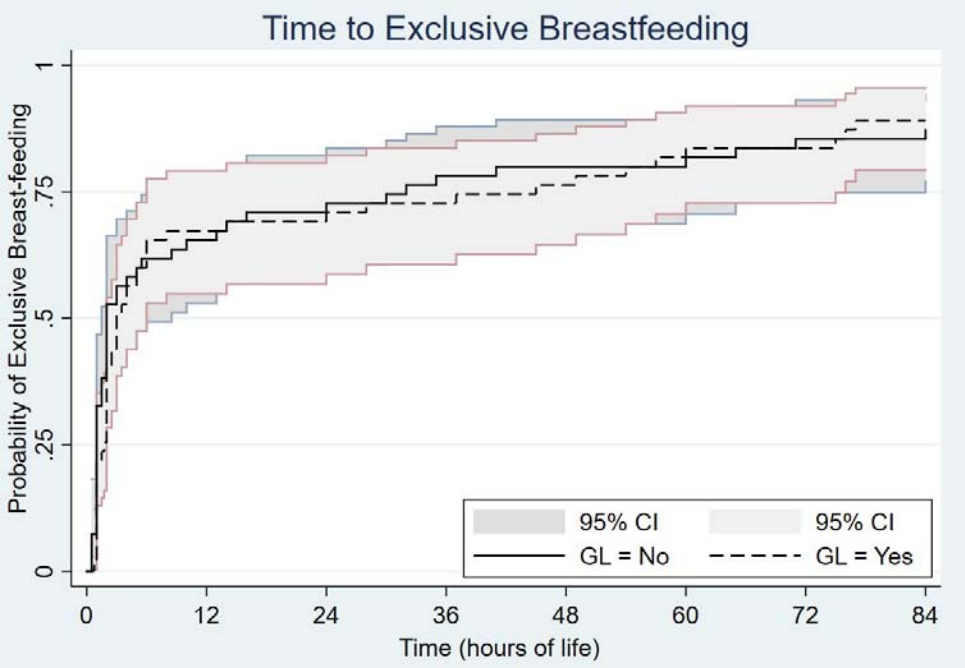
DISCUSSION

The present study sought to clarify the role of gastric lavage in late preterm and term neonates delivered through MSAF, especially with regards to breastfeeding. There was no significant difference in the rate of exclusive breastfeeding at 72 hours and at discharge, as well as the time of initiation and

Table II Breastfeeding Rates and Feeding Pattern Among Neonates With Meconium Stained Amniotic Fluid

Variables	*Gastric lavage (n=55)*	*No gastric lavage (n=55)*	*RR (95% CI)*
Exclusive breastfeeding rate at 72 (±12) h	49 (89.1)	48 (87.3)	1.02 (0.89-1.17)
Age at first breastfeeding (h)[a]	2 (1, 5)	2 (0.5, 10)	-
Initiation of breastfeeding within first hour of birth	16 (29.1)	17 (30.9)	-
Age of establishment of exclusive breastfeeding (h)[a]	3 (1.5, 27)	2 (1, 16)	-
Exclusive breastfeeding rate at discharge	52 (94.5)	53 (96.4)	0.98 (0.90-1.06)

Values in no. (%) or [a]median (IQR).



GL:gastric lavage in delivery room.

Fig. 2 Kaplan-Meier survival plot analysis for the outcome of 'time to achieve exclusive breastfeeding' in gastric lavage and no-gastric lavage groups.

establishment of exclusive breastfeeding. The time of initiation of skin-to-skin contact in delivery room was significantly delayed in GL group, and the duration of skin-to-skin contact was also significantly less. Almost half of the neonates undergoing gastric lavage had retching and 14.5% had desaturation (SpO_2 <85%) as observed during the procedure.

Exclusive breastfeeding rate at 72 hours was chosen as the primary outcome variable because we postulated that a brief single intervention as gastric lavage may impact the initiation and maintenance of exclusive breastfeeding in the initial few days of hospital stay, rather than at discharge. Nearly 90% of neonates in both the groups achieved exclusive breastfeeding at around 72 hours and almost 95% at the time of discharge. The procedure of gastric lavage did not make a significant difference in establishment of exclusive breastfeeding. A possible reason could be strict adherence to BFHI guidelines in our unit and active support for exclusive breastfeeding in both the groups. There is a paucity of studies directly com-paring the effect of gastric lavage on the rate of exclusive breastfeeding in MSAF-delivered neonates.

Table III Secondary Outcomes Among Neonates With Meconium Stained Amniotic Fluid in the Two Groups

Variables	*Gastric lavage (n=55)*	*No gastric lavage (n=55)*
Underwent skin-to-skin contact[a]	9 (16.4)	16 (29.1)
Time of initiation of skin-to-skin contact after delivery (min)[a,b,d]	16 (14, 18)	0.3 (0.2, 0.3)
Duration of skin-to-skin contact (min)[a,b]	50 (50, 55)	62 (60, 64)
Respiratory distress requiring respiratory support	5 (9.1)	8 (14.5)
Duration of respiratory support (h)[b]	6 (4, 49)	4 (2, 26)
Neonatal hyperbilirubinemia requiring phototherapy	10 (18.2)	7 (12.7)
Feeding intolerance	1 (1.8)	3 (5.4)
Hypoglycemia[c]	2 (3.6)	1 (1.8)
Polycythemia (*hematocrit* >65%)[c]	2 (3.6)	1 (1.8)
Duration of hospital stay (h)[b]	85 (57, 120)	80 (48, 97)

Values in no. (%) or [b]median (IQR). [a]One neonate in each group developed respiratory distress soon after birth and were shifted to neonatal intensive care unit; [c]asymptomatic. [d]P<0.001. No child had sepsis screen and/or culture-positive sepsis.

WHAT IS ALREADY KNOWN?

- Delivery room gastric lavage reduces feeding intolerance, and is often claimed to decrease respiratory distress in neonates born through meconium-stained amniotic fluid (MSAF).

WHAT THIS STUDY ADDS?

- Gastric lavage in late preterm and term neonates delivered through MSAF did not affect achieving exclusive breastfeeding, though it delayed the initiation of skin-to-skin contact in delivery room and reduced its total duration.

Initiation of breastfeeding within first hour of birth was possible in only 30% neonates in either group. The rates are less than that reported by NFHS-5 (41.8%) [22] and a recent hospital-based study (43.5%) from southern India [23]. The reason for low rates in our set up could be high rates of cesarean delivery, due to it being a tertiary care referral center. Late shifting of the mother from the operation theater to ward, delayed wearing-off of anesthetic effect, and uncomfortable breastfeeding position after cesarean section probably led to this delay. Several syste-matic reviews corroborate this finding, with Yisma, et al. [24] reporting a 46% lower prevalence of early initiation of breastfeeding among cesarean section delivered mother-infant dyads [25].

The process of gastric lavage caused a significant delay in the initiation and the total duration of skin-to-skin contact. Delay in skin-to-skin contact deprives the neonates from its benefits including the opportunity of early feeding at breast. However, this delay of approximately 15 minutes might not be of much clinical relevance and this delay did not translate into a significant impact towards overall exclusive breastfeeding rates at 72 hours or discharge.

The present study did not find any difference in the incidence of respiratory distress and the duration of respiratory support between the two groups, which is similar to the findings reported by several previous authors [2-4,6]. Performing gastric lavage after delivery may not help to remove meconium that has been already aspirated in the lungs. Moreover, it may be the duration of in utero hypoxia that determines the development of meconium aspiration syndrome and respiratory distress, not the amount of meconium aspirated [26]. The incidence of feeding intolerance in previous trials varied from 4.6-35% and a significant reduction in the incidence of feeding intolerance was observed after gastric lavage [2-7]. The overall incidence of feeding intolerance was low in our study, and no difference was observed between the groups. Meconium-induced gastritis leading to vomiting and feeding intolerance was not a common finding in either group of our study, and needs to be evaluated in a wider group. Though, we did not come across any serious complications of gastric lavage in our study, majority of the neonates were not comfortable during the procedure as indicated by high rate of retching and occasional vomiting and desaturation. Stringent monitoring was lacking in prior trials, except one [6], and most of them did not report any adverse events [2-6].

The major strength of our study was the meticulous observation by pulse oximetry during the procedure of gastric lavage, and strict monitoring during hospital stay. However, there is a possibility that the study was not powered enough to detect a difference of less than 25% in exclusive breastfeeding rate. This effect size for sample size calculation was chosen based on the assumption that gastric lavage would hinder the initiation of skin-to-skin contact, which in turn would lead to lower exclusive breastfeeding rates during hospital stay [27]. However, skin-to-skin contact was not practiced during cesarean deliveries in our unit, which could have attenuated the effect of gastric lavage in the overall population. Additionally, we could not study the effect of gastric lavage in non-vigorous neonates due to the small numbers (n=5). Though MSAF may be associated with delivery of more preterm neonates (around 5% deliveries below 33 weeks in high income countries [28]), our study did not include them and so the results may be considered only for neonates born at ≥34 weeks.

Gastric lavage in late preterm and term neonates delivered through MSAF did not affect the attainment of exclusive breastfeeding. Moreover, it delayed the initiation of skin-to-skin contact in delivery room and reduced its total duration. Further, it did not reduce the incidence of respiratory distress, feeding intolerance, and other in-hospital morbidities. Thus, based on this trial, the procedure of routine gastric lavage appears unwarranted in neonates born through MSAF.

Ethics clearance: Institute Ethics Committee, AIIMS, Rishikesh; No: AIIMS/IEC/21/53/12/02/2021 dated Feb 12, 2021.
Contributors: SB, RKC, SC, PS, MP, NKB, JC: conceptualized and designed the study, coordinated, and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; RKC: collected the data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Viraraghavan VR, Nangia S, Prathik BH, et al. Yield of meconium in non-vigorous neonates undergoing endotracheal suctioning and profile of all neonates born through meconium-stained amniotic fluid: A prospective observational study. Paediatr Int Child Health. 2018;38:266-70.
2. Narchi H, Kulaylat N. Is gastric lavage needed in neonates with meconium-stained amniotic fluid? Eur J Pediatr. 1999;158: 315- 7.
3. Ameta G, Upadhyay A, Gothwal S, et al. Role of gastric lavage in vigorous neonates born with meconium stained amniotic fluid. Indian J Pediatr. 2013;80:195-8.
4. Sharma P, Nangia S, Tiwari S, et al. Gastric lavage for prevention of feeding problems in neonates with meconium-stained amniotic fluid: A randomised controlled trial. Paediatr Int Child Health. 2014;34:115-9.
5. Yadav SK, Venkatnarayan K, Adhikari KM, et al. Gastric lavage in babies born through meconium stained amniotic fluid in prevention of early feed intolerance: A randomized controlled trial. J Neonatal Perinatal Med. 2018;11:39-7.
6. Gidaganti S, Faridi MM, Narang M, Batra P. Effect of gastric lavage on meconium aspiration syndrome and feed intolerance in vigorous infants born with meconium stained amniotic fluid - A randomized control trial. Indian Pediatr. 2018;55:206-10.
7. Deshmukh M, Balasubramanian H, Rao S, Patole S. Effect of gastric lavage on feeding in neonates born through meconium-stained liquor: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2015;100:F394-9.
8. Singh P, Kumar M, Basu S. Gastric lavage for prevention of feeding intolerance in neonates delivered through meconium-stained amniotic fluid: A systematic review and meta-analysis. Indian Pediatr. 2021;58:973-7.
9. Narchi H, Kulaylat N. Feeding problems with the first feed in neonates with meconium-stained amniotic fluid. Paediatr Child Health. 1999;4:327-30.
10. World Health Organisation [WHO]. Indicators for Assess-ing Infant and Young Child Feeding Practices. Part 3: Country profiles. 2010. Accessed on March 20, 2021. Avail-able from: *http://www.who.int/nutrition/publications/infantfeeding/9789241599757/en/*
11. Edmond KM, Zandoh C, Quigley MA, et al. Delayed breast-feeding initiation increases risk of neonatal mortality. Pediatrics. 2006;117:e380-6.
12. Oot L, Sommerfelt A, Sethuraman K, Ross J. Estimating the effect of suboptimal breastfeeding practices on child mortality: A model in PROFILES for country-level advocacy. 2015. Accessed on Aug 2, 2021. Available from: *https://www.fantaproject.org/sites/default/files/resources/PROFILES-Breastfeeding-effect-Technical-Brief-Sept2015.pdf*
13. Moore ER, Bergman N, Anderson GC, Medley N. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev. 2016;11:CD003519.
14. Aziz K, Lee HC, Escobedo MB, et al. Part 5: Neonatal resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142:S524-50.
15. Quandt D, Schraner T, Ulrich Bucher H, Arlettaz Mieth R. Malposition of feeding tubes in neonates: Is it an issue? J Pediatr Gastroenterol Nutr. 2009;48:608-11.
16. Shiao SY, Youngblut JM, Anderson GC, DiFiore JM, Martin RJ. Nasogastric tube placement: effects on breathing and sucking in very-low-birth-weight infants. Nurs Res. 1995;44: 82-8.
17. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. Curr Opin Gastroenterol. 2007;23: 178-82.
18. Widström AM, Ransjö-Arvidson AB, Christensson K, et al. Gastric suction in healthy newborn infants. Effects on circulation and developing feeding behaviour. Acta Paediatr Scand. 1987;76:566-72.
19. Anand KJ, Runeson B, Jacobson B. Gastric suction at birth associated with long-term risk for functional intestinal disorders in later life. J Pediatr. 2004;144:449-54.
20. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (WHO/MCA/17.07). Accessed on August 22, 2020. Available from: *http://apps.who.int/iris*
21. Government of India. Ministry of Health and Family Welfare. National Family Health Survey-4, 2015-2016. Accessed on September 17, 2020. Available from: *http://rchiips. org/nfhs/pdf/NFHS4/India.pdf*
22. Government of India. Ministry of Health and Family Welfare. National Family Health Survey-5, 2019-2021. Accessed October 13, 2022. Available from: *http://rchiips.org/nfhs/factsheet_NFHS-5.shtml#*
23. Mary JJF, Sindhuri R, Kumaran AA, Dongre AR. Early initiation of breastfeeding and factors associated with its delay among mothers at discharge from a single hospital. Clin Exp Pediatr. 2022;65:201-8.
24. Yisma E, Mol BW, Lynch JW, Smithers LG. Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa. BMJ Open. 2019; 9:e027497.
25. Paksoy Erbaydar N, Erbaydar T. Relationship between caesarean section and breastfeeding: evidence from the 2013 Turkey demographic and health survey. BMC Pregnancy Childbirth. 2020;20:55.
26. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome. An update. Pediatr Clin North Am. 1998;45:511-29.
27. Moore ER, Bergman N, Anderson GC, Medley N. Early skin to skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev. 2016;11:CD003519.
28. Tybulewicz AT, Clegg SK, Fonfé GJ, et al. Preterm meconium staining of the amniotic fluid: associated findings and risk of adverse clinical outcome. Arch Dis Child Fetal Neonatal Ed. 2004;89:F328-30.

Web Table 1: Subgroup-wise analysis of the rate of exclusive breastfeeding

Variables	Gastric lavage	No gastric lavage	p-value
Among neonates born at term (gestational age ≥37 wk) (N = 94)			
Achieved exclusive breastfeeding at 72 ±12 h, n (%)	45 (93.8) (n = 48)	41 (89.1) (n = 46)	0.422[a] (NS)
Among neonates born late preterm (*gestational age* 34-36 wk) *(N = 16)*			
Achieved exclusive breastfeeding at 72 ± 12 h, n (%)	4 (57.1) (n = 7)	7 (77.8) (n = 9)	0.377[a] (NS)
Among neonates born vaginally (n = 27)			
Achieved exclusive breastfeeding at 72 ± 12 h, n (%)	9 (90) (n = 10)	16 (94.1) (n = 17)	0.693[a] (NS)
Among neonates born by LSCS (N = 83)			
Achieved exclusive breastfeeding at 72 ± 12 h, n (%)	40 (88.9) (n = 45)	32 (84.2) (n = 38)	0.531[a] (NS)
Among neonates born through thick MSL (N = 61)			
Achieved exclusive breastfeeding at 72 ± 12 h, n (%)	28 (90.3) (n = 31)	27 (90) (n = 30)	0.966[a] (NS)
Among neonates born through thin MSL (N = 49)			
Achieved exclusive breastfeeding at 72 ± 12 h, n (%)	21 (87.5) (n = 24)	21 (84) (n = 25)	0.726[a] (NS)

IQR – Interquartile range, LSCS – Lower section Cesarean section, MSL – Meconium-stained liquor, NS – Not significant, [a]Chi-square test

RESEARCH PAPER

Nasogastric vs Orogastric Feeding in Stable Preterm (≤32 Weeks) Neonates: A Randomized Open-Label Controlled Trial

NAVEEN PARKASH GUPTA, ZIA S AHMAD, REKHA MITTAL, SHYAM KUKREJA, CHETNANAND JHA, KAPIL RAHEJA
Department of Neonatology, Max Superspeciality Hospital, Patparganj, Delhi.
Correspondence to: Dr Naveen Parkash Gupta, Department of Neonatology, Madhukar Rainbow Children's Hospital, Delhi. drgupta.naveen@gmail.com
Received: June 20, 2022; Initial review: Sept 12, 2022; Accepted:March 22, 2023.

Background: Optimal route of tube feeding in preterm babies is not known.

Objective: To compare the frequency of bradycardia and desaturation episodes/hours in hemodynamically stable preterm neonates (≤32 wk gestational age) fed by nasogastric vs orogastric route.

Design: Randomized controlled trial.

Participants: Hemodynamically stable preterm neonates (≤32 wk gestational age) requiring tube feeding.

Intervention: Nasogastric vs orogastric tube feeding.

Primary outcome: Number of episodes of bradycardia and desaturations/hour.

Methods: Eligible preterm neonates fulfilling the inclusion criteria were enrolled. Each episode of insertion of a nasogastric tube or orogastric tube was labelled as a feeding tube insertion episode (FTIE). FTIE lasted from the time of insertion of tube till the time tube needed to be changed. Reinsertion of the tube in same baby was taken as a fresh FTIE. 160 FTIEs were evaluated during the study period, 80 FTIEs each in babies with gestational age <30 weeks and ≥30 weeks. Number of episodes of bradycardia and desaturation per hour were computed using records in the monitor till the time tube was in situ.

Results: The mean episodes of bradycardia and desaturations/hour [mean difference (95% CI) 0.144 (0.067-0.220); *P*<0.001] were higher in FTIE by nasogastric as compared to the oro-gastric route.

Conclusions*:* Orogastric route may be preferable to the nasogastric route in hemodynamically stable preterm neonates.

Keywords: *Apnea, Bradycardia, Desaturation, Tube feeding.*

Trial Registration: Clinicaltrials.gov: NCT03073993

Published online: April 20, 2023; **PII**: S097475591600531

Early nutrition in premature babies has long lasting benefits in form of improved neuro-developmental outcomes [1], with prolonged parenteral nutrition having its own demerits [2]. Guidelines advocate starting enteral nutrition as soon as a neonate is hemodynamically stable [3]. A functional suck-swallow-breathe pattern that allows for safe oral feeding is not present until 32 to 34 weeks postmenstrual age [4], and therefore tube feeding has been the gold standard of care. Infant feeding tube can be put through nose (nasogastric tube) (NGT) or mouth (orogastric tube) (OGT) and neonatal units have their preference depending upon the benefits and harms associated with these routes [5]. Naso-gastric tubes are easier to fix but they may increase airway resistance thereby increasing the possibility of more apneas, bradycardias and desaturations [6-8]. Their pro-longed use may lead to oral aversion. In a small study, babies with nasogastric tubes reached full feeds earlier than the orogastric group [9]. NGT feeding was associated with higher fluctuations in regional saturations (crSO2) and higher preterm infant pain profile (PIPP-R) scores as compared to OGT in a small study [10].

Since premature neonates are obligate nasal breathers, orogastric tube feeding may be associated with lesser chances of apnea, bradycardia and desaturation. Orogastric tube sometimes may provoke bradycardia because of vagal stimulation and their prolonged use is associated with palatal grooving. A recent systematic review included three quasi-randomized and randomized trials and concluded that there is insufficient evidence to support or refute use of one route over the other [11]. In the present study, we compared two feeding methods of tube feeding with respect to adverse effects. We hypothesized that the orogastric route for enteral feeding in preterm ≤32 weeks hemodynamically stable premature babies, who do not require respiratory support, decreases the frequency of bradycardias and desaturations/hour as compared to the nasogastric route.

Invited Commentary: Pages 703-04

METHODS

This was a prospective, open-label randomized controlled trial conducted at the neonatal intensive care unit (NICU) of

Max Superspeciality hospital, Patparganj, Delhi from September, 2015 to March, 2017. Hemodynamically stable preterm neonates (≤32 weeks gestational age) needing tube feeds, who were not receiving respiratory support (continuous positive airway pressure (CPAP)/heated humidified high flow nasal cannula (HHHFNC)/ventilation), were eligible. Neonates born at >32 weeks gestational age, having congenital malformations or chromosomal abnormalities, necrotizing enterocolitis, severe intraventricular hemorrhage (grade 3 or 4) were excluded. After obtaining a written informed consent from the parents, eligible participants were enrolled. Ethical clearance was obtained from institutional review board of the hospital. The trial was registered with clinical trials.gov.

A web-generated, stratified (GA <30 weeks and ≥30 weeks) randomization sequence with variable block sizes (*www.sealedenvelope.com*) was used to randomize the eligible neonates into two groups. A person not involved in the study performed the random number allocation. The allocation was concealed in serially numbered opaque, sealed envelopes with two alphanumerical codes. Owing to the nature of the study, blinding was not feasible.

Each episodes of insertion of either NGT or OGT were labelled as feeding tube insertion episodes (FTIE). FTIE lasted from the time of insertion of tube till time tube needed to be changed because of any reason (looping in mouth, sticking tape is loose, baby needing respiratory intervention, baby is transitioned to direct feeds or nurse preference). Tube was kept *in situ* unless it was necessary to change it because of above mentioned reasons. Duration of stay of tube was recorded in number of hours. Reinsertion of tube in same baby was taken as fresh FTIE. Tube insertion was done by trained NICU nursing staff. A 5F infant feeding tube was used for babies weighing <1000 g. For babies with weight between 1000-1500 g, 6F infant feeding tube was used. Length of NGT/OGT insertion was calculated by distance from bridge of nose to ear lobe and then from ear lobe to midway between xiphisternum and umbilicus (nose-ear-mid-umbilicus, NEMU) [12]. Correct tube placement was checked by first aspirating and then pushing in 2 mL air and listening by stethoscope placed at the left hypochondrium.

The primary outcome of the study was the number of episodes of bradycardia and desaturation/hour. The secondary outcome was duration of stay of tube (hours). We defined bradycardia as heart rate <100/min and desaturation as SpO2 <85% for our study. Alarms on the multi-function monitors (Philips MP 20 Neonatal) were set with the lower limit of heart rate as 100/min and a lower limit of saturation as 85%. The monitors used signal extraction technology. Episodes were recorded on a form, kept at the bedside by the duty nurse. Each time the monitor gave an alarm for desaturation and/or bradycardia, the nurse checked the baby and the monitor. If the waveform was regular and the probe was attached properly to the baby, the episode was recorded. The total number of episodes was calculated till the time tube was *in situ*. Since the duration of NG and OG tubes may vary, the number of episodes of bradycardia and/or desaturation episodes/hour were compared.

Standardized feeding protocol was followed in the unit. Two-hourly feeds were given. For babies with birth-weight <750 g, feeds were initiated at 10 mL/kg/day and advanced at a rate of 20 mL/kg/d depending upon tolerance. For babies with birthweight between 750-1000 g feeds were initiated at 20 mL/kg/d and advanced at 20 mL/kg/d. For babies with birthweight between 1001-1500 g, feeds were initiated at 20 mL/kg/day and advanced at 30 mL/kg/day. Pre-feed abdominal circumference was taken by paper tape. If it increased by more than 2 cm, aspiration of gastric content was done. If aspirates were abnormal (bilious/bloody), feeds were stopped for at least 48 hours. If aspirates were milky, subsequent feeds were decided on the basis of volume. If the volume of aspirate was <50% of the previous feed, the same amount was continued. If the volume was >50%, feeds were withheld. Prophylactic caffeine was used for babies <1000 g and/or ≤30 weeks for the prevention of bronchopulmonary dysplasia. In babies 1000-1500 g and/or 31-34 weeks, caffeine was started when baby had apnea.

As per the unit protocol, nurse to neonate ratio was 1:1 for extremely low birth weight, ventilated/CPAP babies and 1:2 for stable babies not needing any respiratory support. For babies enrolled in the study, we provided 1:1 nurse-to-neonate ratio.

In a previous study [13], the median episodes of bradycardia and desaturation in feeding via nasogastric route were 1.6 episodes/hour [13]. Standard deviation was calculated as 1.35 using the confidence interval provided. With an aim of detecting a difference of 50%, at two-sided 5% level of significance and power of 80%, a sample size of 23 FTIE for each group was needed. We took a larger sample size of 80 for each group.

Statistical analysis: Statistical analysis was done by SPSS 20. Patient data were analyzed as per their assigned group (Intention to treat). For continuous variables, Student *t* test was applied. Chi-square test and Fischer exact test were used to analyze categorical variables.

RESULTS

During the enrolment period (September, 2015 to March, 2017), 50 neonates were admitted to the NICU who were potentially eligible for the study. Of these, 21 babies were stratified in to two groups viz., gestational age <30 weeks and gestational age of 30-32 weeks (**Fig. 1**). A total of 160 FTIE

were done as per randomization sequence with 40 FTIE of each type in each group. The mean (SD) gesta-tional age and birth weight was 29.3 (2.3) weeks and 1112.5 (450) g, respectively. The mean (SD) postmenstrual age at enrolment was 31.3 (1.8) weeks. The mean (SD) number of bradycardia episodes were 3.8 (3.8), and desaturation episodes were 4.04 (4.8) in the study population (**Table I**).

The mean episodes of bradycardia and desaturations/ hour were significantly lower [MD (95% CI) 0.144 (0.067-0.220); *P*<0.001] in the OGT group as compared to the NGT group (**Table II**). This translates to approximately 3.5 (1.6-5.3) lesser episodes of bradycardia and desaturations in 24 hours in the orogastric group. The effect was also consistent in babies with gestational age below 30 weeks [MD (95% CI) 0.241 (0.093-0.388); *P*=0.002]. In babies with gestational age ≥30 wks, combined episodes of bradycardia and desaturation were again less in OGT as com-pared to NGT [MD (95% CI) 0.047 (0.009-0.084); *P*=0.002]. However, when we looked for only bradycardia episodes, no difference was observed.

The mean (SD) duration of tube stay was similar whether it was put through the nasogastric or orogastric route [31.9 (7.5) vs 31 (6.1) hours], the mean difference (95% CI) found was 0.9 hours (-1.3 to 3.0). Tube displacements were similar in both groups. Reasons for tube change like self-pulling by baby, and loosening of sticking tape were similar in both groups. In the orogastric group, maximum tubes were changed because of loop formation. No unintended harms or events were seen in the study related to the intervention.

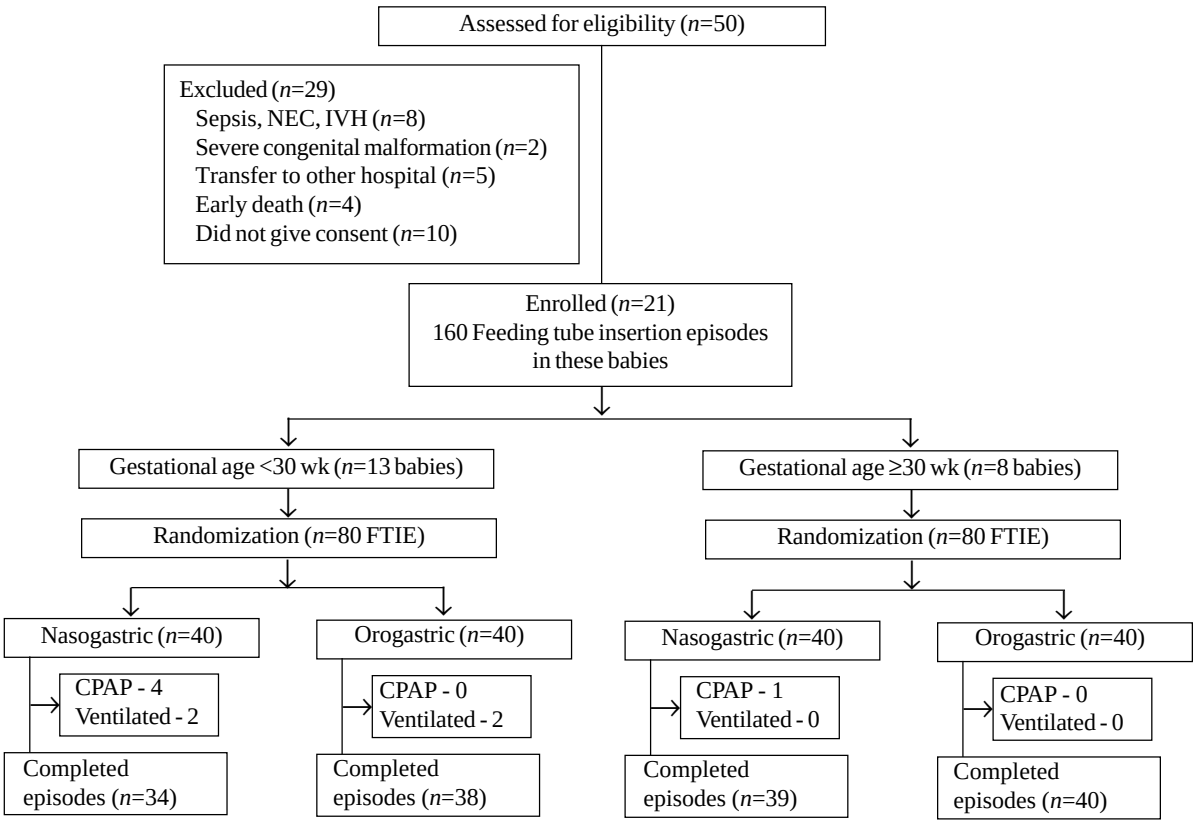
Table I Baseline Characteristics of Neonates Receiving Nasogastric or Orogastric Tube Feeding (*N*=21 babies)

Patient characteristics	*GA <30 wk, n=13*	*GA 30-32 wk, n=8*
FTIE	80	80
Gestational age (wk)[a]	27.5 (2.3)	30.2 (1.5)
Male sex	8 (61.5)	3 (37.5)
Birthweight (g)[a]	1017.53 (300)	1208 (350)

Values in no (%) or [a]mean (SD). FTIE: feeding tube insertion episodes.

DISCUSSION

Our study tested orogastric feeding vs nasogastric feeding to assess clinical outcomes in form of episodes of desatu-



NEC: *necrotizing enterocolitis*; *IVH*: *intraventricular hemorrhage*; *CPAP*: *continuous positive airway pressure.*

Fig. 1 Flow of patients in the study.

Table II Episodes of Bradycardia and Desaturations in Neonates Receiving Nasogastric or Orogastric Tube Feeding

Events	*Nasogastric tube group (n=80)*	*Orogastric tube group (n=80)*	*Mean difference (95% CI)*	*P value*
Episodes of bradycardia and desaturations/h	0.38 (0.426)	0.14 (0.194)	0.24 (0.093-0.388)	0.002
Bradycardia episodes/h	0.17 (0.187)	0.09 (0.112)	0.08 (0.012-0.152)	0.021
Desaturation episodes/h	0.22 (0.262)	0.05 (0.104)	0.16 (0.072-0.253)	0.001

ration and bradycardia in hemodynamically stable preterm babies of ≤32 weeks gestational age not requiring any respiratory support. Fewer adverse events (bradycardia and desaturation episodes) were seen in orogastric route as compared to nasogastric route in our study. Nasogastric tube is easy to put and easy to fix. However increase in nasal resistance and total airway resistance has been associated with NGT [6-8]. More increase in airway resistance was observed when nasogastric tube was put through larger bore nostril as compared to smaller one [6]. Few studies have demonstrated increase in airway resistance while putting NGT [7]. The adverse effects of NGT on respiratory function compromise persist even after a week of NGT placement [8]. There was no apparent clinical compromise seen in a study assessing acute effects of NGT and OGT placement on respiratory function assessed by pneumotachography [7]. However, infants weighing less than 2 kg demonstrated diminished minute ventilation and respiratory rate and had increased pulmonary resistance, resistive work of breathing, and peak transpulmonary pressure change with NGT as compared to OGT placement [7].

In another study [8], on seventh day of tube insertion, a significantly lesser number of central apneas and lesser periodic breathing was found in oro-enteric with palatal appliance tube [8]. We had similar observations. Another study involving 10 neonates showed significantly lower mean oxygen saturations in NGT group while passing the tube and 10-30 minutes after putting the tube [14]. Increase in airway resistance could attribute to more adverse events in nasogastric route as compared to the orogastric route, as also observed in our study. Bornhorst, et al. [13] enrolled spontaneously breathing preterm babies <32 weeks gestational age with history of apnea and desaturation or bradycardia. It was a crossover trial where 12 hours of orogastric route was compared to nasogastric route in terms of desaturation episodes (<80%) and episodes of apnea and bradycardia (<2/3 of baseline). No added advantage of orogastric route over nasogastric was found in this trial. Their results are in contrast with ours. The discrepancy in findings could be explained by differences in way of monitoring adverse events. By using thoracic belt and nasal flow, every apnea episode would have been picked up. In our study we might have missed clinically non-relevant short apnea episodes since we used only pulse oximetry.

In clinical practice, we do not treat each and every episode of apnea. However, desaturations and bradycardia episodes picked up on monitor warrant treatment based on unit guidelines. So, we feel that our study results may be more relevant in clinical practice. Post hoc analysis suggests that our study was underpowered to detect an observed difference of 0.144 episodes/hour, and could only detect a reduction of 0.5 episodes/hour in the oro-gastric group (30% reduction) with 90% power.

We observed similar average duration of stay of tube irrespective of the route used. We tend to not change the tube after a predefined time and keep it as long as it lasts. Tube displacement was also similar in both groups in our study. A recent study of 26 neonates showed lesser frequency of tube displacement in NGT group as compared to OGT group [15]. There was no difference in time to regain birth weight, time to full feeds, and frequency of adverse events in that study [15]. In a recent study [10], NGT feeding was associated with higher preterm infant pain profile (PIPP-R) scores as compared to OGT. We did not check pain scores associated with insertion of tubes in our study. Babies in NGT group are reported to reach full feeds earlier than babies in OGT group [9]. We did not look for time taken to reach full feeds in the two groups owing to the design of the study.

We found babies in the OGT group to have lesser desaturation and bradycardia episodes as compared to NGT in preterm neonates. However, our study may be underpowered to detect these differences. Randomizing one baby multiple times was a major limitation of the study. Randomized controlled trials with improved methodology are needed to conclude superiority of one method over the other.

Ethics clearance: IEC, Max Superspeciality hospital, Patparganj; No. TS/MSSH/BMDRC/PEDIA/IEC/15-07 dated Oct 14, 2015.
Contributors: NPG: conceptualization, planning and monitoring the study and drafting the manuscript; ZSA: data collection and analysis; RM: data collection and analysis, writing of manu-script; SK: supervision and critical input; CJ, KR: data collection and analysis. All authors approved the final version of manu-script, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.

WHAT IS ALREADY KNOWN?

- There is insufficient evidence to prefer one route of tube feeding over another.

WHAT THIS STUDY ADDS?

- Orogastric route of feeding may lead to fewer episodes of bradycardia and desaturations as compared to nasogastric route in preterm neonates.

REFERENCES

1. Poindexter BB, Langer JC, Dusick AM, et al. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. J Pediatr. 2006;148:300-5.
2. Chaudhari S, Kadam S. Total parenteral nutrition in neonates. Indian Pediatr. 2006;43:953-64.
3. Dutta S, Singh B, Chessell L, et al. Guidelines for feeding very low birth weight infants. Nutrients. 2015;7:423-42.
4. Volpe J. Neurology of the Newborn, 4th ed. WB Saunders, 2000. p. 103-33.
5. Shiao SY, DiFiore TE. A survey of gastric tube practices in level II and level III nurseries. Issues of Comprehensive Pediatric Nursing. 1996;19:209-20.
6. Stocks J. Effect of nasogastric tube on nasal resistance during infancy. Arch Dis Child. 1980;55:17-21.
7. Greenspan JS, Wolfson MR, Holt WJ, Shaffer TH. Neonatal gastric intubation: differential respiratory effects between nasogastric and orogastric tubes. Ped Pulmonol. 1990;8:254-8.
8. Van Someren V, Linnett SJ, Stothers JK, Sullivan PG. An investigation into the benefits of resiting nasoenteric feeding tubes. Pediatrics. 1984;74:379-83.
9. Badran AT, Hashish M, Ali A, et al. Nasogastric versus orogastric bolus tube feeding in preterm infants: Pilot rando-mized clinical trial. Am J Perinatol. 2021;38:1526-32.
10. Upadhyay J, Kumar S, Singh P, Basu S. Cortical hemodynamic activity and pain perception during insertion of feeding tubes in preterm neonates: A randomized controlled cross-over trial. J Perinatol. 2022;42:121-5.
11. Watson J, McGuire W. Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants. Cochrane Database Syst Rev. 2013;CD003952.
12. Ellett MLC, Cohen MD, Perkins SM. Predicting the insertion length for gastric tube placement in neonates. J Obstet Gynecol Neonatal Nurs. 2011;40:412-21.
13. Bohnhorst B, Cech K, Peter C et al. Oral versus nasal route for placing feeding tubes: no effect on hypoxemia and brady-cardia in infants with apnea of prematurity. Neonatology. 2010;98: 143-9.
14. Daga SR, Lunkad NG, Daga AS, Ahuja VK. Orogastric vs nasogastric feeding of new-born babies. Trop Doc. 1999;29: 242-3.
15. Rao NK, Udaykanth S. Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants. MRIMS Journal of Health Sciences. 2015;3:190-5.

RESEARCH PAPER

Safety and Outcomes of Midline and Peripherally Inserted Central Catheters in a Pediatric Intensive Care Unit

VEENA RAGHUNATHAN,[1] MANINDER DHALIWAL, [1] DHIRENDRA PRATAP SINGH,[1] GARGI SINGH, [2] SUNIT SINGHI[3]
[1]*Pediatric Intensive Care Unit, Medanta, the Medicity, Sector 38, Gurugram, Haryana.*
[2]*Research and Clinical studies, Medanta Institute of Education and Research, Sector 38, Gurugram, Haryana.*
[3]*Division of Pediatrics, Medanta, the Medicity, Sector 38, Gurugram, Haryana.*

Correspondence to: Dr Veena Raghunathan, Pediatric Intensive Care Unit, Medanta, the Medicity, Sector 38, Gurugram, Haryana 122 001. drvraghunathan@gmail.com
Received: Dec 31, 2022;
Initial review: Jan 23, 2023;
Accepted: Apr 22, 2023.

Objectives: We describe our experience with use of midline catheters in PICU and compare the performance of midline catheters to peripherally inserted central catheters (PICC). **Methods:** A review of hospital records was done to including all pediatric patients admitted in the pediatric intensive care unit of a tertiary care centre who underwent placement of midline catheters or PICC, over a period of 18 months (July, 2019 to January, 2021). Patient details, indication, type of catheter and number of attempts at insertion, type and number of infusions administered, dwell time and complications were retrieved from the records. Comparison was made between the midline and PICC groups. **Results:** The median (IQR) age of children was 7 (3-12) years (75.5% males). 161 midline catheters and 104 PICC were inserted with first attempt success rates of 87.6% and 78.8%, respectively. Median cubital vein was used for majority of the insertions (52.8%). Common complications with midline catheters were pain (*n*=9, 5.6%), blockage (*n*=8, 5%) and thrombophlebitis (*n*=6, 3.7%). Median (interquartile range) dwell time in midline group was 7 (5-10) days. The duration of backflow and dwell time were higher in the PICC group compared to midline group (5.5 vs 3 days; *P*<0.001 and 9 vs 7 days; *P*<0.001, respectively). **Conclusion:** Retrospective data showed that midline catheters had good utility in PICU, especially in moderately sick children (PRISM score up to 12), and provide a secure intravenous access, which can last for a week.

Keywords: *Complications*, *Long peripheral catheter, Outcome, Venous access.*

Published online: May 19, 2023; **PII**:S097475591600536

Securing a venous access for administration of continuous/vesicant medications in the pediatric intensive care unit (PICU), traditionally implies insertion of a central venous catheter (CVC). With the availability of newer catheters and point-of-care ultrasonography, large veins of the upper arm (basilic, brachiocephalic and median cubital veins) have become an option for insertion of peripherally inserted central catheters (PICC). PICCs can serve as an alternative for CVC in certain patients especially for difficult venous access and other short-term indications. Insertion of midline catheters follow the same principles as PICCs, but there are very few studies on its utility in pediatrics [1]. A midline catheter is a long peripheral catheter inserted in the upper limb whose tip lies at or just proximal to the axilla. It is usually inserted using Seldinger technique and can be placed directly or using ultrasound guidance. Unlike PICC/CVC, the midline catheter tip terminates outside the great intrathoracic vessels, hence it is believed to have lesser associated complications. Studies in adults have reported better patient experience with midline catheters compared to PICC along with a decreased incidence of complications such as deep vein thrombosis and catheter-related infections [2,3].

A midline catheter by virtue of its positioning in a larger vein can last longer than a peripheral venous catheter (PVC). PVCs in PICU setting are short-lived due to their small calibre, accidental dislodgement and use of electronic/ syringe pumps [4]. An adult randomized controlled trial showed that in patients requiring more than five days of intravenous therapy, a midline catheter strategy reduced the need for insertion of CVC or multiple PVCs [5]. The objective of the study was to review and compare the indications, clinical performance and complications of midline catheters and PICC as they were utilised in the PICU of our hospital.

METHODS

This was a retrospective observational study in patients aged <17 years who underwent placement of midline catheters or PICC in the 8-bedded PICU in our hospital from July, 2019 to January, 2021. All consecutive patients who underwent

placement of midline catheters and PICC were enrolled. The catheters were inserted by PICU consultants/or resident trainees with a minimum prior experience of >100 line insertions. The catheters were placed as per the unit protocol. Written informed consent of the parent/guardian was obtained prior to the procedure. The study was approved by the hospital's institutional review board.

The veins of the arm and elbow (median cubital, basilic, brachiocephalic) were used for placement of the catheter. Vein and device were selected by intensivist who made his/her decision based on the vein calibre and available devices. The selected vein was punctured within 1-1.5 inches above or below the antecubital fossa. If the vein was well palpated or visible, insertion was attempted without ultrasonic guidance. If the vein was difficult to discern at the outset, Ultrasound (USG) guided insertion was attempted. After identifying insertion site, the sterile field was prepared using 2% chlorhexidine solution. USG probe was wrapped using a sterile sheet and covered with a transparent sterile dressing for sterility. Seldinger's technique was used for insertion. Catheters were fixed with 3-0 sutures and entry site covered with transparent sterile dressing. Post procedure radiograph was done to confirm the position of the tip of catheter.

The demographic details, PRISM-III score at admission and indication for PICC/midline insertion were noted. Indications for catheter placement were recorded as mentioned in procedure form: *i*) Difficult venous access: defined as 3 or more failed attempts at securing PVC; *ii*) Administration of vesicant/hyperosmolar drugs (including vasoactive drugs); *iii*) Anticipated prolonged intravenous therapy requirement >7 days; and *iv*) Requirement of continuous infusions >48 hours [6,7]. The size (2F/5F), length of catheter (8 cm, 20 cm, 40 cm) and number of attempts for insertion were recorded. Type and number of infusions administered, successful sampling duration (days), dwell time and compli-cations were noted. Dwell time was counted as number of days between the date of removal and date of insertion. Premature catheter removal was defined as removal of catheter before indication of intravenous therapy had ceased. The complications noted included blockage, pain, leak, thrombophlebitis, bleeding, swelling, venous thrombosis and positive blood culture. Need for additional CVC/midline/PICC during PICU stay was recorded. All the above information was obtained from the daily checklists in the patient hospital record.

Statistical analysis: SPSS version 24 was used for statistical analysis. The midline catheter group was compared to the PICC group. Quantitative parameters were expressed as mean (SD). Categorical data were expressed as proportions and percentage. Mann-Whitney *U* test was used for testing of median between independent groups. Chi square test was used for testing of associations. *P*-value<0.05 was considered statistically significant.

RESULTS

During the study period, 161 midline catheters and 104 PICCs were inserted. Catheter insertion success was 98.2%

Table I Patient and Catheter Characteristics in Children With Midline Catheters and Peripherally Inserted Central Catheters (PICC)

Characterstics	*Midline (n = 161)*	*PICC (n = 104)*
Male gender[b]	114 (70.8)	86 (82.7)
Age (y)[a,c]	10 (7,14)	3 (1,5.5)
PRISM-III[a]	11 (8,14)	12 (8,18)
INR at insertion[a]	1.2 (1.1,1.3)	1.2 (1.1,1.4)
Platelet at insertion 10^9/L[a]	145 (680, 275)	142 (107, 311)
Indication		
Difficult IV access	23 (14.3)	12 (11.5)
Vesicant /hyperosmolar drug administration	87 (54)	60 (57.7)
Prolonged IV line required[b]	41 (25.5)	44 (42.3)
Continuous infusion requirement[c]	49 (30.4)	7 (6.7)
Vein		
Median cubital	90 (55.9)	50 (48.1)
Basilic	57 (35.4)	46 (44.2)
Brachiocephalic	14 (8.7)	8 (7.7)
Device inserted[c]		
2F 8 cm	28 (17.4)	0
2F 20 cm	133 (82.6)	67 (64.4)
5F 40 cm	0	37 (35.5)
First attempt insertion success[b]	141 (87.6)	82 (78.8)
USG guided	40 (24.8)	49 (47.1)
Continuous infusions		
3% Normal saline	8 (5)	1 (1)
>12.5% dextrose	9 (5.6)	6 (5.8)
N-acetyl cysteine	11 (6.8)	9 (8.7)
Vasoactive infusions	12 (7.5)	7 (6.7)
Intralipid/amino acids	5 (3.1)	7 (6.7)
Bicarbonate	4 (2.5)	4 (3.8)
20% Albumin	44 (27.3)	31 (29.8)
Intravenous immuno-globulin	26 (16.1)	16 (15.4)
Sedation/analgesia	8 (5)	5 (4.8)
Premature removal[d]	25 (15.5)	25 (24)

Values are no. (%) or [a]median (IQR), [b]P<0.05, [c]P<0.001, [d]due to line issue.CVC: central venous catheter, PRISM-III: Pediatric risk of mortality III score, INR: international normalized ratio, IV: intravenous, USG: Ultrasound.

and 97.1% for midline and PICC respectively. In the two groups (midline and PICC), age and gender differences were present; however, PRISM-III and blood coagulation parameters were similar (**Table I**). While type of indications differed, administration of vesicant/hyperosmolar infusions was most common, accounting for 54% and 57.7% of catheter insertions in midline and PICC group respectively. 121 insertions (75.2%) were without USG guidance. Use of USG was higher and first attempt success lower in PICC group (**Table I)**. The most common continuous infusion administered through midline catheter was 20% albumin (*n*=44, 27.3%). Among the complications, the incidence of local site bleeding, blockage, and blood stream infections (BSI) were higher in PICC compared to midline group (**Table II**).

The median duration of backflow (for laboratory draws/ successful sampling) was significantly longer in PICC compared to midline group [5.5 (4-7.5) vs 3 (2-4) days; *P*<0.001]. Median dwell times were also longer in the PICC group [9 (7-13) vs 7 (5-10) days; *P*<0.001] (**Fig. 1**).

Within the midline group, the mean (SD) PRISM-III score of the subset of patients who required additional lines (CVC/midline/PICC) during PICU stay was significantly higher than those who were managed with midline catheter alone [19.7 (6.9) vs 11.2 (5.6); *P*< 0.001]. Similarly, in the PICC group, those requiring additional lines had higher mean (SD) PRISM-III score compared to the rest [20.8 (5.6) vs 12.6 (6.2); *P*<0.001. Also patients in whom midline/PICC was used as a step down access from CVC, had a higher mean (SD) PRISM-III score compared to the non-step down group [20.4 (6.7) vs 11.7 (5.7); *P*<0.001].

Table II Complications in Children With Midline Catheters and Peripherally Inserted Central Catheters (PICC)

Complication	*Midline catheters (n=161)*	*PICC (n=104)*	*P value*
Arterial puncture	1 (0.6)	2 (1.9)	0.32
Dislodgement	2 (1.2)	1 (1)	0.83
Leak	5 (3.1)	1 (1)	0.25
Local site bleeding	3 (1.9)	10 (9.6)	0.004
Pain during use	9 (5.6)	3 (2.9)	0.30
Extravasation/swelling	5 (3.1)	3 (2.9)	0.92
Blockage	8 (5)	12 (11.5)	0.05
Visible thrombophlebitis	6 (3.7)	3 (2.9)	0.71
Blood stream infection	1 (0.6)	7 (6.7)	0.005

Values expressed as no. (%).

DISCUSSION

Our findings suggest that midline catheter served as a reliable venous access device in children admitted to PICU. We observed that midline catheters were comparable to PICCs in several aspects.

There are no clear recommendations for administration of vesicant/irritant medications through midline catheters. Recent studies suggest that CVC placement, solely based on

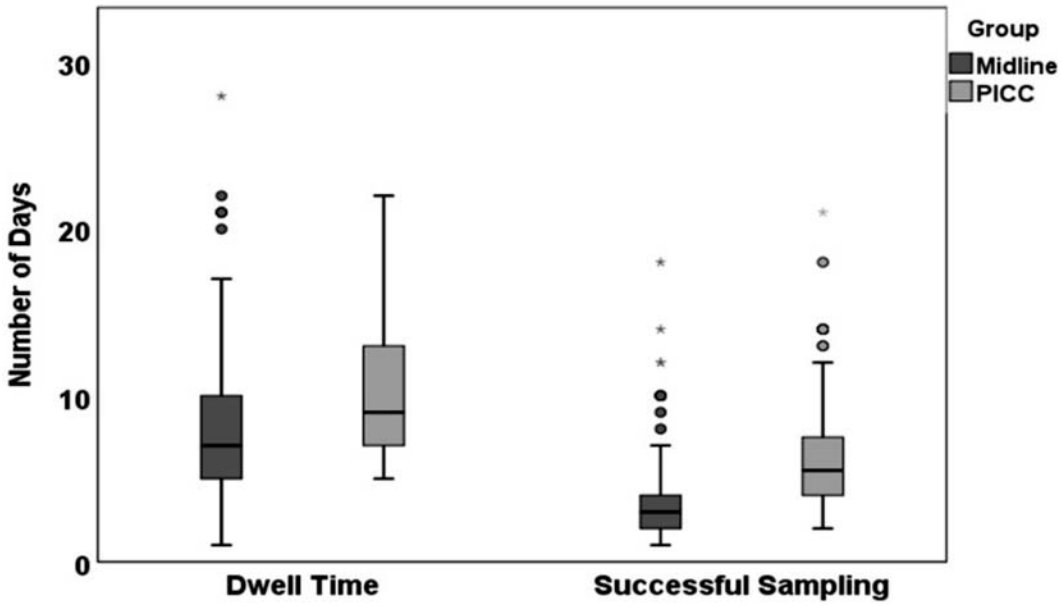


Fig. 1 Dwell time and duration of successful sampling (days) in midline catheter and peripherally inserted central catheter groups.

WHAT THIS STUDY ADDS?

- Midline catheters were found to be safe in moderately sick children in the intensive care unit, providing a secure venous access for up to a week.

pH of drug infusion is not necessary and midline catheters can be used instead [9]. Midline catheters have been used successfully for vasoactive agents [10]. As the midline catheter tip is near the axilla, it allows for more hemodilution of administered medications compared to PVC. Thus the probability of chemical phlebitis and patient discomfort with drug administration is lesser than in a PVC [11].

First attempt success was higher with midline catheter insertion compared to PICC. This is probably because in the smaller sized patient, it is difficult for the guide wire to pass through the curvature of the vein and cross the shoulder area, which makes PICC insertion more difficult. Since the tip of midline catheter terminates at shoulder, the insertion process is easier. The younger age of the PICC compared to midline group (3 vs 10 y) may have also influenced the lower first attempt success and higher USG use in the former.

We observed that PICC had an advantage over midline catheter with respect to its longer duration of successful sampling (6.7 vs 3.5 days). Since 2F catheters were used for all midline catheters and a good proportion of PICC in our study, its narrow lumen could be responsible for limiting the duration of successful blood draws. Catheter dwell times are influenced by required duration of intravenous therapy which depends on patient's clinical condition, hence may not truly be reflective of overall catheter's performance. Our study groups comprised of children with acute critical illness, hence dwell times in both groups were short. The potential midline catheter dwell time for chronic indications is around 28 days [2]. As compared to dwell times, premature catheter removal rate may be a more appropriate indicator of catheter performance. We observed a lower premature removal rate in midline group compared to PICC group (15.5% vs 24%), though statistically insignificant. Blockage accounted for premature removal of 32% of midline catheters and nearly half (48%) of PICC.

Based on our observation, it may be reasonable to suggest the use of midline catheters in PICU patients who are likely to need intravenous therapy for a week. Current CDC guidelines in adults suggest consideration of midline catheters if the expected duration of intravenous therapy is >6 days [12]. This estimation may not always be easy at the outset in a sick pediatric patient.

Complications were nearly same in both groups with few exceptions. Local site bleeding was higher in PICC group which could probably be attributed to use of more wide calibre catheters in that group. The incidence of catheter obstruction and BSI were also higher in the PICC group. Similar observations have been noted in adults [13,14]. Only one patient in our midline group had a BSI. This is consistent with previous studies which have reported low incidence of BSI with midline catheters [15].

One interesting finding in our study was that patients who were managed with either midline or PICC alone had significantly lower PRISM scores than those in whom additional lines (CVC/midline/PICC) were needed. Thus, based on our data, it appears that the practical utility of midline/PICC in PICU seems to be mainly for those with PRISM-III scores of up to 12. CVC can be avoided in such patients who can be managed with midline/PICC alone. This would have several advantages including lack of need for procedural sedation, lesser complications and cost-effectiveness [16]. Also, radiographic confirmation is not necessary for midline catheters. Since the relevance of central venous pressure monitoring in septic shock has decreased in recent times, midline catheter is a good alternative to be considered in cases where there is no absolute indication for CVC [17].

We acknowledge that our study is retrospective and there could have been some selection bias as decision to insert midline catheters/PICC was clinician dependent. However, despite few differences in patient characteristics, PRISM-III scores, coagulation parameters, type of infusions administered were similar, hence comparison of catheter performance is clinically relevant. More studies are required to further clarify the indications for midline catheters in PICU. Presently, evidence-based guidelines for selection of such pediatric venous access devices are sparse.

Based on this retrospective data, it appears that midline catheters have good utility in PICU, especially in moderately sick children, providing a secure intravenous access which can last for a week. Midline catheters are functionally similar to PICCs in several ways, and were associated with lesser complications. Early consideration of midline catheters in PICU in select patients should be encouraged.

Acknowledgements*:* Manish Singh (Senior Biostatistician, M.I.E.R) for his advice on statistical analysis.

Ethics clearance: Medanta Institutional Ethics Committee; No. 1335/2021, dated Aug 10, 2021.

Contributors: VR, MD conceptualized and designed the study, DS collected data, GS carried out statistical analysis of data, VR, MD,

DS carried out the study and drafted the initial manuscript, SS critically reviewed the manuscript for important intellectual content, VR, SS- reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Glazner J, Steinfort K, Hu YJ, et al. Short midline catheters: High success rates for antibiotic therapy in children with cystic fibrosis. J Vasc Access. 2021; 23:11297298211035310.
2. Adams DZ, Little A, Vinsant C, Khandelwal S. The midline catheter: A clinical review. J Emerg Med. 2016;51:252-8.
3. Lescinskas EH, Trautner BW, Saint S, et al. Use of and patient-reported complications related to midline catheters and peripherally inserted central catheters. Infect Control Hosp Epidemiol. 2020;41:608-10.
4. Ben Abdelaziz R, Hafsi H, Hajji H, et al. Peripheral venous catheter complications in children: predisposing factors in a multicenter prospective cohort study. BMC Pediatr. 2017; 17:208.
5. Nielsen EB, Antonsen L, Mensel C, et al. The efficacy of midline catheters-a prospective, randomized, active-controlled study. Int J Infect Dis. 2021;102:220-5.
6. Naik VM, Mantha SSP, Rayani BK. Vascular access in children. Indian J Anaesth. 2019;63:737-45.
7. Kuensting LL, DeBoer S, Holleran R, et al. Difficult venous access in children: taking control. J Emerg Nurs. 2009;35:419-24.
8. Govindan S, Snyder A, Flanders SA, et al. Peripherally Inserted Central Catheters in the ICU: A Retrospective Study of Adult Medical Patients in 52 Hospitals. Crit Care Med. 2018;46:e1136-44.
9. Vallecoccia MS, De Pascale G, Taraschi C, et al. Closed vs open systems: when should short peripheral intravenous catheters be the first choice? J Hosp Infect. 2015;89:72-3.
10. Prasanna N, Yamane D, Haridasa N, et al. Safety and efficacy of vasopressor administration through midline catheters. J Crit Care. 2021;61:1-4.
11. Spiegel RJ, Eraso D, Leibner E, et al. The utility of midline intravenous catheters in critically Ill emergency department patients. Ann Emerg Med. 2020;75:538-45.
12. Centers for Disease Control and Prevention (CDC). Background information – 2011 BSI guidelines – HICPAC 2016. Accessed February 21, 2022. Available from: *http://www.cdc.gov/hicpac/BSI/04-bsi-background-info-2011.html*
13. Swaminathan L, Flanders S, Horowitz J, et al. Safety and outcomes of midline catheters vs peripherally inserted central catheters for patients with short-term indications: A multicenter study. JAMA Intern Med. 2022;182:50-8.
14. Tao F, Wang X, Liu J, et al. Perioperative application of midline catheter and PICC in patients with gastrointestinal tumors. J BUON. 2019;24:2546-52.
15. Tripathi S, Kumar S, Kaushik S. The practice and complications of midline catheters: A systematic review. Crit Care Med. 2021;49:e140-50.
16. Johansson E, Hammarskjöld F, Lundberg D, Arnlind MH. Advantages and disadvantages of peripherally inserted central venous catheters (PICC) compared to other central venous lines: A systematic review of the literature. Acta Oncol. 2013; 52:886-92.
17. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, et al: Goal directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496-506.

RESEARCH PAPER

Association of Thrombotic Markers With Severity of Pediatric-Onset Systemic Lupus Erythematosus

SHEREN ESAM MAHER,[1] AHMED RAGAB ABDUL-BADIA,[1] MOSTAFA AHMED ABU EL-ELA,[2] SUZAN OMAR MOUSA[1]
[1]*Department of Pediatrics, Faculty of Medicine, Minia University, El-Minya, Egypt.*
[2]*Department of Clinical Pathology, Faculty of Medicine, El-Minya, Egypt.*

Correspondence to:
Dr Suzan O Mousa,
Department of Pediatric,
Children's University hospital,
Faculty of Medicine, Minia University,
El-Minya, Egypt.
suzanmousa@mu.edu.eg
Received: Dec 16, 2022;
Initial review: Jan 18, 2023;
Accepted: April 29, 2023.

Objective: To assess the relation of thrombotic markers, thrombomodulin and D-dimer levels to the disease severity in pediatric onset systemic lupus erythematosus (p-SLE) measured by the Systemic Lupus Erythematous Disease Activity Index (SLEDAI). **Methods:** 40 children with p-SLE were grouped according to SLEDAI into: low activity SLE group (laSLE) and moderate-high activity SLE group (mhaSLE). 40 healthy children were included as control group**.** Serum thrombomodulin, and D-dimer levels were measured for all enrolled children. **Results:** The low activity and moderate-high activity SLE groups had significantly higher mean (SD) thrombomodulin [7.2 (1.83) mg/mL and 9.86 (3.29) mg/mL, respectively vs 5.85 (1.41) mg/mL; *P*<0.001] and D-dimer (r=0.42, *P*=0.006) levels than controls. Furthermore, the mhaSLE group had significantly higher thrombomodulin levels and D-dimer (*r* = 0.42, *P*= 0.006) levels than the laSLE group (*P*=0.008 and 0.006). Thrombomodulin and D-dimer had significant positive correlations with SLEDAI. **Conclusion:** Thrombomodulin and D-dimer are valuable markers for p-SLE activity, discriminating children with severe disease activity from those with low disease activity.

Keywords: *D-dimer, Pediatric lupus activity, Thrombomodulin*.

Published online: July 20, 2023; **PII**:S097475591600565

Pediatric onset systemic lupus erythematosus (p-SLE) is a multisystem autoimmune disease occurring before age 16 and is usually graver compared to adult-onset lupus [1]. Many factors, such as genetic predisposition, environmental factors, and hormones, influence the onset and course of the disease [2]. Thrombosis in systemic lupus erythematosus (SLE) is a recognized phenomenon. Several factors are associated with hypercoagulation, such as anti-phospholipid antibodies, inflammation, and thrombophilic factors, such as protein C, protein S, and antithrombin deficiencies [3,4].

Thrombomodulin, an endothelial membrane glycoprotein in an intact endothelium, interacts with thrombin activating protein C, ensuring blood fluidity and natural anticoagulation. In endothelial damage, thrombomodulin is released into circulation, and protein C activation is impaired, aggravating hypercoagulability and thrombotic tendency in many diseases [6]. Studies indicate that thrombomodulin plays a crucial role in the modulation of pathologic conditions such as thrombosis, atherosclerosis, cancer, and stroke [7,8]. D-dimer is an end-product of fibrin degradation, which can be used to screen for venous thrombo-embolism [9]. However, other conditions show elevation of D-dimer, such as aging, cancer, atherosclerosis, and any condition with systemic inflammation [10,11].

We studied the relationship between thrombotic biomarkers and disease severity in pediatric SLE by assessing thrombomodulin and D-dimer levels, and relating them to disease severity measured by the Systemic Lupus Erythematous Disease Activity Index (SLEDAI).

METHODS

This cross-sectional study was carried out at the pediatric department, Minia University Children and Maternity Hospital, Egypt from August, 2020 to January, 2022. It was conducted on 40 children diagnosed with p-SLE attending the pediatric rheumatology outpatient clinic at the hospital. Another, 40 apparently healthy children were included as a control group. All cases were diagnosed with SLE according to the American College of Rheumatology criteria revised in 1997 [12,13].

Written informed consent was obtained from the caregivers of the participants. This study was also approved by Pediatric Department Council and approved by the ethical committee of Faculty of Medicine, Minia University.

We excluded patients with primary or secondary immunodeficiency (e.g., HIV infection) and patients taking anticoagulants or other medicinal products affecting hemostatic function. The SLEDAI was calculated for all children

with SLE. Activity categories were defined as follows: low disease activity (laSLE) SLEDAI ≤4; and moderate-to-high disease activity SLE (mhaSLE), SLEDAI >4 [14].

All children who participated in this study were girls; thus, 40 apparently healthy girls were recruited from children attending the general pediatric outpatient clinic to represent the control group. They were age-matched with the 40 SLE cases and with no family history of rheumatic diseases.

Five mL of venous blood samples were withdrawn from all enrolled children. Immediately following the venipuncture, the samples were centrifuged at 4000 rpm for 15 minutes. The plasma samples were stored at -80ºC till the beginning of each analysis. Thrombomodulin level was determined using a ELISA diagnostic kit (Bioassay Technology Laboratory). Thrombomodulin >7.8 mg/mL was considered high. The D-dimer level was determined using a ELISA diagnostic kit (Abcam). D-dimer level <0.5 mcg/mL was considered normal.

Statistical analysis: SPSS software version 26.0 was used for statistical analysis. Shapiro-Wilk test was used to determine whether the data followed a normal distribution. Mann-Whitney was used to compare two groups regarding non-parametric quantitative data. Kruskal-Wallis test was used to determine statistically significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable. Chi-square test and Pearson correlation coefficient test was used to test association between continuous variables. *P* was considered significant if the value was below 0.05.

RESULTS

This study included 80 girls. They were grouped into the following three groups: 20 girls in the laSLE group with a mean (SD) age of 12.8 (2.46) years, 20 girls in mhaSLE group with mean (SD) age of 11.9 (2.54) years), and 40 girls in the control group (mean (SD) age of 12.3 (2.54) years). The demographic data and results of laboratory investigations of the three studied groups are shown in **Table I**. Additional disease related data of the two SLE groups are represented in **Web Table I**.

The two SLE groups had significantly higher mean (SD) thrombomodulin levels [7.2 (1.83) mg/mL and 9.86 (3.29) mg/mL, respectively] than controls [5.85 (1.41) mg/mL] (*P*< 0.001). They were significantly more frequently having an abnormally high thrombomodulin level than controls (35% and 65% vs 2%; *P*=0.02 and *P*<0.001, respectively). Furthermore, the mhaSLE group had significantly higher mean (SD) thrombomodulin levels than the laSLE group [9.86 (3.29) vs 7.2 (1.83) mg/mL; *P*=0.008]. The two SLE groups had significantly higher D-dimer levels than the controls. [0.58 (0.39) and 1.02 (0.5) mcg/mL vs 0.35 (0.19) *P*<0.001]. Furthermore, the mhaSLE group had significantly higher D dimer levels than the laSLE group [1.02 (0.5) vs 0.58 (0.39) mcg/mL*; P*=0.006]. In addition, the two SLE groups were significantly more likely to have an abnormally high D-dimer level than controls (45% and 75% vs 10%; *P*<0.001 and 0.03, respectively). Thrombomodulin (r = 0.342, *P*=0.003) and D-dimer (r = 0.42, *P*=0.007) had significant positive correlations with SLEDAI. Moreover, thrombomodulin had a significant positive correlation with D dimer (r = 0.621, *P*< 0.001).

DISCUSSION

This study explored thrombomodulin and D-dimer as markers of hypercoagulability in children with SLE and their relation to disease severity measured by SLEDAI. When compared to controls, we found that SLE children had significantly higher thrombomodulin and D-dimer levels. Additionally, SLE children with moderate-to-high disease activity had significantly higher levels of the two studied thrombotic markers than those with low disease activity. These results agreed with previous adult studies [6,15]. A recent systemic review and meta-analysis [16] confirmed that the circulating thrombomodulin levels in SLE patients are increased and reflect the disease activity. This finding suggests that hypercoagulability in SLE is more related to inflammation and endothelial injury rather than to the autoimmune component of the disease [15]. At the same time, the rise in D-dimer level in SLE was imputed to exacerbated fibrin formation in SLE due to associated tissue inflammation [17]. Our study found that thrombomodulin had a significant positive correlation with D-dimer, which may be attributed to the reciprocal relationship between

Table I Laboratory Value in Children With Systemic Lupus Erythematosis Enrolled in the Study

Characteristic	*Low activity group n=20*	*Moderate-high group n=20*	*Control group n=40*
Hemoglobin (g/dL)	8.74 (0.68)	7.75 (0.81)	11.72 (0.91)
BUN (mg/dL)	26.9 (6.54)	38.1 (6.43)	14.9 (2.06)
Creatinine (mg/dL)	0.59 (0.06)	0.75 (0.08)	0.47 (0.05)
ALT (U/L)	38.4 (5.42)	48.4 (5.77)	22.6 (3.54)
AST (U/L)	41.9 (2.84)	45.4 (6.19)	25.1 (6.09)
Thrombomodulin (mg/mL)	7.2 (1.83)	9.86 (3.29)	5.85 (1.41)
High thrombomodulin[a]	7 (35)	13 (65)	2 (5)
D-dimer (mcg/mL)	0.58 (0.39)	1.02 (0.50)	0.35 (0.19)
High D-dimer[a]	9 (45)	15 (75)	4 (10)

Values in mean (SD) or [a]no. (%). Low activity group: low SLE disease activity, moderate-high group: moderate to high SLE disease activity, based on Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

WHAT THIS STUDY ADDS

- Thrombomodulin and D-dimer levels were associated with p-SLE activity, having different values in children with disease activity and children with low disease activity.

inflammation causing endothelial injury and hypercoagulability in SLE [18]. Endothelial injury causes tissue factor exposure and activation of the extrinsic coagulation pathway, resulting in fibrin formation and contributing to SLE thrombotic tendency [19].

Enrolling only girls, a small sample size, and being a single-center study are the main limitations of this study. Further studies including both sexes and on larger geographical scales and sample sizes are needed to address the hemostatic changes and hypercoagulability in p-SLE. Moreover, the relation of thrombomodulin and D-dimer levels to the occurrence of thrombotic events in p-SLE should be further elucidated.

In conclusion, thrombomodulin and D-dimer are associated with p-SLE activity, being different in children with severe disease activity and those with low disease activity, which may assist in patient stratification, implementing preventive measures, and for better clinical disease management.

Ethics clearance: Ethical committee of Faculty of Medicine Minia-University; No. 691:11/2020, dated Nov 1, 2020.
Contributors: SEM,SOM,MAA: design and planning of the study; MAA: lab work; SEM,SOM,ARA: data collection, analysis of results and preparation of drafts of the manuscript. All authors read and approved the final manuscript.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Tan JH, Hoh SF, Win MT, et al. Childhood-onset systemic lupus erythematosus in Singapore: clinical phenotypes, disease activity, damage, and autoantibody profiles. Lupus. 2015;24: 998-1005.
2. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016;12:716-30.
3. Nojima J, Iwatani Y, Ichihara K, et al. Acquired activated protein C resistance is associated with IgG antibodies to protein S in patients with systemic lupus erythematosus. Thromb Res. 2009;124:127-31.
4. Choi SC, Morel L. B cell contribution of the CD4+ T cell inflammatory phenotypes in systemic lupus erythematosus. Autoimmunity. 2017;50:37-41.
5. Pan L, Lu MP, Wang JH, et al. Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr. 2020;16:19-30.
6. Cicarini WB, Duarte RF, Ferreira KS, et al. Impact of markers of endothelial injury and hypercoagulability on systemic lupus erythematosus. Lupus. 2020;29:182-90.
7. Remkova A, Kova cova E, Prikazska M, et al. Thrombomodulin as a marker of endothelium damage in some clinical conditions. Eur J Intern Med. 2000;11:79-84.
8. Weiler H, Isermann BH. Thrombomodulin. J Thromb Haemost. 2003;1:1515-24.
9. Wells PS, Ihaddadene R, Reilly A, Forgie MA. Diagnosis of venous thromboembolism: 20 years of progress. J Vasc Surg: Venous Lymphat Disord. 2019;7:618-9.
10. Kim JY, Kim KH, Cho JY, et al. D-dimer/troponin ratio in the differential diagnosis of acute pulmonary embolism from non-ST elevation myocardial infarction. Korean J Intern Med. 2019;34:1263-71.
11. Kim SA, Yhim HY, Bang SM. Current management of cancer-associated venous thromboembolism: focus on direct oral anticoagulants. Journal of Korean Medical Science. 2019; 34:052.
12. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheumatism.1982;25:1271-7.
13. Hochberg MC. Revised Criteria of the American College of Rheumatology for the Classification of SLE. Modified from Hochberg. Arthritis Rheum. 1997;40:1725-34.
14. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29: 288-91.
15. Ferreira KS, Cicarini WB, Alves LC, et al. Correlation between active disease and hypercoagulability state in patients with systemic lupus erythematosus. Clin Chim Acta. 2019; 490:107-12.
16. Hu YQ, Wang ZX, Xiang K, et al. Elevated circulating thrombomodulin levels in systemic lupus erythematosus: a systematic review and meta-analysis. Curr Pharm Design. 2022;28:306-12.
17. Olson JD. D-dimer: An overview of hemostasis and fibrinolysis, assays, and clinical applications. Adv Clin Chem. 2015; 69:1-46.
18. Oh YJ, Park EH, Park JW, et al. Practical utility of D-dimer test for venous thromboembolism in systemic lupus erythematosus depends on disease activity: a retrospective cohort study. Journal of Korean Medical Science. 2020;35:e356.
19. Cicarini WB, Ferreira KS, Loures CM, et al. Systemic lupus erythematosus: disease activity may influence the release of endothelial microparticles? Blood Coagulation and Fibrinolysis. 2018;29:189-95.

RESEARCH PAPER

Factors Affecting Quality of Life in Adolescent Siblings of Children With Autism Spectrum Disorder

YAJIKA ARYA, DEVENDRA MISHRA, MONICA JUNEJA, ARPITA GUPTA

Department of Pediatrics, Maulana Azad Medical College (University of Delhi) and Associated Lok Nayak Hospital, Delhi 110002.

Correspondence to:
Dr. Yajika Arya,
Senior Resident,
Department of Pediatrics,
Lok Nayak Hospital,
New Delhi 110002.
yajikachutani95@gmail.com
Received: Oct 19, 2022;
Initial review: Dec 7, 2022;
Accepted: April 28, 2023.

Objectives: To compare the quality of life (QoL) of adolescent siblings of children with autism spectrum disorder (ASD-Sibs) with siblings of typically developing children (TD-Sibs), and study the factors affecting the QoL. **Methods;** Between 1 February, 2021 and 31 September, 2021, 40 children aged 10-18 years, whose sibling was suffering from ASD, were enrolled (Study group). 40 age- and sex-matched siblings of children with no clinically apparent neuro-developmental abnormality or behavioral problem were also enrolled (Control group). Severity of autism was assessed by using the childhood autism rating scale 2 (CARS-2) score. QoL was assessed by a validated version of the World Health Organi-zation Quality of Life questionnaire Brief version (WHO QoL BREF), and compared between cases and controls using Wilcoxon rank sum test. **Results:** The mean (SD) age of study participants was 13.55 (2.75) years. The mean (SD) CARS-2 score of our sample was 35.78 (5.23). Mild to moderate autism was seen in 23 (57.5%) children, and 13 (32.5%) had severe autism. The median (IQR) QoL in ASD-Sibs was worse than TD-Sibs in physical domain (24 (19,26) vs 32 (29,32); P<0.001), psychological domain (22 (17,23) vs 25 (23,25); P<0.001), social domain (11 (8,12) vs 13 (11,14); P<0.001), and environmental domain (28 (26,31) vs 35 (31,35); P<0.001). Among the ASD-Sibs, severity of the sibling's ASD and the family's socioeconomic status were the only two factors significantly affecting one of the domains of QoL. **Conclusions:** The observed lower QoL score in adolescent siblings of children with ASD, more so in those whose siblings had more severe ASD, suggests the need for targeting the family as a unit while formulating plans for holistic management of children with ASD.

Key words: *Family, Management, Neurodevelopmental disorders, Stress.*

Published online: 19 May, 2023; **PII**: S097475591600537

Autism spectrum disorder (ASD) describes a spectrum of neurobiological developmental disabilities involving impairments such as difficulties with social interaction and communication, repetitive behaviors, and restricted interests [1]. Chronic neurological disorders in children, including ASD, place the family at a greater risk for stress, psychosocial difficulties, and need for taking care. Siblings are more vulnerable to these stressors than other family members due to their attitudes, early sense of responsibility, worry about the future, issues with friendship, and difficulty in talking about their siblings [2]. Many studies report poor quality of life (QoL) and increased stress in siblings of children with ASD [3-6], but the Indian studies addressing these issues are limited [7]. Information on QoL status of sibling is essential to address these factors proactively, so that the physical, mental and social well-being of the siblings is not affected due to the child with autism. Hence, this study was undertaken to compare the QoL in siblings of children with ASD, with the QoL of siblings of typically developing children, and factors affecting the same.

METHODS

After institutional ethics committee clearance, we conducted this study between 1 February, 2021 and 31 September, 2021 (except periods of intermittent coronavirus disease 19 (COVID-19) related discontinuation of non-COVID services) at a public-sector tertiary care hospital attached to a medical college with a dedicated Child Development Centre (CDC). Institutional ethics committee cleared the study proposal, and a written informed consent was taken from the parents, and assent from the children being enrolled.

A sample size of 40 in each group was calculated based on the data from a previous study [7], which reported the mean (SD) QoL in psychological domain in siblings of cases and controls as 3.19 (0.52) and 3.52 (0.43), respectively. To measure a similar difference with 95% confidence, the sample size of 40 in each group was considered adequate.

We prospectively enrolled the typically developing eldest child (aged 10-18 year) whose younger sibling was suffering from ASD and attending the CDC at our hospital

(ASD-sibs group). Families with more than one child having a neurodevelopmental disorder were excluded. For selection of cases, parents of children diagnosed with ASD and following up in the child development center were approached to enquire about the presence of an older healthy sibling at home. Families having another unaffected child between 10-18 years of age at home were requested to bring the sibling during the next scheduled visit (only the eldest sibling was enrolled if there were more than one eligible sibling). These families were approached at their next CDC visit and informed about the study. No specific follow-up period was considered while enrolling the patients.

A similar number of age- and sex-matched eldest siblings of children with no clinically apparent neurodevelopmental abnormality or behavioral problem (typically developing) were also enrolled (TD-sibs group), from among children attending the outpatient department or admitted in wards. Those with no siblings, obvious chronic medical/surgical disease affecting QoL, or clinically apparent speech or hearing problem were excluded.

A detailed history was taken and entered in a pre-designed study form. This form included the socio-demographic data, and clinical details of the sibling with ASD. Socioeconomic status was assessed using the updated modified Kuppuswamy socioeconomic status scale [8]. Family details and past history of the enrolled adolescents were taken, and their physical examination done. Anthropometric measurements were recorded using standard methodology according to revised Indian Academy of Pediatrics (IAP) charts. ASD related information of the children with autism whose siblings were enrolled, their developmental quotient/intelligence quotient (DQ/IQ), co-morbidities, and duration of illness were extracted from the CDC records. Severity of autism in the siblings was assessed by using Childhood autism rating scale (CARS-2) and interpreted as per the manual. Based on the total raw scores obtained, there are three levels of severity as per the CARS-2 manual: minimal or no symptoms, mild to moderate autism and severe autism. Past history of siblings of the adolescents in control group was also elicited and recorded. Details of developmental quotient/intelligence quotient of the children with autism were taken from the patients' records.

A single un-blinded investigator filled the pre-structured study forms after interviewing the child as well as the accompanying parent/parents. QoL of cases and controls was assessed by WHO QoL-BREF [9], which has four domains viz., Physical, Psychological, Social relationships, and Environment. The Hindi adaptation of the tool, which has previously been validated for Indian adolescents, was used for the study [10]. The response to items was recorded on a 5-point Likert scale. The participants filled the form in the presence of their parents and the researcher. The researcher or the parents only assisted the child for administrative issues and did not assist the child in filling the form. This tool took about 15-20 minutes to complete. Domain scores were scaled in a positive direction (higher scores denote better QoL).

Statistical analysis: Statistical analysis was done using Statcalc of Epi Info 7 software. QoL scores were summarized as median (IQR). Comparison of QoL between the groups was done using the Wilcoxon rank sum test. For other continuous variables, Student *t* test was used, and chi-square test was used for discrete variables. For comparison of more than two medians, Kruskal-Wallis test was used.

RESULTS

A total of 158 children with ASD were assessed for enrolment, of which 107 were not fulfilling inclusion criteria (no sibling, 48; age <10 or >18 years, 53; siblings not staying in the same house, 6). Of the 51 eligible for enrolment, 11 children were excluded (unable to converse in Hindi, 2; clinically apparent neurodevelopmental or behavioral problem, 5; clinically apparent speech or hearing problem, 4), and finally 40 of these families that followed-up with the sibling were enrolled for the study. Forty age- and sex-matched healthy children who were attending the Pediatric Department for acute illnesses or their accompanying relatives were enrolled as controls.

The baseline participant characteristics of adolescents with a sibling having autism (ASD-sibs) or with Typical development (TD-sibs) are presented in **Table I**. The mean (SD) age was 8.82 (3.10) years with 80% males. The baseline characters of the children with ASD are presented in **Web Table I**. More than a third of children with ASD (14, 35%) had comorbid global developmental delay. None of the patients had any other diagnosed comorbidity like epilepsy or attention-deficit hyperactivity disorder (ADHD). The mean (SD) CARS-2 score of our sample was 35.78 (5.23), and the majority (57.5%) had mild-moderate ASD. Approximately one- third (32.5%) of children with ASD had IQ/DQ in the severe delay range.

The QoL in ASD-sibs was worse than TD-sibs in all domains (**Table II**). A statistically significant lower QoL was found in the social domain (P=0.04) in children with sibling having more severe ASD (**Table III)**. However, no statistically significant correlation was found between CARS-2 scores of children with ASD and their sibling's QoL score: 0.069 (P=0.67), 0.15 (P=0.33), 0.26 (P=0.10), and 0.15 (P=0.33) in in physical, psychological, social and environmental domains, respectively. Similarly, there were no differences in QoL in sibling of children with ASD with and without GDD/ID. There was no difference in QoL of

Table I Baseline Characteristics of Adolescents With a Sibling Having Autism (ASD-Sib) or With Typical Development (TD-Sibs)

Characteristic	*ASD-sibs (n=40)*	*TD-sibs(n=40)*
Age (y)		
10-13	20	20
14-16	11	11
16-18	9	9
Males	14 (35)	14 (35)
Nutritional status		
Obese	7 (17.5)	6 (15)
Overweight	10 (25)	8 (20)
Normal	18 (45)	18 (45)
Thin	5 (12.5)	8 (20)
Education status		
Never been to school	0	0
Dropped school	2 (5)	0
Going to school	37 (92.5)	37 (92.5)
Passed school	1 (2.5)	3 (7.5)
Type of family		
Nuclear	31 (77.5)	29 (72.5)
Joint	9 (22.5)	10 (25)
Single parent	0	1 (2.5)
Socioeconomic status[a]		
Upper	4 (10)	4 (10)
Upper middle	9 (22.5)	7 (17.5)
Lower middle	9 (22.5)	5 (12.5)
Upper lower	13 (32.5)	19 (47.5)
Lower	5 (12.5)	5 (12.5)

All values in no. (%). ASD: autism spectrum disorder; as per modified Kuppuswamy socioeconomic status scale [8].

siblings based on gender, weight and the type of family. However, there was a statistically significant higher QoL in ASD-sibs in the higher socioeconomic group, but only in the physical domain (P=0.01) (**Web Table II**).

DISCUSSION

This cross-sectional study with matched controls compared the QoL of unaffected siblings (aged 10-18 year) of children with ASD (ASD-sibs) and age- and sex-matched healthy children who had a typically developing younger sibling (TD-sibs). We found a significantly lower QoL among ASD-sibs than TD-sibs in all domains. Among the ASD-sibs, severity of sibling's ASD and the family's socioeconomic status were the only two factors significantly affecting one of the domains QoL.

The finding of poorer QoL of ASD-sibs is similar to previous studies done in various countries across the world in the last 15 years [4-7,11]. A previous Indian study [7] done in a similar research setting enrolled siblings of children with chronic neurological diseases, including ASD, and reported lower QoL in these children. A meta-analysis [6] comparing ASD-sibs with TD-sibs, siblings of patients with intellectual disability and siblings of patients of Down syndrome, also reported lower QoL in ASD-sibs as compared to controls [6]. Contrary to these findings, recent studies [12] from developed countries have reported either better [12] or similar [13,14] QoL in ASD-sibs as compared to controls. Among these, the study by Walton, et al. [12] (USA, 2019) was an online surveys, and thus the reliability of information maybe sub-optimal. The studies by Vieira, et al. [12] and Merwe, et al. [15] employed face-to-face interview, similar to us, but one of the reasons for the differences could be that the sample size was smaller (15-21 participants). Another difference between these studies and ours is the higher proportion of severe ASD in our sample (32.5% severe ASD). In addition, the better QoL in the developed countries in recent times could also be related to the better availability of support services for families with a child with ASD.

Table II Comparison of Quality of Life (QoL) of Adolescents with a Sibling Having Autism (ASD-Sib) or With Typical Development (TD-Sibs)

QoL domain	*ASD-sibs (n=40)*	*TD-sibs (n=40)*	*P value*
Physical	24 (19, 26)	32 (29, 32)	<0.0001
Psychological	22 (17, 23)	25 (23, 25)	<0.0001
Social	11 (8, 12)	13 (11, 14)	<0.0001
Environmental	28 (26, 31)	35 (31, 35)	<0.0001

All values in median (IQR). Higher scores depict better QoL. ASD: autism spectrum disorder.

The lower QoL in the social domain in siblings of children with more severe autism has also been previously reported which could be either due to the more socially inappropriate behaviors in those with severe ASD [3,11], thus affecting the QoL in this domain for the elder sibling.

Table III Severity of Autism in Children and Quality of Life in Their Siblings

QoL domain	*Mild ASD (n=4)*	*Moderate ASD (n=23)*	*Severe ASD (n=13)*	*P value*
Physical	23 (16,25)	24 (21,27)	26 (19, 28)	0.79
Psychological	22 (21, 23)	22 (14,24)	20 (17, 22)	0.14
Social	12.5 (11,13)	12 (10, 13)	9 (8, 11)	0.04
Environmental	27.5 (26,29)	31 (26, 36)	27 (25, 29)	0.17

All values in median (IQR). Quality of life by WHO Bref-QoL. ASD: autism spectrum disorder.

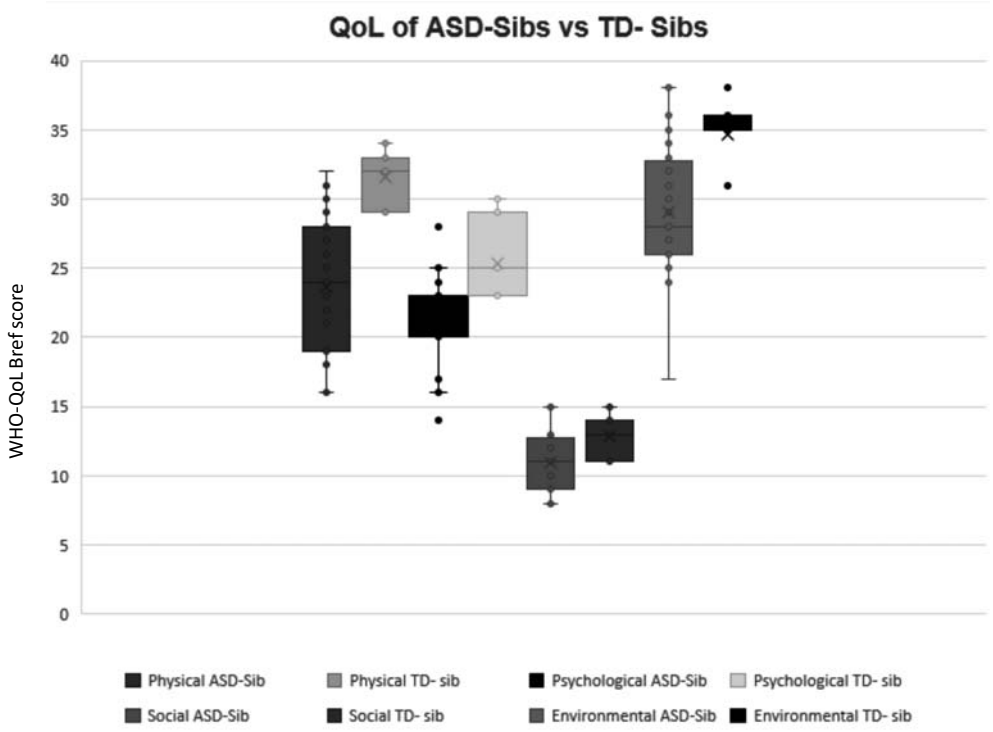


Fig. 1 Box and whisker plot depicting quality of life (QoL) in different domains among adolescents with a sibling having autism (ASD-Sibs) or with a sibling having typical development (TD-Sibs).

Another reason could be the possibility of more caretaking required for children with severe ASD [3], which leads to diverting some of the responsibility to the sibling, thereby affecting his/ her social life and QoL. However, a study from Brazil [12], which used the same QoL tool, found lower QoL only in the environmental domain, explaining it by the difficulties in accessing specialized medical care and other health areas, besides lack of information on access to leisure and education for this specific population, which ultimately intensifies stress and negatively influences the QoL.

The strengths of this study are that it employed a relatively large sample size as compared to previous studies, used age- and sex-matched siblings of TD children as controls, used a tool that was validated for the study population, and employed a rigorous face-to-face inter-view process. The study was done at a center with a large child development center, thereby ensuring children with the full spectrum of severity of ASD could be enrolled. There are quite a few limitations of this study, the most important being that the study was done in the setting of the COVID-pandemic, which itself affected the QoL of the entire population, more so of children and adolescents [16]. However, it is expected that such an event would have affected the QoL of children in both groups. Although, we enrolled the requisite sample size, the small numbers precluded multivariate analysis for independent associations. The study utilized a restricted age group i.e., adolescents, and could be used only in the Hindi speaking population, thereby affecting the generalizability of the study results.

Our study findings have major implications for practice in the domain of developmental and social pediatrics. Given that, ASD-sibs have been shown to have a worse QoL than TD-sibs, our results underscore the need to develop and implement targeted interventions for these siblings and their families. Healthcare providers should look to identify the impact of ASD on unaffected siblings, and recommend appropriate support measures to the family including regular counselling of these siblings. Researchers may look at factors that independently affect QoL of these siblings, and interventions to address these factors.

We found a lower QoL in adolescent siblings of children with ASD, it being worse in those with the sibling having more severe ASD. This would guide policy makers developing programs for children with ASD to target the family as a unit, rather than the affected child alone.

Ethics clearance: IEC,MAMC, Delhi; No. 70/05/2019/No550 dated Nov 1, 2019.
Funding: None; *Competing interests*: None stated.

WHAT THIS STUDY ADDS?

- We observed lower quality of life scores in adolescent siblings of children with autism, which were more affected in those whose siblings had more severe disease.

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

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Association; 2013.
2. Macks RJ, Reeve RE. The adjustment of non-disabled siblings of children with autism. J Autism Dev Disord. 2007: 37;1060-7.
3. Shivers CM, McGregor C, Hough A. Self-reported stress among adolescent siblings of individuals with autism spectrum disorder and Down syndrome. Autism: Int. J Res. Prac. 2019;23:112-22.
4. Hastings RP, Petalas MA. Self-reported behavior problems and sibling relationship quality by siblings of children with autism spectrum disorder. Child Care Health Dev. 2014; 40: 833-9.
5. Rankin JA, Tomeny TS, Barry TD. Multi-informant assessment of siblings of youth with autism spectrum disorder: Parent-child discrepancies in at-risk classification. Res Dev Disabil. 2017; 68:78-87.
6. Shivers CM, Jackson JB, McGregor CM. Functioning among typically developing siblings of individuals with autism spectrum disorder: A meta-analysis. Clin Child Fam Psychol Rev. 2019; 22:172-96.
7. Rana P, Mishra D. Quality of life of unaffected siblings of children with chronic neurological disorders. Indian J Pediatr. 2015; 82:545-8.
8. Mishra D, Singh HP. Kuppuswamy's socioeconomic status scale – a revision. Indian J Pediatr. 2003; 70:273-4.
9. World Health Organization. WHOQOL-BREF- Introduction, Administration, Scoring. WHO; 1997.
10. Agnihotri K, Awasthi S, Chandra H, et al. Validation of WHO QOL-BREF instrument in Indian adolescents. Indian J Pediatr. 2010; 77:381-6.
11. Koukouriki E, Soulis SG. Self-reported health-related quality of life (HRQOL) and anxiety among Greek school-age siblings of individuals with autism spectrum disorders (ASD) in relation to parental mental health and social support. J Autism Dev Disord. 2020; 50:2913-30.
12. Vieira CB, Fernandes FD. Quality of life of siblings of children included in the autism spectrum. Codas. 2013; 25: 120-7.
13. Walton KM, Ingersoll BR. Psychosocial adjustment and sibling relationships in siblings of children with autism spectrum disorder: risk and protective factors. J Autism Dev Disord. 2015; 45:2764-78.
14. Lamsal R, Ungar WJ. Impact of growing up with a sibling with a neurodevelopmental disorder on the quality of life of an unaffected sibling: a scoping review. Disab Rehab. 2019;18:1-9.
15. Van der Merwe C, Bornman J, Donohue D, Harty M. The attitudes of typically developing adolescents towards their sibling with autism spectrum disorder. S Afr J Commun Disord. 2017; 64: e1-7.
16. Nobari H, Fashi M, Eskandari A, et al. Effect of COVID-19 on health-related quality of life in adolescents and children: a systematic review. Int J Environ Res Public Health. 2021; 25:45-63.

Web Table I Systemic Lupus Erythematosus Manifestations Among Enrolled Children in the Two Groups

Data of the disease	*Low activity (SLEDAI ≤4) n = 20*	*Moderate-high activity (SLEDAI ≤4) n = 20*
Seizure	0	1 (5)
Visual disturbance	0	1 (5)
Arthritis[a]	1 (5)	13 (65)
Proteinuria[a]	1 (5)	15 (75)
Urinary casts [a]	1 (5)	8 (40)
Rash[a]	3 (15)	13 (65)
Alopecia[a]	3 (15)	14 (70)
Mucosal ulcers[a]	2 (10)	12 (60)
Pleurisy[b]	1 (5)	6 (30)
Low complement[b]	4 (20)	12 (60)
Increase DNA binding[b]	2 (10)	9 (45)
Fever[b]	5 (25)	12 (60)
Thrombocytopenia	9 (45)	15 (75)
Leukopenia	7 (35)	13 (65)

Values in no. (%). SLEDAI: System lupus erythematosus disease activity index. [a]*P<0.001,* [b]*P<0.05.*

RESEARCH PAPER

Effect of Electronic Infrared Tap With Voice Reinforcement on Hand Hygiene Compliance of Healthcare Personnel

M KATHIRVEL,[1] A MURUGESAN,[1] APURBA SASTRY,[2] B ADHISIVAM[1]

[1]*Department of Neonatology, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry.*
[2]*Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry.*

Correspondence to:
Dr B Adhisivam, Professor, Department of Neonatology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry.
adhisivam1975@yahoo.co.uk
Received: Jun 11, 2022;
Initial review: Sep 9, 2022;
Accepted: May 22, 2023.

Objective: To assess the efficacy of an electronic infrared tap with voice reinforcement to improve hand hygiene compliance among health care workers. **Methods:** This pre-post intervention study used an automated electronic infrared tap with voice reinforcement as intervention in the neonatal intensive care unit (NICU) and the pediatric intensive care unit (PICU). Hand hygiene adherence rates of health care workers were monitored using a video camera. **Results:** A total of 2718 hand hygiene events were observed. Baseline rates of hand hygiene (complete or partial adherence rates) were 86.9% in NICU and 81.2% in PICU, that improved to 94.9% for NICU and 92.9% for PICU post-intervention (*P*=0.001). **Conclusion:** Use of an electronic infrared (EIR) tap with voice reinforcement in handwashing stations of NICU and PICU improved hand hygiene compliance among health care workers.

Keywords: *Electronic monitoring, Hand hygiene, Health care associated infections*.

Published online: July 20, 2023; **PII**:S097475591600564

There is a global increase in healthcare associated infections (HAI), especially among neonates [1]. Hand hygiene, antibiotic stewardship and sepsis care bundles are important measures for decreasing HAI. As promotion of hand hygiene is a cost-effective intervention with higher impact, newer technologies are being tried for improving the same [2-9] This study was done to assess the efficacy of an electronic infrared (EIR) tap with voice reinforcement to improve hand hygiene compliance among health care workers. The secondary objectives were to analyze hand hygiene compliance with alcohol-based hand rub among health care personnel in each moment of hand hygiene, and the respective rates of HAI.

METHODS

This pre-post intervention study was done in the NICU and PICU of a tertiary care hospital in Puducherry between May, 2019 and May, 2020, after approval from the institute ethics committee. Waiver of consent was also obtained for this quality improvement initiative.

All residents and nursing officers working in both the pediatric (PICU) and the neonatal (NICU) intensive care units in all shifts were oriented to the use of the EIR tap before enrolment. The study was con-ducted in four phases (pre-intervention phase I and II, post-intervention phase III and IV) (**Fig. 1**) in the handwashing stations located outside the PICU and NICU. Each phase was completed over a duration of 2 weeks. A motion capture network camera (CP PLUS 1.3 MP Net-work WIFI Cube Cameras) was installed at the hand-washing areas and continuous video recording was done. The recordings from the cameras were periodically transferred to a hard disk using a memory card.

An automated EIR tap programmed with voice reinforcement was used as the intervention for the study. The automated tap facilitated the handwashing process by automatic detection, regulating water flow (every 10 seconds) and elaborating handwashing steps with timed voice messages, by a 3W speaker. Each step was displayed in number and duration on a 16×2 LCD display, to facilitate synchronization with the user. The completion of the process was marked by the return of water flow, followed by a message congratulating the user for compliance.

Baseline hand hygiene compliance was studied in pre-intervention phase 1 (May, 2019) and preintervention phase II (October, 2019) after five months of installing video surveillance to avoid the Hawthorne effect. The automated EIR tap was introduced as an intervention during post-intervention phase III (March, 2020) and phase IV (May, 2020). These phases were done for two weeks each.

The first contact of the healthcare personnel with a tap before entry into the ICU for each day was taken as an event. The compliance of health care personnel was assessed by the principal investigator, who reviewed the video recordings of

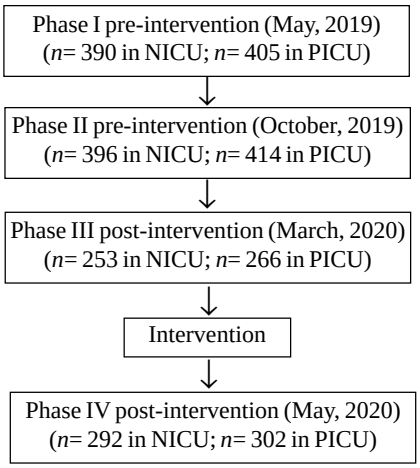


Fig. 1 Flow chart depicting the study procedure.

each phase. Handwashing duration (>60s) and compliance were assessed as complete adherence with duration of handwashing >60 second and compliance to all hand washing steps; partial adherence with either duration of handwashing >60 or compliance to all hand washing steps; and nil adherence when the duration of handwashing <60 second and no compliance to hand washing steps.

The percentages of hand hygiene complete adherence rate (CR), partial adherence rate (PR), and nil adherence rate (NR) using a common denominator of total events was observed [10,11].

A separate hand hygiene audit was conducted by a senior nursing officer from the Hospital Infection Control Committee (HICC) using Ibhar software (NABH accredited), which incorporated a comprehensive set of features that implement and manage the infection prevention and control program. Data collected for the year 2019 (Jan - Dec), on hand hygiene compliance and incidence of hospital-acquired infection including catheter-associated urinary tract infections (CAUTI), central line-associated bloodstream infection (CLABSI) and ventilator associated pneumonia (VAP) from both the ICUs were estimated.

The sample size was calculated considering 30% as the previous hand hygiene compliance data of NICU and PICU for 2018, and expecting a 10% clinical difference with the intervention. The sample size was calculated as 480 units of the study using nMastersoftware, with 80% power, 5% alpha error, and 95% confidence interval. Each first entry of resident/ nursing officer and access to tap was taken as a single event. Considering the staffing pattern, a sample population of 50 units was obtained per day. The study was carried for 14 days, each for four phases. Statistical analysis was done using the SPSS software version 20 (IBM Corp). $P<0.05$ was considered as significant.

Table I Effect of the Study Intervention on Hand Hygiene Compliance Among Healthcare Personnel

Hand hygiene compliance	*Baseline n=1605*	*Post-intervention n=1113*
Pediatric intensive care unit		
Complete adherence	20.3	37.4
Partial adherence	60.9	55.4
Non-adherence	18.8	7.1
Neonatal intensive care unit		
Complete adherence	31.9	49.2
Partial adherence	54.9	46.8
Non-adherence	13.0	3.5

Values are adherence rates in percent. P<0.001 for comparison between baseline and post-intervention hand hygiene compliance in both the units.

RESULTS

A total of 2718 events were documented and studied over all the 4 phases of the study in NICU (*n*=1331) and PICU (*n*=1387) (**Fig. 1**). The baseline rates of hand hygiene (CR or PR) was 683/786 (86.9%) events in NICU and 665/819 (81.2 %) events in PICU. Post intervention, the rates of hand hygiene (CR or PR) improved to 517/545 (94.9%) in NICU and 528/568 (92.9%) in PICU. The comparison of hand hygiene compliance rates as per duration and compliance is shown in **Table I**. The compliance was highest among nursing officers (42% in NICU, 26% in PICU) than residents (40.3% in NICU, 16.5% in PICU). The hand hygiene compliance rate of WHO hand hygiene moments is depicted in **Table II**. There was no significant correlation between hand hygiene adherence rates and rates of HAI, except for CAUTI rates in PICU (r=0.619, P=0.03).

DISCUSSION

The present study showed a significant increase in hand compliance rate after implementation of EIR tap.

Table II Hand Hygiene Compliance Rate of Each Hand Hygiene Moment

Hand hygiene moments	*PICU*	*NICU*
Before patient contact	469/575 (85.0)	484/627 (82.1)
Before aseptic task	86/102 (80.7)	36/42 (72.9)
After aseptic procedure	33/39 (84.6)	15/17 (66.6)
After patient contact	285/332 (86.0)	303/391 (76.6)
After contact with the patient surroundings	97/130 (82.6)	97/159 (63.0)

Hand hygiene moments as defined by World Health Organization [3]. *Hand hygiene compliance rate=(complete adherence moments+partial adherence moments)/total moments available. Data shown as n/N (%). PICU: pediatric intensive care unit; NICU: neonatal intensive care unit.*

WHAT THIS STUDY ADDS?

* Use of an electronic infrared tap with voice reinforcement in handwashing stations of pediatric and neonatal intensive care units improved the hand hygiene compliance among health care workers.

The events enrolled during phase III, and phase IV were less compared to phase I and phase II, that can be attributed to the decline in patient load and staffing patterns during COVID pandemic. Hand hygiene was analyzed and categorized into CR, PR, and NR in the present study, as previously used [10], which demons-trated a better stratification of compliance. The increase in hand hygiene compliance noted with EIR tap was comparable to a previous study [11], which used electronic moni-toring, coupled with voice prompts. The reduction in NR in NICU and PICU during the post-intervention phase can be explained by the use of regulated water flow in the intervention tap, thereby forcing the user to engage for a longer duration.

The common reasons for non-compliance to hand hygiene were perception of patient needs as immediate priority, and forgetfulness of the health worker [12]. There was a notable increase in compliance between phase 3 and phase 4 post-intervention in PICU and NICU. This can be attributed to the COVID pandemic, which led to increased hand hygiene behavior among participants.

On analyzing the five WHO hand hygiene moments in the NICU, maximum compliance was observed for moment 1 (before contact with the patient), and least compliance during moment 5 (after contact with patient surroundings). Our study also identified a decreased compliance rate in moment 2 and 3, which warranted improvement. Basic interventions such as training modules for health care workers, upgrading infrastructure, and implementing feedback sessions increases compliance [13]. The highest compliance was noted among interns, technicians and allied health workers. This can be attributed to the lesser opportunities of moments than a physician and nursing officer, unlike data from previous studies [14,15]. The lowest compliance was observed among resident doctors, both in the PICU and the NICU.

There was no significant correlation between CR of alcohol-based hand rub and CLABSI in NICU probably as the baseline rates of CLABSI were low even before the intervention.

The voice prompt in intervention also made the hand washing experience livelier and more interactive. This method would have minimized the use of water and was eco-friendly, though was not measured. The study had few limitations. Data was collected only at two time points and the trends in between these time points were not analyzed. Confounders in the study due to inconsistency in preference of tap by participants and restriction of monitoring to only two handwashing stations were present. A part of the study period overlapped with the first wave of COIVD-19 pandemic in the country, which might have contributed to the behavior change.

We found that the use of an EIR tap with voice reinforcement in handwashing stations of NICU and PICU improved hand hygiene compliance among healthcare workers.

Ethics clearance: Institutional Ethics Committee (Human studies), JIPMER: No. JIP/IEC/2018/0207 dated Sep 11, 2018.
Contributors: KM: collected and analyzed the data; MA: reviewed data analysis and drafted manuscript; AS: helped in the lab work; BA: designed the study, supervised clinical work and edited the manuscript. All authors have seen and approved the submission of this manuscript and take full responsibility for the manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Zingg W, Hopkins S, Gayet-Ageron A, et al. ECDC PPS study group. Health-care-associated infections in neonates, children, and adolescents: An analysis of paediatric data from the European Centre for Disease Prevention and Control point-prevalence survey. Lancet Infect Dis. 2017; 17:381-89.
2. Allegranzi B, Sax H, Pittet D. Hand hygiene and healthcare system change within multi-modal promotion: A narrative review. J Hosp Infect. 2013;83:S3-10.
3. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care is Safer Care. World Health Organization; 2009. 21, The WHO multimodal hand hygiene improvement strategy. Available from: *https://www.ncbi.nlm.nih.gov/books/NBK144032/HHSVulnerability Disclosure*
4. Al Salman JM, Hani S, de Marcellis-Warin N, et al. Effectiveness of an electronic hand hygiene monitoring system on healthcare workers' compliance to guidelines. J Infect Public Health. 2015;8:117-26.
5. Marra AR, Edmond MB. New technologies to monitor healthcare worker hand hygiene. Clin Microbiol Infect Dis. 2014; 20:29-33.
6. McCalla S, Reilly M, Thomas R, et al. An automated hand hygiene compliance system is associated with improved monitoring of hand hygiene. Am J Infect Control. 2017;45:492-7.
7. Sánchez-Carrillo LA, Rodríguez-López JM, Galarza-Delgado DÁ, et al. Enhancement of hand hygiene compliance among health care workers from a hemodialysis unit using video-monitoring feedback. Am J Infect Control. 2016; 44:868-72.

8. Marra AR, Sampaio Camargo TZ, Magnus TP, et al. The use of real-time feedback via wireless technology to improve hand hygiene compliance. Am J Infect Control. 2014;42:608-11.
9. Boyce JM, Laughman JA, Ader MH, et al. Impact of an automated hand hygiene monitoring system and additional promotional activities on hand hygiene performance rates and healthcare-associated infections. Infect Control Hosp Epidemiol 2019;40:741-7.
10. Laskar AM, Deepashree R, Bhat P, et al. A multimodal intervention to improve hand hygiene compliance in a tertiary care center. Am J Infect Control. 2018;46:775-80.
11. Swoboda SM, Earsing K, Strauss K, et al. Electronic monitoring and voice prompts improve hand hygiene and decrease nosocomial infections in an intermediate care unit. Crit Care Med. 2004;32:358-63.
12. Patarakul K, Tan-Khum A, Kanha S, et al. Cross-sectional survey of hand-hygiene compliance and attitudes of health care workers and visitors in the intensive care units at King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2005; 88:S287-293.
13. Labi A, Obeng-Nkrumah N, Nuertey BD, et al. Hand hygiene practices and perceptions among healthcare workers in Ghana: A WASH intervention study. J Infect Dev Ctries. 2019;13: 1076-85.
14. Rosenthal VD, McCormick RD, Guzman S, et al. Effect of education and performance feedback on handwashing: The benefit of administrative support in Argentinean hospitals. Am J Infect Control. 2003;31:85-92.
15. Mahfouz AA, El Gamal MN, Al-Azraqi TA. Hand hygiene non-compliance among intensive care unit health care workers in Aseer central hospital, south-western Saudi Arabia. Int J Infect Dis. 2013;17:e729-32.

RESEARCH PAPER

Severe Pulmonary Arterial Hypertension in Healthy Young Infants: Single Center Experience

SHRIKIRAN AROOR,[1] KOUSHIK HANDATTU,[1] SUNEEL C MUNDKUR,[1] ADITYA VERMA,[1] PRAVEEN C SAMUEL,[1] AKKATAI S TELI,[2] GUNJAN BANGA[2]

[1]*Department of Paediatrics, Kasturba Medical College (Manipal Academy of Higher Education), Manipal, Karnataka.*
[2]*Department of Cardiology, Kasturba Medical College (Manipal Academy of Higher Education), Manipal, Karnataka.*

Correspondence to:
Dr Koushik Handattu,
Assosciate Professor,
Department of Pediatrics,
Kasturba Medical College
(Manipal Academy of Higher
Education), Manipal, Karnataka.
koushik.h@manipal.edu
Received: Oct 20, 2022;
Initial review: Dec 5, 2022;
Accepted: May 23, 2023.

Objectives: We studied the clinical presentation and management of acute pulmonary arterial hypertension (PAH) in healthy young infants, and the effect of thiamine therapy **Methods:** Review of hospital records was conducted for 56 healthy infants (aged below 6 month) who developed sudden onset of pulmonary arterial hypertension as diagnosed on 2D echocardiography, and were admitted at our institution. **Results:** All patients received supportive care and pulmonary vasodilator therapy, whereas those admitted after September, 2019 (*n*=28) received thiamine in addition, as per the institute's protocol. Overall, complete recovery was seen in 80% (*n*=45). Infants who died had significantly lower mean pH (7.05 vs 7.27; *P*=0.001) and serum bicarbonate (9.1 vs 14.9; *P*=0.007), higher arterial lactate (72.7 vs 61.5; *P*=0.92), ventricular dysfunction (16 vs 10; *P*=0.01) and shock (7 vs 9; *P*=0.008) when compared to those who survived. Baseline characteristics, severity of acidosis and pulmonary hypertension, time taken to recover from PAH, presence of ventricular dysfunction were comparable among those who received thiamine and those who did not receive it. Similarly, recovery (89% vs 71%; *P*=0.17) and mortality (11 % vs 29%) were also comparable between the two groups. **Conclusion:** A significant proportion of infants with PAH improve with supportive treatment and pulmonary vasodilator therapy. Thiamine supplementation may not give any additional benefit in these patients.

Keywords: *Management, Outcome, Thiamine deficiency.*

Published online:May 30, 2023; **PII**:S097475591600551

In the last few years, acute severe pulmonary artery hypertension (PAH) in previously healthy young infants has been increasingly reported from different parts of India [1,2]. They present with poor feeding/ lethargy, severe metabolic acidosis, pulmonary artery hypertension and heart failure. Considering associated socio-epidemiological factors like predominantly polished rice consumption by lactating mothers, post-partum food restriction, response to empiric thiamine therapy, this catastrophic conundrum has been assumed to be secondary to thiamine deficiency [1,3]. However, causal relationship could not be established with controlled studies [1-4]. Since September, 2019, our institutional protocol included routine thiamine supplementation in all children with PAH. Hence, this study was conducted to analyze the spectrum of PAH cases, and compare the outcomes based on exposure to thiamine therapy.

METHODS

This was a retrospective study conducted in the Department of Pediatrics of a tertiary care hospital. We retrieved hospital records of 56 previously healthy infants aged between 1-6 months of age, admitted in the department between October, 2018 and September, 2020 with the diagnosis of PAH at admission. PAH was defined as pulmonary artery peak systolic pressure (PAP) >1/3 of systemic systolic blood pressure (SBP) [5] assessed by 2-dimensional echocardiography (2D-echo). A fall in pulmonary artery PAP to normal levels, assessed in the 2D- echo done at the time of discharge, was considered as a significant decline in PAP. Children with congenital heart disease, pneumonia, bronchiolitis, culture-proven sepsis, diagnosed cases of inborn error of metabolism on treatment, and other pre-existing systemic diseases at the time of admission were excluded. After obtaining institute ethics committee clearance, previous medical records of eligible patients were accessed and relevant data were analyzed.

Invited Commentary: Pages 707-08

Anthropometric parameters were recorded and interpreted as per standard guidelines [6]. PAP was recorded in 2D-Echo, performed by an experienced pediatric cardiologist in the pediatric intensive care unit (PICU). As PAP varies widely in infants, especially while crying and during

acute illness, it was measured when infant was calm/sleeping. Peak PAP was measured and reported as a fraction of SBP. Further, PAH was categorized as mild, moderate and severe whenever PAP was 1/3-2/3, 2/3-1 and >1 of SBP value, respectively [5,7]. Metabolic acidosis was diagnosed if blood pH was <7.35 with serum bicarbonate <20 mmol/L and arterial lactate >20 mmol/L. Children with PAH admitted between September, 2019 and October, 2020 had received additional empirical thiamine therapy [intravenous (100 mg) thiamine infusion over 1 hour, followed by oral thiamine (100 mg) till normalization of PAP] [1,2]. The outcome of these infants was compared with those admitted before September, 2019, who were treated with supportive care and pulmonary vasodilator therapy alone without thiamine supplementation [1,2].

All infants received supportive care in the form of hydration, humidified oxygen, antipyretics, antiemetics, intravenous fluids and mechanical ventilation as per the need. Pulmonary vasodilator therapy (sildenafil and or milrinone) was administered orally or parenterally to all infants, depending on the severity of illness and general condition of the patient.

Table I Characteristics of Infants With Pulmonary Arterial Hypertension (*N*=56)

Parameter	*Observation*
Age <3 mo	43 (77)
Male sex	40 (71)
Birthweight (kg)[a]	2.86 (0.496)
Weight SDS[b]	-2.00 (-2.95,-1.41)
Investigations	
pH[a]	7.23 (0.19)
Serum bicarbonate (mmol/L)[b]	14 (9.7, 16.1)
Serum lactate (mg/dL)[b]	66.9 (14.2, 112.75)
Pulmonary artery hypertension (PAH)	
Moderate	7 (13)
Severe	49 (87)
RA/ RV dilation	53 (95)
RV dysfunction	26 (46)
LV diastolic dysfunction	14 (25)
PAP at admission (mm Hg)[a]	74 (18.07)
PAP at discharge (*n*=45)[a]	24 (10)
Pulmonary vasodilator therapy	
Sildenafil	50 (89)
Milrinone	11 (20)
Both	10 (18)
Time for resolution of PAH (d)[b]	7 (3, 60)
Death	11 (20)

Values in no. (%),[a]mean (SD) or [b]median (IQR). RA: right atrium, RV: right ventricle, LV: left ventricle, PAP: pulmonary arterial peak systolic pressure.

Statistical analysis: Data were entered in Excel sheets and imported to EZR software version 3.2 (Jichi Medical University) for analysis. Qualitative variables are expressed as numbers and percentages, quantitative variable are expressed as mean (SD) or median (IQR) based on the pattern of distribution. Chi-square test or Fischer exact test were used to compare the frequency of qualitative variables, whereas the Student *t* test was used for quantitative variables among different groups.

RESULTS

We retrieved data of 56 children, and the baseline characteristics are presented in **Table I**. The majority of infants were below 3 months of age. All infants were born at term and weighed appropriate for gestational age with normal postnatal growth. Poor feeding was the most common symptom seen in 66% infants, whereas tachypnea and/or tachycardia were the most common sign. Severe PAH was seen in 87.5% infants. Pulmonary pressure declined significantly at the time of discharge and normalized in 97% infants (*n*=44 among those who survived), except in one baby in whom PAH normalized by 60th day of onset.

Variables were compared between survivors and non-survivors (**Table II**). Mean pH and serum bicarbonate was significantly lower in those who died. Similarly, the presence of shock, ventricular dysfunction (RV and/or LV diastolic

Table II Outcome Among Infants With Pulmonary Arterial Hypertension (*N*=56)

	Survived (n = 45)	*Deaths (n = 11)*	*P value*
Age (y)[a]	0.20 (0.07)	0.20 (0.07)	0.935
Weight (kg)[a]	4.32 (0.78)	4.66 (0.88)	0.264
pH[a]	7.27 (0.18)	7.05 (2.13)	0.001
Serum bicarbonate (mmoL/L)[b]	14.90 (5.10, 15.00)	9.1 (5.8, 17.3)	0.007
Lactate (mmol/L)[b]	61.5 (16.4, 200)	72.7 (26.6, 182.4)	0.918
Hypoxia	20 (44.2)	8 (77.7)	0.177
Shock	9 (16.3)	7 (63.6)	0.008
PAP at admission (mmHg)[a]	72.2 (7.97)	83.09 (16.44)	0.073
RV dysfunction	16 (35.5)	10	0.001
LV diastolic dysfunction	5 (11)	8 (72)	<0.001
Thiamine therapy	25 (55.6)	3 (27.3)	0.177
Mechanical ventilation	8 (17.78)	11 (100)	<0.001
Inotropic support	9 (20)	11 (100)	<0.001

Values in no. (%), [a]mean (SD) or [b]median (IQR). PAP: pulmonary arterial peak systolic pressure, RV: right ventricle, LV: left ventricle.

Table III Parameters Among Children With Pulmonary Arterial Hypertension Based on Exposure to Thiamine

	Received thiamine (n=28)	*Not received thiamine (n=28)*	*P value*
pH[a]	7.19 (0.22)	7.28 (0.17)	0.11
HCO3 (mmol/L)[b]	13.3 (5.1, 25.0)	14.3 (6.5, 22.4)	0.17
Shock	8 (28.6)	8 (28.6)	1.00
Time for resolution of PAH (d)[b]	7 (3,60)	8 (3,15)	0.56
RV dysfunction	13 (46)	12 (42)	1.00
LV diastolic dysfunction	6 (21)	7 (25)	1.00
Mechanical ventilation	9 (32.1)	10 (35.7)	1.00
Inotropic support	9 (80)	11(90)	1.00
Died	3 (10.7)	8 (28.6)	0.17

Values in no. (%), [a]mean (SD) or [b]median (IQR). RV: right ventricle, PAH: pulmonary arterial Hhypertension, PAP: pulmonary arterial peak systolic pressure, LV: Left ventricle.

dysfunction), requirement of inotropes, need for mechanical ventilation and duration of hospital stay was significantly higher in infants who did not survive.

Among infants who received thiamine and those who did not, both the groups were comparable with respect to general condition, severity of pulmonary hypertension and acidosis. The incidence of ventricular dysfunction, the time taken for resolution of PAH, need for mechanical ventilation, inotrope requirement, and outcome also did not differ in the two groups (**Table III**).

DISCUSSION

In this hospital record review, we report recovery in most patients with supportive treatment alone, presence of severe acidosis, shock as a common finding among those died and lack of significant difference in terms of recovery and mortality among those who received and those who did not receive thiamine supplementation.

The baseline characters and clinical profile in our study was similar to previous studies [1,2,4,8-10]. Few earlier Indian studies attributed similar symptom complex to encephalitis or metabolic acidosis, as 2D-echo was not part of their workup or facility was not available [2,11]. At our center, diagnosis of PAH was ascertained by bedside 2D echo in the PICU at the time of admission. Previous studies reported pulmonary pressures based on absolute values at admission [1,3,4]; however, we described peak pulmonary arterial pressure as a fraction of concurrent systemic blood pressure [5]. Although, cardiac catheterization is the gold standard for PAH diagnosis, considering the poor general condition of patients, we did not undertake invasive procedure in acute care settings. The presence of concomitant left ventricular diastolic dysfunction in more than a quarter of the infants was a striking finding, mostly attributed to RV dilatation and septal deviation to left [12].

In most of the recent reports, similar presentation was thought to be an acute cardiogenic form of thiamine deficiency similar to wet beriberi [13,14]. This was attributed to the predominant intake of polished rice by lactating mothers with severe restriction of other foods resulting in maternal and infantile thiamine deficiency [2,4]. In a previous study from Hyderabad [3], a set of 55 infants who presented with respiratory distress, cardiomegaly and PAH were found to have low erythrocyte transketolase activity, suggesting thiamine deficiency. However, thiamine levels in mothers or controls were unavailable in this study. Sastry, et al. [1] from Bangalore described a set of infants with acute life-threatening metabolic acidosis, PAH, and varying degrees of heart failure. They observed that 231 (*n*=250) responded to empiric thiamine. However, thiamine levels in infants or lactating mothers or controls were not tested.

All outcome measures were also comparable among those who received thiamine and those who did not. It is crucial to note that three infants with severe PAH died despite receiving thiamine at admission. Thiamine therapy did not make significant change in mortality or time taken for recovery. In previously published literature, consumption of polished rice and post-partum food restriction are assumed to be risk factors for thiamine deficiency and PAH. However, majority of pregnant and lactating mothers in our region consume unpolished parboiled rice and fish, both of which are rich source of thiamine. These findings raise questions against empirical use of thiamine and the need to explore the possibility of an alternative etiology. Reported mortality varies from 3%-67% in earlier studies; whereas, in our study, it was 19% [1,15]. Limitations of our study include small sample size, retrospective data collection, unavailability of markers of thiamine deficiency, and lack of cardiac catheterization.

Acute PAH seen in previously healthy young infants can be severe enough to result in mortality despite good care. A significant proportion of infants improve with supportive treatment alone, whereas outcome is poor in case of severe PAH with shock. Large-scale prospective studies addressing the etiology, role of thiamine, risk factors and management is the need of the hour.

Ethics clearance: Ethics Committee of Kasturba Medical College and Hospital, Manipal No. 581/2020 dated Dec 18, 2020.
Contributors: SA, KH: conceptualized the study design, prepared the manuscript; KH, SA, SCM, PS, AV: were part of treating team and manuscript writing; AST, GB: rendered cardiology services. All the authors equally contributed in the editing and final revision of the manuscript.

WHAT THIS STUDY ADDS

- A significant proportion of infants with the severe pulmonary artery hypertension (PAH) improve with supportive treatment alone.
- Thiamine supplementation was not found to significantly affect recovery or outcome of severe PAH in infants.

Funding: None; *Competing interest*s: None stated.

REFERENCES

1. Sastry UMK, Jayranganath M, Kumar RK et al. Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: A prospective observational study. Arch Dis Child. 2021;106:241-46.
2. Qureshi UA, Sami A, Altaf U et al. Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. Nutrition. 2016;32:213-16.
3. Narasimha Rao S, Chandak GR. Cardiac beriberi: Often a missed diagnosis. J Trop Pediatr. 2009;56:284-85.
4. Bhat JI, Rather HA, Ahangar AA et al. Shoshin beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India. Indian Heart J. 2017;69:24-27.
5. Skinner GJ. Echocardiographic assessment of pulmonary arterial hypertension for pediatricians and neonatologists. Front Pediatr. 2017;5:1-8.
6. De Onis M, Garza C, Victora CG et al. The WHO multicentre growth reference study: planning, study design, and methodology. Food Nutr Bull. 2004;25:S15-26.
7. Lauren McDaniel. Blood chemistry and body fluids. *In*: Kleinman, K. Harriet Lane Handbook, 22nd ed. Elsevier Inc; 2021.p.640-52.
8. Qureshi UA, Bhat AS, Qureshi U et al. Infantile thiamine deficiency: Redefining the clinical patterns. Nutrition. 2021; 84.
9. Newton-Cheh C, Johnson T, Gateva V et al. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet. 2009;41:666-76.
10. Panigrahy N, Chirla DK, Shetty R, et al. Thiamine-responsive acute pulmonary hypertension of early infancy (TRAPHEI)-a case series and clinical review. Children (Basel). 2020;7:199.
11. Narasimha Rao S, Mani S, Madap K et al. High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. J Trop Pediatr. 2008;54:328-32.
12. Burkett DA, Slorach C, Patel SS, et al. Left ventricular myocardial function in children with pulmonary hypertension: relation to right ventricular performance and hemodynamics. Circ Cardiovasc Imaging. 2015;8: 10.1161/CIRCIMAGING. 115. 003260 e003260.
13. Whitfield KC, Bourassa MW, Adamolekun B, et al. Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. Ann NY Acad Sci. 2018;1430:3-43.
14. Hiffler L, Rakotoambinina B, Lafferty N, Martinez Garcia D. Thiamine deficiency in tropical pediatrics: new insights into a neglected but vital metabolic challenge. Front Nutr. 2016;3: 16.
15. Sangeeta VB, Adarsh E, Divya N, Amrutha S. Idiopathic acute onset pulmonary artery hypertension in infancy need for research. Int J Contemp Pediatr. 2017;4:2050-4.

SYSTEMATIC REVIEW

Iron Preparations in the Management of Iron Deficiency Anemia in Infants and Children: A Systematic Review and Meta-Analysis

CUDDALORE SUBRAMANIAN ARULPARITHI,[1] THIRUNAVUKKARASU ARUNBABU,[2] SEKAR MANJANI[3]

[1]*Department of Pediatrics, Sri Lalithambigai Medical College, Adayalampattu, Maduravoyal, Chennai, Tamil Nadu.*

[2] *Department of Pediatrics, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh.*

[3] *Department of Pathology, Bharath Medical College, Chennai, Tamil Nadu.*

Correspondence to: Dr CS Arulparithi, Professor of Pediatrics, Sri Lalithambigai Medical College, Adayalampattu, Maduravoyal, Chennai 600 095, Tamil Nadu. cs_arulparithi@yahoo.co.in

Background: Various therapeutic iron preparations are available in the market, which differ in their pharmacokinetic and safety profiles. There is insufficient evidence regarding the superior safety or efficacy of one over the other.

Objectives: To study the effects of iron preparations on various parameters like hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and serum ferritin.

Study design: A systematic review and meta-analysis of randomized controlled trials (RCT) was conducted from inception till 3 June, 2022.

Data sources and selection criteria: Databases like MEDLINE and COCHRANE were searched for RCTs evaluating the effects and safety profile of various iron salts in the management of iron deficiency anemia in children and adolescents.

Main results: Eight studies with a total of 495 children were included the review. Pooled analysis showed ferrous sulphate to cause a significant increase in hemoglobin compared with other iron compounds [mean difference (95% CI) 0.53 (0.22 to 0.83; *P* <0.001]. Also ferrous sulphate is superior to iron polymaltose complex (IPC) (*P*<0.001). However, there was a significant increase in gastrointestinal adverse effects with ferrous sulphate compared to IPC (*P*=0.03). Other iron compounds were more efficacious than IPC in raising hemoglobin levels (*P*<0.001). Among the few studies evaluating iron indices like MCV, MCH, and serum ferritin, there was no significant difference between the iron preparations (*P*>0.05). **Conclusions**: A low quality evidence suggests that ferrous sulphate is more efficacious than other compounds (*P*<0.001); though, there is an increase in gastrointestinal side effects with ferrous sulphate.

Key words: *Ferrous sulphate, Iron polymaltose complex, Hemoglobin*.

Protocol registration: PROSPERO: CRD 42022336988 **Published online:** May 19, 2023; **PII:** S097475591600539

Nutritional deficiency of iron is common in the population because most naturally occurring iron is in Ferric form which is poorly absorbed from the diet [1]. As per World Health Organization (WHO) estimates, the global prevalence of anemia in children aged 6-59 months is 39.8% in the year 2019 [2], and according to the National Family Health Survey 5, the prevalence of anemia in India during the year 2019 was 53.4% [3].

Iron is not only important for hemoglobin synthesis but also for a variety of enzyme systems. Therefore iron deficiency produces anemia as well as other symptoms like organ and tissue dysfunction, impaired immunity, fatigability, decreased cognitive capabilities and poor weight gain [1,4].

Iron supplementation is one of the key strategies for the treatment of iron deficiency anemia (IDA). Most iron salts used for treatment of iron deficiency exist in ferrous form which is easily bioavailable. After supplementation, it takes around 24 hours to replace intracellular enzymes, followed by increase in hemoglobin over a month. Replenishing of iron stores takes one to three month time [5]. Various iron salt preparations are available including ferrous sulphate, iron polymaltose complex (IPC), iron bisglycinate chelate, ferrous ascorbate, colloidal iron, iron-zinc and lactoferrin 100. There is insufficient evidence regarding the superior safety or efficacy of one over the other.

This systematic review was undertaken with the objective of comparing various iron compounds with ferrous sulphate and IPC, and to correlate with hematologic indices including hemoglobin, means corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and serum ferritin.

METHODS

This systematic review and meta-analysis was conducted and is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database prior to commencement of the study.

Search eligibility: Randomized controlled trials from inception till 3 June, 2022, comparing the efficacy of different iron preparations in children aged between 6 months and 15 years of age, diagnosed to have IDA, based on hemoglobin values, were included in the review. The primary outcome measure was the effect on hemoglobin, and secondary outcomes include serum ferritin, changes in hemoglobin, MCV, MCH and gastrointestinal adverse effects.

Search strategy: The authors independently conducted searches of medical databases namely MEDLINE and COCHRANE center register of controlled trials published in English language. The electronic search strategy included a combination of keywords along with their representative Medical Subject Headings (MeSH). The details of search strategy are provided as **Web Box 1**.

Data extraction: Two authors independently searched the data using a pre-designed form. Disagreement, if any, was resolved by a third author. Details of study including author, place and year of study and characteristics of infants were included.

Quality assessment: Quality of studies was assessed independently by authors for each study using the risk of bias (RoB) criteria outlined in the Cochrane handbook for systematic review of intervention in the domains of random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting of results.

Statistical analysis: Statistical analysis was done using Review Manager version 5.4 (The Cochrane Collaboration, 2020). Outcome variables were noted as mean differences with 95% CI for continuous data. For dichotomous data, outcome variables were noted as risk ratio (RR) with 95% CI. When hemoglobin and other iron parameters were measured at different time points after starting therapy, those values obtained at the longest follow-up of each study were included in the analysis. Results were pooled using either fixed or random effects model based on heterogeneity. Between studies heterogeneity was assessed with a chi-square test and the I^2 statistic. A P value of <0.1 for the chi-square statistic indicated significant heterogeneity. Sensitivity analysis was done after excluding other studies comparing ferrous sulphate with other iron preparations excepting IPC, which revealed no heterogeneity after exclusion. Quality of evidence was assessed by Grading of recommendations, Development and Evaluation (GRADE) approach [7] to assess the quality of evidence using GRADE pro GDT tool.

RESULTS

Using the search strategies mentioned, 1878 records from two databases COCHRANE and MEDLINE were identified and screened for eligibility. Of these, 15 studies were found to be eligible, but after exclusions, eight studies with a total of 495 children were included in the review (**Fig. 1**). The age group of children ranged from 6 months to 17 years. The dosage of iron used ranged from 3 mg/kg/day to 6 mg/kg/day. Ferrous sulphate was compared with IPC in four of the studies. The other comparisons included iron bisglycinate chelate and IPC, ferrous sulphate and iron bisglycinate chelate, ferrous ascorbate and colloidal iron, and IPC and ferrous ascorbate. Rise in hemoglobin was the final outcome evaluated in all the studies, whereas serum ferritin, MCV, MCH and hematocrit were the secondary outcomes evaluated. The duration of iron therapy ranged from 28 days to 3 months. Adverse effects were evaluated in three studies [8-10] (**Table I**).

Two of the studies [10,11] had high risk of bias due to improper randomization (**Fig 2** and **3**). In one study [10], randomization was altered on a weekly basis, whereas in the other study [11], children were randomized to treatment groups in a consecutive fashion. Pineda, et al. [12] had some concerns due to improper randomization and deviation from intended interventions. Other five studies had low risk of bias. Though blinding of participants and people delivering interventions was done in only two studies [9,13], all the included studies had low risk of performance bias. Also, an appropriate analysis (Intention to treat analysis) was used in all the studies. In summary, 25% of studies had high risk of bias, whereas 12.5% had some concerns of risk of bias.

Outcome data were available for nearly all participants in five studies [8,10,12-14]. Though there was significant loss to follow-up at the end of the treatment period in three studies [9,11,15], the result was not biased by the missing outcome data and the loss to follow-up could not be attributed to

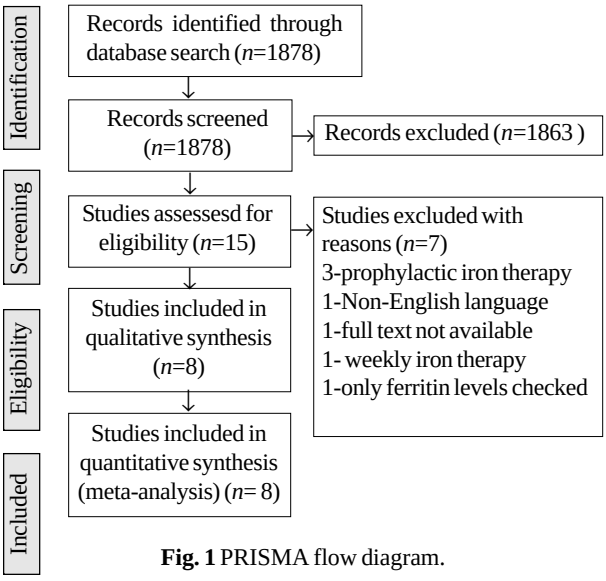


Fig. 1 PRISMA flow diagram.

Table I Characteristics of Included Studies

Author, country, year	*Participants (N; age)*	*Dose of iron (mg/kg/d)*	*Duration of treatment*	*Interventions (n)*	*Outcomes assessed*	*Study findings*
Powers, USA, 2013-2016 [9]	59 9-48 mo	3	12 wk	Ferrous sulphate (28), Iron polysaccharide (31)	Hb, Ferritin, TIBC, Adverse effects	E[a]: FeS[c] >IPC (P<0.001) SE[b]: IPC >FeS (P=0.62)
Name, Brazil, 2016 [13]	20; 1-13 y	3	45 d	Iron bisglycinate Chelate (FeBC), Polymaltose iron	Hb, Ferritin, Transferrin, MCV, MCH, RDW	E: IPC[d] = FeBC (P =1)
Yasa, Turkey, 2009 [10]	103; 7 mo 17 y	5	4 mo	IPC (52), Ferrous sulphate (51)	Hb, Ferritin, Serum Fe, TIBC, Transferrin saturation, MCV, MCH, MCHC, RBC count, Hct, Adverse effects	E: FeS >IPC (<0.001) SE: FeS >IPC (P=0.012)
Patil, India, 2016-2017 [15]	100; 1-12 y	6	3 mo	IPC (50), Ferrous ascorbate (50)	Hb, MCV, RDW, Reticulocyte count	E: FA[e] >IPC(P<0.001)
Pineda, Guatemala, 2001 [12]	40; 6-36 mo	5	28 d	Ferrous sulphate (20), Ferrous bisglycinate chelate (20)	Hb, Ferritin	E: FeS=FEBC (P=1)
Yewale, India, 2008 [14]	66; 6 mo - 12 y	3	12 wk	Ferrous ascorbate (37), Colloidal iron (29)	Hb, Hct, MCV, MCH, MCHC	E: FA >C.iron[f] (P<0.001)
Bopche, India, 2004 - 2005 [8]	106; 1-6 y	6	1 mo	IPC (53), Ferrous sulphate (53)	Hb, side effects	E: FeS >IPC (P<0.001) SE: FeS=IPC (P=0.14)
Ozsurekci, Turkey, 2008-2009 [11]	60; 6 mo - 15 y	6	8 wk	ferrous sulphate, Polymaltose complex, Iron-zinc	Hb, reticulocyte count	E: FeS=IPC (P=0.068)

[a]Efficacy defined by significant increase in hemoglobin (P< 0.05); [b]gastrointestinal side effects. [c]FeS: ferrous sulphate; IPC: iron polymaltose complex;FA: ferrous ascorbate; C.Iron: colloidal iron. Hb: hemoglobin; TIBC: total iron binding capacity; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; MXH: mean corpuscular hemoglobin.

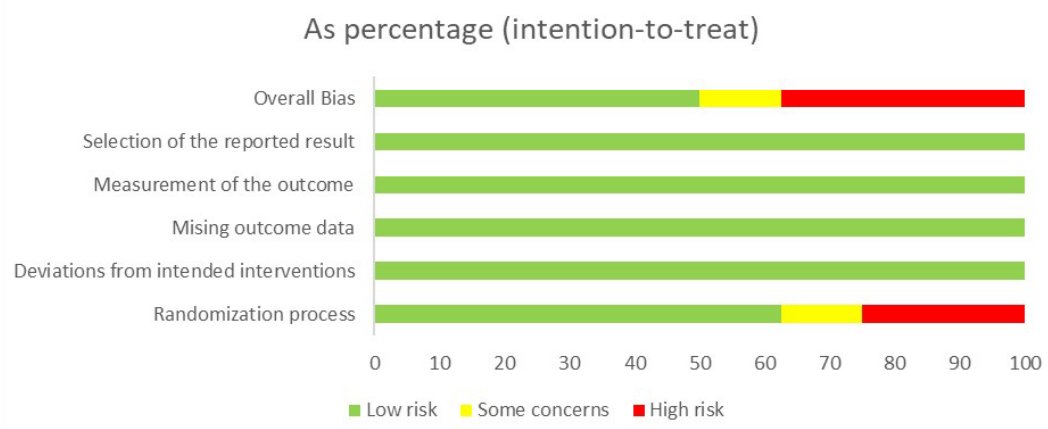


Fig.2 Risk of bias in the included studies.

Fig. 3 Risk of bias summary for included studies, showing authors' judgements about each risk of bias item for each included study.

decreased efficacy or significant side effects of the interventions. None of the studies had bias due to selective reporting.

The pooled effect size of the five studies [8-12] comparing ferrous sulphate with other iron compounds showed that ferrous sulphate caused a statistically significant increase in the mean hemoglobin when compared to other iron compounds [mean difference (95% CI) 0.53 (0.22-0.83); *P*<0.001] (**Fig.4**). The pooled effect sizes of the six studies [8-11,13,15] comparing IPC with other iron compound showed that other iron compounds cause a significant increase in hemoglobin compared with IPC [MD (95% CI) -0.70 (-0.99 to -0.41); *P*<0.001] (**Fig.4**). Sensitivity analysis was done due to difference in comparators. In four studies [8-11] comparing ferrous sulphate with IPC, ferrous sulphate caused a statistically significant increase in hemoglobin compared to other IPC [MD (95% CI) 0.68 (0.5-0.86); *P*<0.001]. In two studies comparing ferrous ascorbate with other iron compounds, ferrous ascorbate caused a significant increase in hemoglobin compared with other iron compounds [MD (95% CI) 1.45 (1.00-1.91); *P*<0.001].

Regarding the outcome of change in hemoglobin from baseline, three studies [10,12,15] evaluated this outcome. In two of these studies [10,12] comparing ferrous sulphate with other iron compounds, the change in hemoglobin was not statistically significant [MD (95% CI) 0.15 (-0.41 to 0.72); *P*=0.60]. In studies [10,15] comparing IPC with other iron compounds, there was a statistically significant change in hemoglobin in the other iron compound group [MD (95% CI) -1.27 (-1.68 to -0.85); *P*<0.001].

In two studies evaluating MCH [10,13], comparison of IPC with other iron compounds showed no significant difference [MD (95% CI) 0.11 (-0.43 to 0.65); *P*=0.68]. With regard to MCV, two studies [10,13] comparing IPC with other iron compounds, there was no significant change in MCV [MD (95% CI) -0.05 (-1.37 to 1.28); *P*=0.94]. Data on serum ferritin was obtained in four studies [9,10,12,13] including 222 children. In two studies [12,13] comparing iron bisglycinate chelate with other iron compounds, the change in ferritin levels were not statistically significant [MD (95% CI) 3.47 (-0.51 to 7.45); *P*=0.09].

Gastrointestinal side effects were significantly more in ferrous sulphate [OR (95% CI) 1.86 (1.06 to 3.26); *P*=0.03) compared with IPC [8-10] (**Fig.4**).

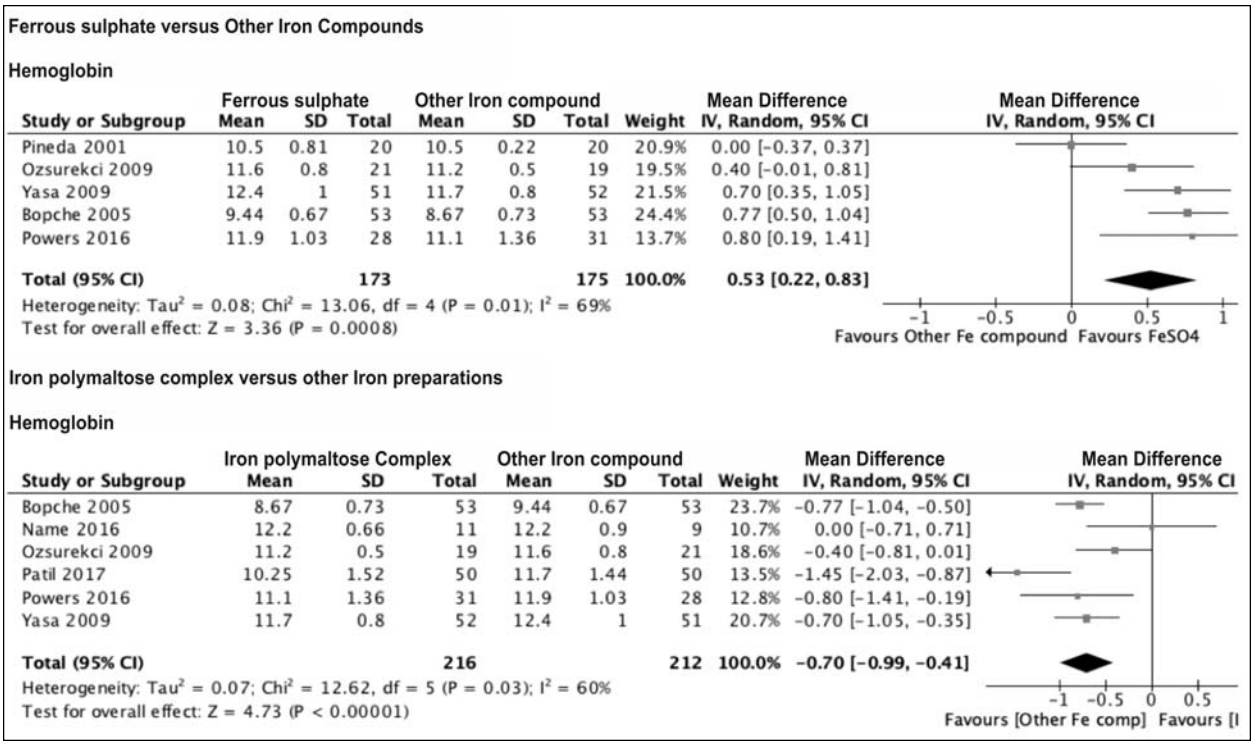


Fig. 4 Effect on hemoglobin levels of ferrous sulphate and iron polymaltose complex preparations vs other iron compounds for iron deficiency anemia in infants and children.

DISCUSSION

In the present review, a low quality of evidence suggests that ferrous sulphate causes a significant increase in hemoglobin when compared to other iron compounds. Also, a moderate quality of evidence showed that other iron compounds are better than IPC. Gastrointestinal side effects are slightly more with ferrous sulphate than IPC.

There are several limitations regarding the comparability of studies included in the review. The dosage of iron used in these studies ranged from 3-6 mg/kg/day. The duration of therapy ranged from 28 days to 3 months. The age group ranged from 6 months to 17 years. Blinding was done only in three studies [9,12,13]. The quality of evidence was low regarding hemoglobin levels in trials comparing ferrous sulphate with other iron compounds. While hemoglobin levels were reported in all studies, other outcomes like MCV, MCH, change in hemoglobin and serum ferritin were reported in only some of the studies.

In an earlier review done by Gera, et al. [16], it was found that iron supplementation modestly improves iron deficiency anemia in children. In most of the studies included in this review, different iron formulations were compared with placebo. In a review done by Rosli, et al. [17], it was shown that ferrous sulphate was superior to IPC. Also there was no significant difference in the side effects between the two

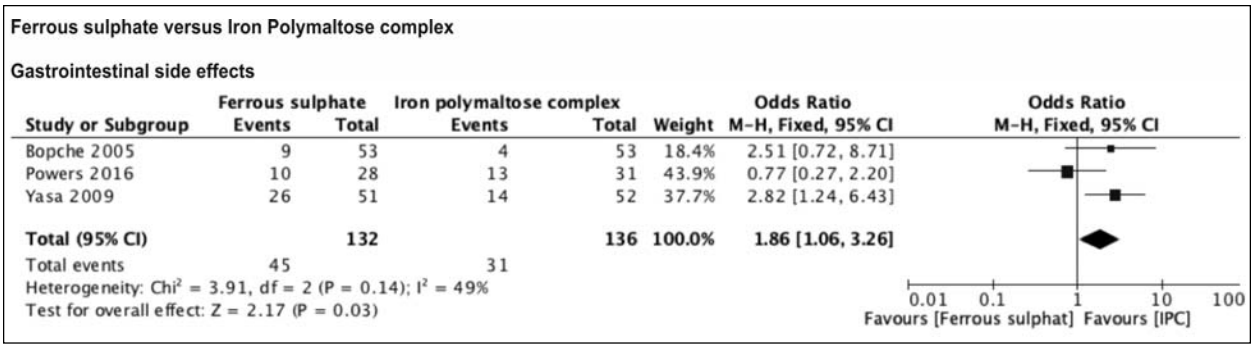


Fig 5. Gastrointestinal side effects of ferrous sulphate vs iron polymaltose computer for iron deficiency anemia in infants and children.

preparations. In an iron supplementation trial in preterm and low birth weight infants [18], it was found that there were no beneficial effects in the short term, but resulted in an improvement in iron status and iron deficiency. In another meta-analysis done by Low, et al. [19], it was found that iron supplementation safely improves hematologic and non-hematologic parameters in primary school aged children in low- and middle-income countries. It was also found that ferrous sulphate, when compared to placebo, improves global cognitive performance.

In an overview of reviews done by Mithra, et al. [20], it was found that in pre-school children, iron with multiple micronutrients (MMN) fortification significantly reduced the risk of anemia (by 55%), whereas, in school-aged children (under 12 years of age), the same showed better response (84% reduction in risk of anemia). In two reviews [21,22], it was found that in infants, home fortification (adding packets containing multiple micronutrients i.e., vitamins and minerals including iron with complementary foods of children) was better than iron supplementation in prevention of anemia. However, in anemic infants, medical iron drops is better than home fortification alone. In older children and adolescents (3.5 to 18 years), daily iron with or without multivitamins is better than intermittent iron [23,24]. However, these reviews did not compare different iron formulations in the management of anemia.

A review of anemic children in malaria endemic areas [25] compared iron with placebo or other supplemental nutrients like multivitamins, vitamin A, zinc, albendazole or mebendazole. The review included many outcome measures like clinical malaria, all-cause mortality, hospitalizations, weight, anemia, including hemoglobin at the end of treatment and change in hemoglobin with treatment. The pooled analysis of 13 trials in the review found that iron supplements (commonly ferrous sulphate) significantly improved hemo-globin compared with placebo. Importantly, all these studies, except one [26], did not compare different iron preparations, which was a prerequisite for our review and meta-analysis. Of these, Zlotkin, et al. [27] was the only study which had four treatment arms, of which two were different iron preparations i.e., microencapsulated iron fumarate and ferrous sulphate drops. But it was given as a supplement to non-anemic children (presence of anemia defined by hemoglobin levels is a prerequisite in our review). In fact, placebo group showed better response than ferrous sulphate drops in these non-anemic children in the study. In other studies, treatment arms included iron along with other supplements like zinc [27], vitamin A [28], antihelminthic agents [29,30], or multivitamins, micronutrients [31,32]. In all of these studies, placebo was one of the treatment groups. Hence these studies were not included in our meta- analysis.

In summary, a low quality of evidence suggests that ferrous sulphate is superior to other iron compounds in the management of iron deficiency anemia in young infants, children and adolescents. Moderate quality of evidence on adverse effects suggests that there is slightly more adverse effects with ferrous sulphate compared to IPC. Further research is needed to investigate the efficacy and safety of other less known compounds like ferrous gluconate, ferrous fumarate, etc.

Contributors: CSA: conceptualized the review, literature search, data analysis and manuscript writing; ABT: literature search, data analysis and manuscript writing; SM: conceptualized the review, literature search, data analysis and manuscript writing.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Will AM. Disorders of iron metabolism: iron deficiency, iron overload and the sideroblastic anemias. *In*: Arceci RJ, Hann IM, Smith OP, editors. Pediatric Hematology, 3rd ed.;2006. p.79.
2. WHO. Anaemia in women and children. [Online]. Accessed May 2, 2023. Available from: *https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children*
3. International Institute for Population Sciences (IIPS) and ICF. National Family Health Survey (NFHS-5), India, 2019-21. IIPS; 2021. Accessed May 2, 2023. Available from: *https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf*
4. Orkin S, Nathan D, Ginsburg D. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed.; 2014.
5. Rothman JA. Iron-deficiency anemia. *In*: Robert M, Kliegman M, Joseph W. St. Geme III M. Nelson Textbook of Pediatrics. 21st ed.; 2019. p. 2522-5.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ. 2021;372:n71.
7. Schunemann H, Brozek J, Guyatt G. GRADE Handbook; 2013. Available from: *https://gdt.gradepro.org/app/handbook/ handbook.html*
8. Bopche AV, Dwivedi R, Mishra R, Patel GS. Ferrous sulfate versus iron polymaltose complexfor treatment of iron deficiency anemia in children. Indian Pediatr. 2009;46:883-85.
9. Powers JM, George R. Buchanan M. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia a randomized clinical trial. JAMA.2017;317. 2297-304
10. Yasa B, Agaoglu L, Unuvar E. Efficacy, tolerability, and acceptability of iron hydroxide polymaltose complex versus ferrous sulfate: a randomized trial in pediatric patients with iron deficiency anemia. International Journal of Pediatrics. 2011; 2011:1-6.
11. Ozsurekci Y, Unal S, Cetin M, Gumruk F. Comparison of ferrous sulfate, polymaltose complex and iron-zinc in iron deficiency anemia. Minerva Pediatrica. 2015;71:449-54.

12. Oscar Pineda P, Ashmead HD. Effectiveness of treatment of iron-deficiency anemia in infants and young children with ferrous bisglycinate chelate. Nutrition. 2001;17:381-84.
13. Name JJ , Vasconcelos AR , Valzachi Rocha Maluf MC. Iron bisglycinate chelate and polymaltose iron for the treatment of iron deficiency anemia: A pilot randomized trial. Current Pediatric Reviews. 2018;14:261-68.
14. Yewale VN, Dewan B. Treatment of iron deficiency anemia in children: A comparative study of ferrous ascorbate and colloidal iron. Indian J Pediatr. 2013;80:385-90.
15. Patil P, Geevarghese P, Khaire P. Comparison of therapeutic efficacy of ferrous ascorbate and iron polymaltose complex in iron deficiency anemia in children:a randomized controlled trial. Indian J Pediatr. 2019;86;1112-17.
16. Gera T, Sachdev HPS, Nestel P. Effect of iron supplementation on haemoglobin response in children: Systematic review of randomised controlled trials. J Pediatr Gastroenterol Nutr. 2007;44:468-86.
17. Mohd RR, Norhayati MN, Ismail SB. Effectiveness of iron polymaltose complex in treatment and prevention of iron deficiency anemia in children: A systematic review and meta-analysis. Peer J. 2021;9:e10527
18. McCarthy EK, Dempsey EM, Mairead. Iron supplementation in preterm and low-birth-weight infants: a systematic review of intervention studies. Nutrition Reviews. 2019;77:865-77.
19. Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school– aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ. 2013;185:E791-802
20. Mithra P, Khatib MN, Sinha AP, et al. Interventions for addressing anemia among children and adolescents: An overview of systematic reviews. Frontiers in Pediatrics. 2021;8: 549549.
21. De-Regil LM, Suchdev PS, Vist GE, Walleser S. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database Syst Rev. 2011;9:CD008959.
22. Dewey KG, Yang Z, Boy E. Systematic review and meta-analysis of home fortification of complementary foods. Matern Child Nutr. 2009;5:283-321.
23. Low MSY, Speedy J, Styles CE, De-Regil LM, Pasricha. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. Cochrane Database Syst Rev. 2016;4:CD009747.
24. Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ. 2013;185:791-802.
25. Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev. 2016;2:CD006589.
26. Zlotkin S, Antwi KY, Schauer C, Yeung G. Use of micro-encapsulated iron(II) fumarate sprinkles to preventrecurrence of anaemia in infants and young children at high risk. Bull World Health Organ. 2003;81:108-15.
27. Fahmida U, Rumawas JS, Utomo B, Patmonodewo S. Zinc-iron, but not zinc-alone supplementation, increased linear growth of stunted infants with low haemoglobin. Asia Pacific Journal of Clinical Nutrition. 2007;16:301-9.
28. Mwanri L, Worsley A, Ryan P, Masika J. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. J Nutr. 2000;130:2691-6.
29. Dossa RA, Ategbo EA, Van Raaij JM, et al. Multivitamin-multimineral and iron supplementation did not improve appetite of young stunted and anemic Beninese children. J Nutr. 2001;131:2874-9.
30. Le Huong T, Brouwer ID, Nguyen KC, Burema J, Kok F. The effect of iron fortification and de-worming on anaemia and iron status of Vietnamese schoolchildren. British J Nutr. 2007; 97:955-62.
31. Esan MO, van Hensbroek MB, Nkhoma E, Musicha C. Iron supplementation in HIV-infected Malawian children with anemia: A double-blind, randomized, controlled trial. Clinical Infectious Diseases. 2013;57:1626-34.
32. Hop le T, Berger J. Multiple micronutrient supplementation improves anemia, micronutrient nutrient status, and growth of Vietnamese infants: double-blind, randomized, placebo controlled trial. J Nutr. 2005;135:660S-5.

Web Box I Details of the search strategy

MEDLINE

("Oral iron preparation" or iron supplements* or ferrous ascor-bate* or ferrous gluconate* or colloidal iron* or ferrous fuma-rate* or ferrous sulphate* or ferrous sulfate* or iron salt* or Carbonyl iron* or iron polysaccharide complex* or iron poly-maltose complex* or Iron Protein Succinylate* or ferri manni-tol ovalbumin* or iron bisglycinate* or ferrous bisglycinate* or ferrous glycine sulfate* or ferrous glycine sulphate* or ferric pyrophosphate* or sucrosomal Iron* or ferrous compounds* or ferric compounds* or lactoferrin*) and ((("iron deficiency ane-mia" or nutritional anemia* or microcytic hypochromic ane-mia*))) and (("children" or infants* or child*))

CENTRAL

Search words: Iron preparations for iron deficiency anemia in children

ID Search

#1 iron deficiency in Trials (Word variations have been searched)

#2 MeSH descriptor: [Anemia, Iron-Deficiency] explode all trees

#3 #1 or #2

#4 iron compound in Trials

#5 iron preparation in Trials

#6 MeSH descriptor: [Iron Compounds] explode all trees

#7 ferrous

#8 ferric

#9 #4 or #5 or #6 or #7 or #8

#10 infant

#11 children

#12 #10 or #11

#13 #3 and #9 and #12

American Academy of Pediatrics, 2023: Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

SARIKA GAIKWAD,[1] ARVA BHAVNAGARWALA[2]

[1]*Department of Pediatrics, Jawaharlal Nehru Medical College, Wardha, Maharashtra.*

[2]*Department of Pediatrics, Masina Hospital and Saifee Hospital, Mumbai, Maharashtra.*

Correspondence to: Dr Sarika Gaikwad, Flat no. 101, Building no. A2, Vyankatesh Apartment, Near Agnihotri College of Engineering, Nagathana Road, Wardha 442 001, Maharashtra. drsarika.gaikwad@gmail.com

American Academy of Pediatrics (AAP) have released their first comprehensive clinical practice guideline that outlines evidence-based evaluation and treatment of children and adolescents with overweight and obesity. This article reviews the same, along with implication in our setting and the need for updating our guideline, which is almost two decades old.

Keywords: *Management, Overweight, Prevalence.*

The global epidemic of child and adolescent obesity affects all regions of the world, even in countries where under nutrition is prevalent. 14.4 million children and adolescents are affected by obesity in United States [1]. Obesity prevalence among children and adolescents aged 5-19 year, in India ranged between 3.6 % and 11.7%. By 2025, 17 million Indian children will be obese. Urbanization is a significant factor related to obesity [2]. Other factors include epigenetic, nutritional, familial, psychosocial, parental education and occupation. Obesity and overweight have effects on physical and mental health and these are the risk factors for major chronic illness in adults such as cardiovascular disease, diabetes and premature death.

Recently, the American Academy of Pediatrics (AAP) released their comprehensive guidelines on management of childhood and adolescent obesity [1]. The recommendations in the AAP guidelines are child-centric, not specific to a particular health care set up, and are written to inform pediatricians and other health care practitioners about the standard of care for assessing and managing children with overweight, obesity and their comorbidities. However, these guidelines exclude prevention strategies.

ASSESSMENT, EVALUATION AND PREVENTION

According to Centre for Disease Control and Prevention (CDC) and AAP, the weight status in children in 0 - 2 years of age is screened by using the World Health Organization (WHO) weight for length, age and sex-specific charts. In patients with certain syndromes like trisomy 21, specialized growth charts can be used.

The AAP emphasises on various social determinants of health (SDoHs). These are the environmental factors where children are born, live, learn, and grow. SDoHs are divided into five areas: financial stability, education access and standard, home and neighborhood environment, social and community context. These guidelines do not include children aged below 2 year. The main screening and diagnostic tool used by them is the body mass index [3,4].

More importance is given to evaluation of overweight and obesity. This includes a complete medical and social history, history of nutrition and physical activity, behavioral health, eating disorders, and the most important being the assessment of patient's readiness to change.

The current guidelines also emphasizes the initial evaluation and diagnostic tests for several common comorbidities such as dyslipidemia, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), hypertension, obstructive sleep apnea, polycystic ovarian syndrome, depression and slipped capital femoral epiphysis.

TREATMENT

Obesity being a chronic disease, AAP endorses intensive and long-term care treatment plan. Motivational interviewing (MI) has a significant role in the treatment. MI focuses on the patient. It is a form of counselling that identifies and promotes the child/adolescent patient's willingness for change. This is unlike the old strategy in which care provider suggests behavioral changes. MI helps families to identify the behavior that needs to be changed, taking into account parent and adolescent desire [5].

Another focus is on intensive health behavior and lifestyle treatment (IHBLT). However, this has some limitations as it needs access to a multidisciplinary team in partnership with the patient and their families promptly when overweight

or obesity is diagnosed. This method employs health education, behavior counselling and skill building on multiple topics given in a healthcare setting over a period of 3 to 12 months, and with a contact period of ideally more than or equal to 26 hours [6].

Behavior strategies that are given importance by the AAP guidelines include:

Reduction of sugar sweetened beverages (SSB): According to AHA, added sugar of each day should not be more than 25 g or 6 teaspoons, and not more than one 8 ounce serving of SSB per week. AAP recommends no fruit juices for children below 12 years and even during exercise the main source for hydration should be water [7-9].

This is quite similar to Indian Academy of Pediatrics (IAP) Guidelines on the Fast and Junk Foods, Sugar Sweetened Beverages, Fruit Juices, and Energy Drink [10], in child less than 2 year it encourages the intake of local and seasonal fruits in diet, avoidance of fruit juice and SSB. Older children and adolescents should avoid these drinks, too. In case there is an intake of fruit juice, it should not be more than 125 mL/day for children between 2 to 5 years, and 250 mL/day for above 5 years, and preferable given as fresh juices. Water is promoted as the best drink. Children should completely avoid carbonated drinks, tea and coffee [10].

Traffic light diet and 5210: In the 5-2-1-0 strategy, 5 fruits and vegetables a day as per USDA Choose MyPlate recommendations, 2 hours or less of screen time is similar to previous AAP guidelines [11]; 60 min or more of moderate to vigorous physical activity is similar with the physical activity [12,13]. Recommendations for Americans, and 0 SSBs is consistent with guidelines by USDA, AHA and AAP [14].

Food Safety and Standards Authority of India (FSSAI) had proposed a ban on sale of High in fat, salt and sugar (HFSS) foods in school canteens in 2016. Food items were categorized as 'green' for healthy foods, 'red' for HFSS foods that should be banned, and 'yellow' foods should be available less frequently in school canteens [15].

PREVENTION

Prevention strategies are not included in the AAP guidelines; however, WHO recommends [16]:

- At primary health-care set up, in overweight children aged below 5 years, doctors should provide counselling on general nutrition and for physical activity to caregivers.
- Children aged more than 5 years with obesity should be evaluated and an appropriate management plan should be given.

Box I Key Messages

- Social determinants of health that are emphasised in the AAP guideline, also play a role in our milieu.
- Motivational interviewing and involving the family plays a major role in the management.
- Involving schools in educating children and adolescents, along with psychological counselling for triggers of overeating can have a better impact on health and nutrition
- Establishing adolescent health care centres in each district enables timely detection of overweight and co-morbidities, and ultimately reducing disease burden.

IMPLICATIONS FOR PRACTICE

Parents/caregivers play a major role in the management of childhood obesity through various strategies including regular weight monitoring, screen time limit setting, minimizing barriers, strengthening family relations, and maintain positive home environment [17]. Regular screening of child and adolescent with the use of body mass index (BMI) percentile charts in office practice along with proper history of the patient's nutrition, lifestyle, sleep detail, physical activity and mental health helps in early detection of obesity in children.

For children, parents are their role models and they tend to emulate their behavior. Hence, it is important to spread awareness amongst parents to adopt healthy lifestyle. Early modifications in lifestyle have great impact in prevention of chronic diseases of adulthood.

Emphasis on nutrition education in the school should be initiated to promote awareness among the children. Schools should also organize various competitions (poster, essay, etc.) and debates on importance of healthy and balanced diet and adverse effects of the junk foods to spread awareness.

Frequent monitoring of adolescents for overweight and those with BMI >85 percentile for potential comorbidities should be done in adolescent clinic [4]. Psychiatry or behavioral history should be always asked: detail dietic history history of junk food ,history of screen time, any stressor , boredom – these are causative factor for binge eating, enables early detection and intervention [6].

The key messages are listed in **Box I**. We do not have any guidelines that include the changes in lifestyle brought about by increasing use of smartphones resulting in increase in sedentary behaviour amongst children and adolescents. The psychological impact of social media also needs to be addressed. Also, updates regarding bariatric surgery should be made available for practitioners. With the rise in obesity seen in many regions of the country, it is high time that the Indian Academy of Pediatrics also brings out comprehensive management guidelines for this hidden epidemic.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity. Pediatrics. 2023;151: e2022060640.
2. Krishnaswamy SV, Dudeja P. Obesity in school children in India. Public Health in Developing Countries - Challenges and Opportunities. Accessed Sep 9, 2020. Available from: *http://dx.doi.org/10.5772/intechopen.89602*
3. Freedman DS, Sherry B. The validity of BMI as an indicator of body fatness and risk among children. Pediatrics. 2009; 124:S23–S34
4. Javed A, Jumean M, Murad MH, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: A systematic review and meta analysis. Pediatric Obesity. 2015;10: 234-44.
5. Resnicow K, Davis R, Rollnick S. Motivational interviewing for pediatric obesity: conceptual issues and evidence review. J Amer Dietetic Association. 2006;106:2024-33.
6. Grossman DC, Bibbins-Domingo K, Curry SJ, et al. Screening for Obesity in Children and Adolescents: US Preventive Services Task Force recommendation statement. Jama. 2017; 317:2417-26.
7. Vos MB, Kaar JL, Welsh JA, et al. Added Sugars and Cardiovascular Disease risk in Children: A Scientific Statement from the American Heart Association. Circulation. 2017;135: e1017-34.
8. Committee on Nutrition and the Council on Sports Medicine and Fitness. Sports Drinks and Energy Drinks for Children and Adolescents: Are They Appropriate? Pediatrics. 2011; 127:1182-89.
9. Heyman MB, Abrams SA; Section on Gastroenterology, Hepatology, and Nutrition; Committee on Nutrition. Fruit Juice in Infants, Children, and Adolescents: Current Recommendations. Pediatrics. 2017;139:e20170967
10. Gupta P, Shah D, Kumar P, et al. Indian Academy of Pediatrics Guidelines on the Fast and Junk Foods, Sugar Sweetened Beverages, Fruit Juices, and Energy Drinks. Indian pediatrics. 2019;56:849-63.
11. Council on Communications and Media. Media and Young Minds. Pediatrics. 2016;138:e20162591
12. Lobelo F, Muth ND, Hanson S, et al. Physical activity assessment and counseling in pediatric clinical settings. Pediatrics. 2020;145;e201933992.
13. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans from the US Department of Health and Human Services: Cardiovascular Benefits and Recommendations. Circulation: Cardiovascular Quality and Outcomes. 2018;11: e005263.
14. USDA. *choosemyplate.gov*
15. Ghoul I. Training Manual for Food Safety Regulators. Food Safety and Standards Authority of India, 2013.
16. WHO releases guidelines to address overweight and obesity in children Guideline: assessing and managing children at primary health-care facilities to prevent overweight and obesity in the context of the double burden of malnutrition. Updates for the Integrated Management of Childhood Illness (IMCI) Accessed July 28, 2023. Available from: *https://www.who.int/news/item/04-10-2017-*
17. Rosenkranz RR, Bauer A, Dzewaltowski DA. Mother-daughter resemblance in BMI and obesity-related behaviors. International J Adolesc Med Health. 2010;22:477-90.

Short-Course Therapy for Pediatric Urinary Tract Infections

***Source Citation*:** Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children. JAMA Pediatr. 2023 Jun 26:e231979. Epub ahead of print.

SUMMARY

The SCOUT study is a multicenter, placebo-controlled, double-blind randomized controlled trial conducted to evaluate if a shorter 5-day course of antibiotics is non-inferior to a standard 10-day course of antibiotics in children with urinary tract infection (UTI) [1]. The eligible population included children aged 2 months to 10 years who were being treated for UTI with one of the five chosen antibiotics (amoxicillin-clavulanate, cefixime, cefdinir, cephalexin, or trimethoprim-sulfamethoxazole) and have become afebrile and free of symptoms of UTI after 5 days of therapy. At this time point, the eligible children were randomized to either the short-course arm, in which antibiotics were replaced by a matching placebo or the standard-course arm, in which antibiotics were continued. The study drugs (placebo or antibiotics) were continued to complete 10 days of therapy. The study's primary outcome was the recurrence of symptomatic UTI between two hospital visits - first on day 6 i.e., at the time of randomization, and second between days 11 and 14. A definition with high specificity was used to identify the primary outcome and included three criteria: symptoms, pyuria, and positive urine culture. Secondary outcomes included the individual components of the primary outcome, and UTI between days 11-14 and days 38-44. The study also reported the adverse effects of the drugs and the incidence of gastrointestinal colonization with resistant organisms. The sample size was calculated for investigating the non-inferiority of the shorter antibiotic course. The study was powered to detect a non-inferiority margin of 5%. This meant that if the baseline incidence of treatment failure with the use of a standard course of antibiotics was 5%, investigators were willing to accept a treatment failure rate of 10% in the shorter antibiotic course to consider it as a 'clinically' non-inferior therapy. The primary analysis was conducted following the intention-to-treat (ITT) principle. The primary outcome was observed in 14 (4.2%) children in the short-course group and 2 (0.6%) children in the standard-course group. The upper margin of the confidence interval of the risk difference was 5.5%. As this was more than the preset non-inferiority margin of 5%, the non-inferiority of the short-course therapy could not be proven. Children randomized to the short-course therapy were also more likely to have asymptomatic bacteriuria and a positive urine culture. The two study groups had similar rates of adverse events and antimicrobial resistance of stool flora. The authors concluded that although the non-inferiority could not be proven, given the low incidence of failure (i.e., recurrence of symptomatic UTI) with the short-course therapy, the latter can be a reasonable option in children with UTI who show improvement after 5 days of antibiotics.

CRITICAL APPRAISAL

Evidence-Based Medicine Viewpoint

This was a well-planned and conducted non-inferiority RCT. The following are some important discussion points about the critical appraisal of the study.

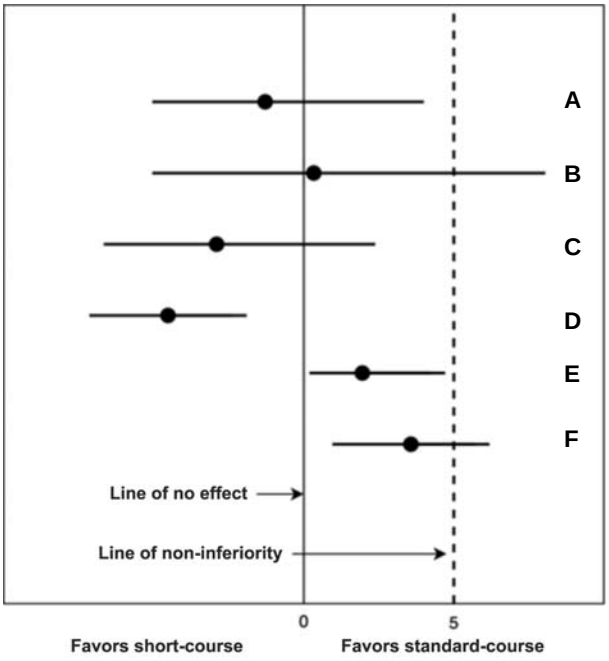
Assumptions regarding sample size and non-inferiority margin: The study observed a much lower than expected incidence of treatment failure with only 0.6% of children in the standard-course arm and 4.2% of children in the short-course arm developing symptomatic UTI. The upper margin of the confidence interval of the difference between the incidence of UTI in the two study groups was estimated to be 5.5% which is higher than the pre-specified non-inferiority margin of 5%. Therefore, the study was not able to prove the non-inferiority of the short course. However, these results raise two important issues.

First, the lower incidence of symptomatic UTI translates into a much higher relative risk difference in the two study groups. With the assumptions used during the sample size calculation - an event rate of 5% in the standard-course group and a non-inferiority margin of 5%, a 2-fold higher relative risk of UTI was acceptable as non-inferior. However, with the reported event rate of 0.6% in the standard-course arm, the preset non-inferiority margin of 5% translates into an 8.3 times higher relative risk of UTI as non-inferior. Second, if the short course is not proven to be statistically 'non-inferior,' is it also statistically inferior to the standard course? [2]. The study reports only the upper margin of the confidence interval of the difference between the incidence of UTI in the two study groups. The authors have used a 1-sided statistical test and are therefore justified in not reporting the lower margin of the CI [3]. However, we can

calculate the lower margin of the confidence interval with the given data. Such a post hoc analysis (not reported in the study) shows that the short course is also statistically inferior (**Fig.1**) to the standard course (two-sided 95% CI: 1.3% to 5.8%, *P*=0.002).

Given these two important issues - almost an eight times greater relative risk of treatment failure and inferiority of the short-course regimen, this treatment option may not be acceptable to many families and clinicians.

Per protocol analysis: In an RCT designed to test superiority, intention-to-treat (ITT) analysis is the primary statistical approach [4]. Following ITT analysis means that once a patient is randomized to a study group, (s)he will be analyzed in that group irrespective of whether the assigned intervention is adhered to completely, incompletely, not at all, or reversed (patient randomized to experimental arm has received the comparator or vice versa). This approach has two advantages. First, it maintains the balance of prognostic factors achieved by randomization. Study subjects who are not compliant or do not receive the assigned intervention may be inherently different with respect to their baseline characteristics and prognostic factors from the study subjects who are compliant and have received the full intervention. Removing the non-compliant patients from analysis breaks the balance achieved with randomization and therefore increases the risk of bias in the study results. Second, for most interventions, some degree of non-adherence or non-compliance is inevitable in the 'real world' outside the realm of a tightly managed RCT. If an intervention is truly superior to the comparator, mixing of compliant and non-compliant patients in the analysis will move the estimated effect size to null thus making the intervention appear less (or non) efficacious. If the intervention remains efficacious in the study population despite the inclusion of non-compliant subjects in the analysis, it increases the belief of researchers and clinicians in the superiority of the intervention. However, in a non-inferiority trial, the second advantage of the ITT (increased belief about superiority in the real world) interferes with the purpose of the study. If in an ITT analysis, the experimental intervention (short course of antibiotics) comes out to be non-inferior to the active control (standard course of antibiotics) - one may ask if this is true non-inferiority or just due to the inclusion of non-compliant patients in the analysis which has made the groups appear similar (e.g., UTI occurring in non-compliant patients in both the study groups would reduce the estimated risk difference). For a non-inferiority trial, the objective of finding out true non-inferiority takes precedence over the possible loss of the balance of prognostic factors achieved by randomization. Therefore, primary analysis in a non-inferiority trial is per-protocol analysis, in which only those patients who have adhered to the assigned study intervention are included. However, excluding too many patients from analysis because of non-adherence can not only make the study underpowered but also cast doubt on reasons for non-compliance (is the intervention non-acceptable?). In this study, the authors have chosen ITT as the primary analysis. Although, the authors do not provide a reason to do so, probably they gave greater weightage to the preservation of the balance of prognostic factors with ITT analysis and were not concerned about non-compliance to the intervention. A very low incidence of UTI in the standard course arm reassures that the active control worked well, rather, better than expected. Also, we would have been more concerned about the use of ITT analysis in the study if it had shown non-inferiority. Nevertheless, the authors also present per-protocol analysis as a secondary approach. However, due to the exclusion of about 10% of patients due to non-compliance, this analysis is underpowered. Interestingly, the statistical plan provided with the manuscript as a supplement targets recruiting 362 patients (not 326 as mentioned in the manuscript) in each group to account for the post-randomization exclusions from the analysis.



Interpretation
A. Short-course non-inferior
B. Non-inferiority not proven
C. Short-course non-inferior
D. Short course non-inferior and superior
E. Short course non-inferior and inferior
F. Short course inferior (non-inferiority not proven)

Fig. 1 Possible results of a non-inferiority trial. Scenario F presents the interpretation of the results of the SCOUT study.

Generalization of study results - population and setting: The authors conclude that the incidence of UTI is low even

in the short-course antibiotic group and therefore this is a reasonable alternative for children showing clinical improvement after 5 days of therapy. If some readers agree with this conclusion, before applying to their own clinic they need to consider two factors. First, the children included in the study constituted a selective population. If we exclude children with a negative urine culture from the screened cohort, 11880 children were potentially eligible for the study. Of these, a large number were excluded due to various reasons including the prescription of antimicrobials other than those used in the study, the presence of genitourinary abnormalities, recurrent UTI, and declined participation. The latter is important as probably parents were not willing to even take a 50% chance of randomization to a shorter course of antimicrobials. Second, the incidence of infections with antibiotic-resistant bacteria is much higher in India and similar settings in low- and middle-income countries [5]. Curing UTIs due to these bacteria may need a longer duration of therapy. At the same time, shorter courses of antibiotics can potentially reduce the chances of the appearance of drug-resistant colonies of bacteria and are therefore even more needed in settings with a high prevalence of antimicrobial resistance. Also, shorter courses of antibiotics save costs and are more convenient.

This well conducted study presents the results achieved with a short course of antibiotics in children with uncomplicated UTI and early response by 5 days of therapy. Before applying the results of the study, clinicians need to think of balance between a slightly higher risk of recurrence of UTI and benefits of shorter course to patient/family (more convenience and lower cost of therapy) and community (lower chances of emergence of resistant bacteria).

Funding: None; *Competing interests*; None stated.

DEEPAK CHAWLA
Department of Neonatology
Government Medical College Hospital, Chandigarh.
drdeepak@gmch.gov.in

REFERENCES

1. Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children. JAMA Pediatr. 2023 Jun 26:e231979. Epub ahead of print.
2. US Department of Health and Human Services, Administration F and D, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Non-Inferiority Clinical Trials to Establish Effectiveness - Guidance for Industry. 2016. Accessed July 23, 2023. Available from: *https://www.fda.gov/media/78504/download*
3. Kaji AH, Lewis RJ. Non-inferiority trials: is a new treatment almost as effective as another? JAMA. 2015;313:2371–2.
4. Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomization exclusions: the intention to treat principle and excluding patients from analysis. BMJ. 2002;325:652.
5. Sugianli AK, Ginting F, Parwati I, Jong MD de, Leth F van, Schultsz C. Antimicrobial resistance among uropathogens in the Asia-Pacific region: a systematic review. JAC-Antimicrob Resist. 2021;3:dlab003.

Pediatric Nephrologist's Viewpoint

Urinary tract infection (UTI) is one of the most common bacterial infections encountered in children, with an overall prevalence of 7% among infants presenting with fever [1]. About 3-7% of children experience at least one episode of UTI before their sixth birthday [2]. Recurrent UTI is associated with scarring, hypertension and chronic kidney disease; with reflux nephropathy accounting for 8-21% of all end stage kidney diseases in children [3].

Given the increased morbidity with UTI, it is important to identify and treat it promptly. In this randomized, placebo-controlled, double-blinded, multicentre non-inferiority clinical trial [4], the authors evaluated the efficacy and safety of short-course (5 days antibiotic followed by 5 days placebo) against standard-course (10 days antibiotic) antimicrobial therapy in 664 children [4].

This meticulously done trial with strict criteria did not show any meaningful benefit in prolonging the duration of antibiotics in simple uncomplicated UTI. The number needed to treat was 67 to prevent one febrile UTI, and 469 to prevent one child from developing kidney scarring. This suggests that five additional days of antibiotics in uncomplicated UTI in children who are recovering after 5 days of oral antibiotics may not make much difference in routine office practice. This is in line with recent data suggesting a lower risk of kidney scars (2.8%) in children following an episode of febrile UTI [5]. Although, the National Institute for Health and Clinical Excellence (NICE) guidelines [6] suggest a shorter 3-day course for cystitis in children older than three months, the Swiss [7], the American [8] and the Canadian [9] guidelines recommend 7-14 days therapy for febrile UTI. The findings from the SCOUT RCT may be an eye-opener demonstrating lack of benefit in longer antibiotic courses, and over time, may help modify these guidelines. Further randomized trials on this topic are currently underway [10,11], and may shed more light into this hitherto unresolved issue.

Funding: None; *Competing interests*: None stated.

SUDARSAN KRISHNASAMY
Department of Paediatrics,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006.
sudarsanjipmer@gmail.com

REFERENCES

1. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008;27:302-8.
2. Becknell B, Schober M, Korbel L, Spencer JD. The diagnosis, evaluation and treatment of acute and recurrent pediatric

urinary tract infections. Expert Rev Anti-Infect Ther. 2015;13: 81-90.
3. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol 2012; 27:363-73.
4. Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children: the SCOUT randomized clinical trial. JAMA Pediatr. 2023 Jun 26:e231979 [epub ahead of print].
5. Shaikh N, Haralam MA, Kurs-Lasky M, Hoberman A. Association of renal scarring with number of febrile urinary tract infections in children. JAMA Pediatr. 2019;173:949–52.
6. National Institute for Health and Care Excellence. Urinary tract infection in under 16s: diagnosis and management (NICE guideline 224). 2022. Accessed 20 July, 2023. Available from: *https://www.nice.org. uk/guidance/ng224/resources/urinary-tract-infection-in-under-16s-diagnosis-and-management-pdf-66143835667141*
7. Buettcher M, Trueck J, Niederer-Loher A, et al. Swiss Consensus Recommendations on Urinary Tract Infections in Children. Eur J Pediatr. 2021;180:663-74.
8. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management; Roberts KB. Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months. Pediatrics. 2011;128:595-610.
9. Robinson JL, Finlay JC, Lang ME, Bortolussi R; Canadian Paediatric Society, Infectious Diseases and Immunization Committee, Community Paediatrics Committee. Urinary Tract Infections in Infants and Children: Diagnosis and Management. Paediatr Child Health. 2014;19:315-25.
10. Daniel M, Szajewska H, Pańczyk-Tomaszewska M. 7-day compared with 10-day antibiotic treatment for febrile urinary tract infections in children: protocol of a randomised controlled trial. BMJ Open. 2018;8:e019479.
11. Sethi N, Carlsen ELM, Schmidt IM, Cortes D, Nygaard U, Sehested LT. Individualised versus standard duration of antibiotic therapy in children with acute uncomplicated febrile urinary tract infection: a study protocol and statistical analysis plan for a multicentre randomised clinical trial. BMJ Open. 2023;13:e070888.

Pediatrician's Viewpoint

The optimal duration of antimicrobial therapy for pediatric UTIs has been a subject of debate, with the aim of balancing effective treatment against antibiotic overuse resulting in antibiotic resistance, side effects, and costs. The current treatment guidelines endorse a longer duration of antibiotic use i.e., 7 to 14 days for the treatment of UTI [1-6]. However, several studies have explored short courses of antibiotic treatment (3-7 days) and found contradictory evidence [7-10]. Given these varied findings and recommendations, there's a pressing need for more pediatric-specific comparative data to guide therapy duration recommendations for UTIs in children.

The SCOUT clinical trial is a recently conducted randomized clinical non inferiority trial which compared short-course (5 days) to standard-course (10 days) antibiotic therapy for UTIs in children aged 2 months to 10 years, who were diagnosed with symptomatic UTI [11]. Notably, while the short-course therapy had a statistically significant higher failure rate, the absolute numbers were still reasonably low. There was a higher rate of asymptomatic bacteriuria and positive urine culture at the day 11 to 14 in the short course therapy; however, the rates of UTI after day 11 to 14 visit were similar in the two groups. These findings highlight the need to weigh the benefits of reduced antibiotic exposure against the risk of treatment failure. The absence of a difference in adverse events or gastrointestinal colonization with resistant organisms between the two groups is reassuring.

The possibility of using a shorter course of treatment for UTIs in children could have significant implications by reducing the financial burden on the families and the healthcare system at large. Additionally, the aim of the study aligns with the global antibiotic stewardship efforts to combat the emergence of antibiotic-resistant strains by reducing the antibiotic overuse.While the study suggests potential benefits of shorter treatment, the impact of local epidemiology, prevalent uropathogens, resistance patterns, individual factors such as the age of the child, type of UTI, and the presence of underlying comorbidities like vesico-uretric reflux and bladder and bowel dysfunction, on determining the antibiotic duration needs to be explored. There is thus a need for additional research to validate these findings and ensure their applicability across diverse patient populations.

Funding: None; *Competing interests*: None stated.

SWARNIM RANJAN
Department of Pediatrics,
AIIMS, Patna, Bihar.
itsswarnim@gmail.com

REFERENCES

1. Yang SS, Tsai J-D, Kanematsu A, Han C-H. Asian Guidelines for Urinary Tract Infection in Children. J Infect Chemother. 2021;27:1543-54.
2. 't Hoen LA, Bogaert G, Radmayr C, et al. Update of the EAU/ESPU Guidelines on Urinary Tract Infections in Children. J Pediatr Urol. 2021;17:200-7.
3. Buettcher M, Trueck J, Niederer-Loher A, et al. Swiss Consensus Recommendations on Urinary Tract Infections in Children. Eur J Pediatr. 2021;180:663-74.
4. Moustafa BH, Rabie MM, El Hakim IZ, et al. Egyptian Pediatric Clinical Practice Guidelines for Urinary Tract Infections in Infants and Children (Evidence Based). Egyptian Pediatric Association Gazette. 2021;69:43.
5. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management; Roberts KB. Urinary tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months. Pediatrics. 2011;128:595-610.

6. Bagga A, Babu K, Kanitkar M, Srivastava R, Pediatrics IPNGIAo. Consensus Statement on Management of Urinary Tract Infections. Indian Pediatr. 2001;38:1106-15.
7. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomised controlled trials. Arch Dis Child. 2002;87:118-23.
8. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. Cochrane Database of Systematic Reviews. 2012;8:CD006857.
9. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative effectiveness of antibiotic treatment duration in children with pyelonephritis. JAMA Network Open. 2020;3:e203951.
10. Desai S, Aronson PL, Shabanova V, et al. Parenteral antibiotic therapy duration in young infants with bacteremic urinary tract infections. Pediatrics. 2019;144:e20183844.
11. Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children: the SCOUT randomized clinical trial. JAMA Pediatr. 2023;177:782-9.

Maternal Nutrition Supplementation and Neonatal Birth Weight: A Basic, Yet Indispensable Intervention

SWETA KUMARI, PIYUSH GUPTA

Department of Pediatrics, University College of Medical Sciences and GTB Hospital, Delhi.
Correspondence to: Dr Piyush Gupta, Professor of Pediatrics, University College of Medical Sciences, Delhi 110095.
prof.piyush.gupta@gmail.com

The September issue of *Indian Pediatrics*, in 1973, featured original research articles from heterogenous topics, but predominantly pertaining to maternal-neonatal health issues including perinatal mortality, maternal nutrition, gestational age estimation score, and necrotizing enterocolitis. We selected a paper regarding the effect of maternal nutrition supplementation on the birth weight of the newborn. The objective was to revisit the importance of a basic and cost-effective intervention with potential of huge public health impact.

THE PAST

The Study

The research paper by Qureshi, et al.[1] was a quasi-experimental interventional study of dietary supplementation in pregnant women of low socioeconomic status on their newborn's birth weight. This prospective study assigned the intervention in the form of nutrition supplements to 76 pregnant mothers in addition to their home diet from 20 weeks till term: Group I received iron (60 mg/day) and folic acid (0.5 mg/day) supplementation daily; Group II received a standardized nutrition supplement powder carrying 500 calories and 20 g protein per day along with similar iron-folic acid dosage. The study outcomes included neonatal birth weight and gain in maternal weight. Both groups were also compared to a control group who did not receive any antenatal care or dietary supplement (this would have been unethical in the current era!). Mean (SD) birthweight of babies born to Group I, Group II, and controls was 2.78 (0.27), 3.32 (0.47) and 2.51 (0.25) kg, respectively. Birth weight was statistically higher in Group II as compared to Group I; and higher in both Group I and II as compared to controls. Although maternal weight gain was also higher in Group II with standardized supplement, the serum albumin was comparable in both Group I and Group II, which was possibly due to utilization of extra supplemented protein for fetal growth. Authors concluded that better antenatal care and nutrition supplements to the pregnant mothers will improve pregnancy outcome and neonatal health.

The Background

Awareness regarding the influence of maternal nutrition for healthy pregnancy can be traced back to the medical literatures of ancient civilizations like Indus valley civilization (*Sushruta* and *Charaka Samhita*), Greeks (*Corpus Hippocraticum*), Romans (*Natural History*) and in subsequent medieval European civilizations [2]. In the early nineteenth century, it was common perception that large size of babies was a result of over-nutrition; this also led to practice of restriction in maternal food intake. Average gestational weight gain was approximately 9.1 kg in published studies till 1940s. Davis, in 1921, advocated the use of maternal weight gain as an indicator of maternal nutrition, which in turn influences the fetal weight gain. Increase in average birth weight (from 3100 g to 3600 g) was observed with increasing gestational weight gain (from 7 kg to 13.6 kg) [3]. During 1970-80s, different nutritional committees from Food and Nutrition Board (FNB), American College of Obstetricians and Gynaecologists (ACOG), and American Dietetic Association (ADA) emphasized on linear weight gain in addition to total weight gain. Over the span of 50 years between 1930s to 1980s, the recommended gestational weight gain has almost doubled from 6.8 kg to 15.9 kg, which reflects the standard practice change from restricting to encouraging weight gain during pregnancy. Data from Western countries show an increase in average weight gain of 3.6 to 4.5 kg in 1980s as compared to 1940s [4]. Food supplementation programs for underprivileged groups were initiated in the

1970s in USA, and in India from the year 1975 onwards, under different schemes like Integrated Child Development Services Scheme (ICDS), and Special Nutrition Programs (SNP). Iron and folic acid supplementation for pregnant mothers was incorporated as a routine policy practice following the launch of National Nutritional Anemia Control Program in India in the year 1970.

THE PRESENT

Nutritional interventions during pregnancy have been studied in detail for their impact on infant health in the last 50 years. Maternal undernutrition along with micronutrient deficiency (e.g., anemia) have been linked with poor outcomes like low birth weight, preterm birth, and increased maternal and childhood mortality. Balanced protein and energy, Iron-folic acid (IFA) and multi-micronutrient (MMN) supplementation are hypothesized to decrease the risk of being born as low birthweight (LBW) [5]. A systematic review of trials from low- and middle-income countries showed that balanced energy protein supplement can contribute to a 61% reduction in stillbirth [RR (95% CI), 0.39 (0.19-0.80)], 40% reduction in LBW [RR (95% CI) 0.60 (0.41-0.6)], 29% reduction in small for gestational age (SGA) [RR (95% CI) 0.71 (0.54–0.94)] and increased birth weight by 107.28 g [MD (95% CI) 107.28 g (68.51-146.04)] [6]. In addition to balanced protein and calorie supplementation, importance of multi-micronutrient supplementation has been stressed upon in the last two decades, as pregnant women are deficient in micronutrients and macronutrients alike. Multi-micronutrient supplement comprises of multiple elements including antioxidants, minerals, and vitamins, besides IFA. United Nations Inter-national multiple micronutrient preparation is one of such standardized preparation containing 15 different micronutrients at their RDA level [7]. These nutrients have the potential to improve fetal outcome through modulation of placental inflammation, oxidative stress, and multiple enzymatic pathways. Significant negative impact of their deficiency on fetus, which extends to their adulthood, has led researchers to focus on the role of multi-micronutrient supplementation in pregnancy. Gupta, et al. [8] observed a 70% decrease in low birthweight and 58% decrease in risk of early neonatal morbidity with MMN supplement in undernourished pregnant mothers, which highlights its relevance in resource constrained countries like India. A meta-analysis of similar studies from multiple low-income countries showed that decrease in multiple micronutrient deficiency led to an increase in mean birthweight [MD (95% CI) 22.4 g (8.3-36.4)], a decrease in proportion of low birth weight [OR (95% CI) 0.89 (0.81-0.97] and SGA birth [OR (95% CI) 0.90 (0.82-0.99)] as compared to routine IFA supplementation. This positive effect was not seen in mothers with low body mass index, which indicates that micronutrients are not optimally utilized in the presence of a negative energy balance [9,10]. This observation may suggest for recommending the replacement or augmentation of routine IFA supplementation with MMN supplementation.

A recent two-stage meta-analysis by Smith, et al. [11] tried to address this issue. They included data from 17 randomized controlled trials conducted in 14 low-income and middle-income countries, comparing MMN supplements containing IFA and IFA alone in 1,12,953 pregnant women. The results indicated that antenatal MMN supplements improved survival for female neonates, and resulted in greater reductions in low birthweight, small for gestational-age births, and 6-month mortality in infants born to anemic mothers. The benefit was maximum if the supplementation is started early (before 20 weeks gestation) and high compliance (≥95%) can be ensured.

CONCLUSION

Infant health is directly and indirectly related to pre pregnant, pregnant, and lactating mother nutrition. Although, burden of malnutrition and underweight infants has improved over the last four decades, around one-fifth women of reproductive age group, and neonates are still undernourished. Further community-based research on protein, calorie and MMN supplement in combination, and calcium, zinc, and fortification of staple food with micronutrients, is needed to improve maternal-child health. Research on MMN supplementation needs to focus on infant health, considering the maternal nutritional status.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Qureshi S, Rao NP, Madhavi V, et al. Effect of maternal nutrition supplementation on the birth weight of the newborn. Indian Pediatr. 1973;10:541-4.
2. Weiss-Amer M. Medieval women's guides to food during pregnancy: Origins, texts, and traditions. Canadian Bulletin of Medical History. 1993;10:5-23.
3. Davis CH. Weight in pregnancy; its value as a routine test. Am J Obstet Gynecol. 1923;6:575-81.
4. Institute of Medicine (US) Committee on Nutritional Status During Pregnancy and Lactation. Nutrition During Pregnancy: Part I Weight Gain: Part II Nutrient Supplements. National Academies Press (US); 1990.
5. Ramakrishnan U, Imhoff-Kunsch B, Martorell R. Maternal nutrition interventions to improve maternal, newborn, and child health outcomes. Nestle Nutr Inst Workshop Ser. 2014;78:71-80.
6. Lassi ZS, Padhani ZA, Rabbani A, et al. Effects of nutritional interventions during pregnancy on birth, child health and development outcomes: A systematic review of evidence from low- and middle-income countries. Campbell Syst Rev. 2021;17: e1150.
7. World Health Organization, United Nations University and United Nations Children's Fund (UNICEF). Composition of a

multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: Report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO) and United Nations university workshop. UNICEF, 1999. Accessed on June 17, 2023. Available from: *https://apps.who.int/iris/handle/10665/75358*
8. Gupta P, Ray M, Dua T, et al. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: A double-blind, randomized, placebo-controlled trial. Arch Pediatr Adolesc Med. 2007;161:58-64.
9. Christian P, Tielsch JM. Evidence for multiple micronutrient effects based on randomized controlled trials and meta-analyses in developing countries. J Nutr. 2012;142:173S-7S.
10. Fall CH, Fisher DJ, Osmond C, Margetts BM. Multiple micronutrient supplementation during pregnancy in low-income countries: A meta-analysis of effects on birth size and length of gestation. Food Nutr Bull. 2009;30:S533-46.
11. Smith ER, Shankar AH, Wu LS, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: A meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. Lancet Glob Health. 2017;5:e1090-e1100.

Reversible Basal Ganglia Changes in a Child With Infantile Tremor Syndrome

Cobalamine or vitamin B12 plays an important role across various metabolic pathways mainly as co-factors viz., methylcobalamin and adenosyl cobalamine, required for enzymes methionine synthase, and methyl malonyl coenzyme A mutase, respectively [1]. In its deficiency, these pathways are blocked, resulting in homocysteine and methylmalonic acid accumulation which causes neurological manifestations. Infantile tremor syndrome (ITS), classified as a neuro-cutaneous disorder under the defi-ciency of vitamin B12 is characterized by a constellation of developmental disorders, pallor, and pigmentation defects of hair and skin [2]. Herein, we present a case of ITS with reversible basal ganglia lesions.

A 9-month-old girl, born to non-consanguineous parents, presented with delayed development with gradual loss of milestones noticed from 7 months of age. At the age of 6 months, she was able to roll over, had attained bi-dextrous reach, and could recognize her parents. On initiating complementary feeds, she would spit out or vomit, and therefore was continued on exclusive breast feeds. Mother was on dietary restrictions during pregnancy and lactation – would consume only a vegetarian diet with restrictions on dairy products. Over the next 2 months, she developed hyperpigmentation of knuckles and sparse and hypopigmented hair. By the ninth month, she lost pre-viously attained milestones—was unable to roll over, had lost head control, would not recognize parents with reduced playfulness, and was persistently irritable. On examination, weight for age was 6.5 kg (<-3*z* score), head circumference 41cm (-2 to -3*z* score), had glossitis, sparse hypopigmented lustreless hair, pallor, and hyperpigmentation of knuckle (**Fig. 1 A-C**). She was listless and irritable, both hypotonia and dystonia were noted with decreased reflexes.

Investigations revealed megaloblastic anemia (haemoglobin -10. 3 g/dL and MCV 102.1 fL) with hyper segmented neutrophils, low vitamin B12 (79 pg/mL), and elevated serum homocysteine levels (161 µmol/L) with normal folate levels. Blood gas, ammonia (<10 µmol/L), lactate (17.5 mg/dL), and tandem mass spectrometry (TMS) were normal. MRI of the brain showed diffuse cortical atrophy with heterogenous signal changes in bilateral basal ganglia (**Fig 1 E, F**).

The mother's investigations showed dimorphic anemia (haemoglobin -9 g/dL and MCV 73.8 fL), low vitamin B12 (176.4 pg/mL), and elevated serum homocysteine (35.57 µmol/L). The child was started on intravenous vitamin B12 (methylcobalamin) 1000 mcg once daily. After 3 days of intravenous vitamin B12, she developed tremors and showed improvement in general well-being. By the end of the second week of vitamin B12 therapy, the child regained head control and partial rollover, was able to reach for objects again, started to recognize her mother, and deve-loped stranger anxiety. The child was also started on nutritional rehabilitation and oral vitamin B12 supplements of 1000 mcg per day. Oral vitamin B12 supplements were also given to the mother. Her hair and skin changes had normalized during the three months of follow-up. She had learned to sit without support, was able to creep, spoke one word with meaning, and waved bye (**Fig. 1D**) Repeat MRI of the brain on follow-up showed cortical atrophy; although, signal changes in basal ganglia had reversed (**Fig 1G, H**). The whole exome sequencing and mitochondrial exome did not reveal any pathogenic variants.

The differential diagnosis considered with symmetric basal ganglia disease with regression includes inborn errors of metabolism involving organic acids, aminoacidopathies, defects of cobalamine synthesis, and Leigh-like disease due to mitochondrial disorder.

A previous case series reported the involvement of globus pallidus, substantia nigra, and caudate nucleus [4]. Kesavan, et al. [5] reported a case of basal ganglia lesions noted due to severe vitamin B12 deficiency which was completely reversed as seen in the current case. However, our case has bilateral putamen findings in the MRI of the brain, with no variants detected in the whole exome and mitochondrial exome sequencing [5].

We propose that basal ganglia lesions may be due to the accumulation of methylmalonic acid both intra and extracellular, which affects the succinate-dependent mitochondrial oxygen utilization [6]. The basal ganglia lesions had complete reversal upon cobalamine supplementation. Thus, we herein document that Vitamin B12 deficiency can have reversible basal ganglia lesions in the MRI of the brain and this treatable cause should be suspected if clinical features are suggestive of vitamin B12 deficiency.

VYKUNTARAJU K GOWDA,[1] ARUN Y BYLAPPA,[2] UDDHAV KINHAL,[2] VARUNVENKAT M SRINIVASAN[1]
[1]Department of Pediatric Neurology, Indira Gandhi Institute of Child Health,

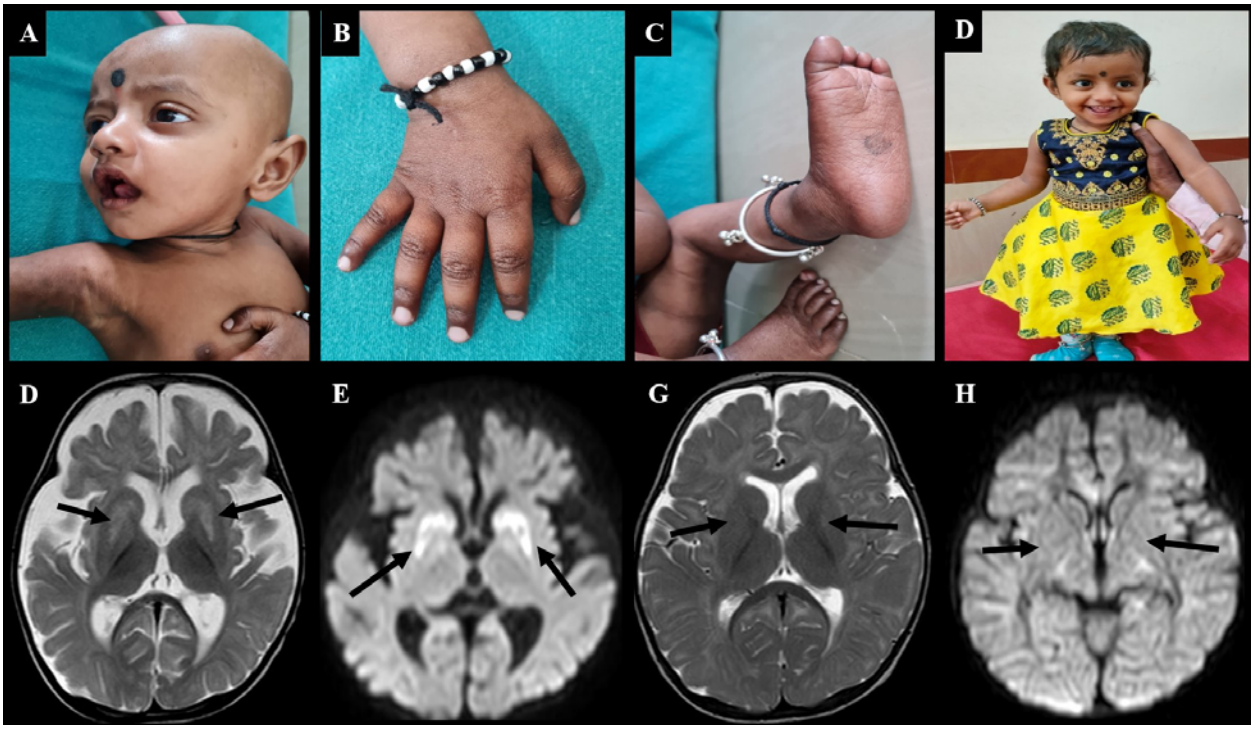


Fig. 1 Upper panel before treatment (**A-C**). At 9 months of age, looks lethargic, has alopecia with hyperpigmented skin changes, and knuckle hyperpigmentation with chalky white nails. **1D** During follow-up, a playful child with normalization of skin and hair changes (at 16 months). Magnetic resonance image of brain axial T2WI (**1E**) shows bilateral heterogenous hyperintense signal changes (arrows) in the putamen and caudate nucleus with dilated extra-axial spaces with deepened sulci suggestive of cortical atrophy. DWI image (**1F**) showing diffusion restriction (arrows) in the putamen and globus pallidus. Three months after treatment: Axial T2WI (**1G**) showing reversal of hyperintense signal changes in bilateral putamen and caudate nucleus (arrows) with reversal of cortical atrophy. DWI (**1H**) showing no evidence of diffusion restriction.

Bangalore, Karnataka.
[2]Department of Pediatrics, Indira Gandhi Institute of Child Health, Bangalore, Karnataka.
**drknvraju08@gmail.com*

REFERENCES

1. Stabler SP. Megaloblastic anemias: pernicious anemia and folate deficiency. In: Young NS, Gerson SL, High KA, editors. Clinical Hematology. Mosby; 2006. p. 242-51
2. Goraya JS, Kaur S. Infantile tremor syndrome: A review and critical appraisal of its etiology. J Pediatr Neurosci. 2016;11: 298-304.
3. Kumar P, Nagarajan B, Vyas S, et al. Nutritional recovery batwing dystonia in infantile vitamin B12 deficiency. Mov Disord. 2022;37:2308-310.
4. Kesavan S, Dhawan S, Saini L, et al. Reversible basal ganglia changes and metabolic crisis in infantile tremor syndrome. Indian J Pediatr. 2020;87:464-65.
5. Wajner M, Coelho JC. Neurological dysfunction in methylmalonic acidaemia is probably related to the inhibitory effect of methylmalonate on brain energy production. J Inherit Metab Dis. 1997;20:761-8.

Expectant Management in the BeNeDuctusTrial

We would like to thank the editors for discussing our recently published results of the BeNeDuctus trial in the journal [1,2]. We would like to comment on some concerns about open label treatment, paracetamol exposure and daily fluid intake, which were raised in the neonatologist's viewpoint [1].

Regarding the open label treatment, the data is actually presented in the article [2]. Only one patient (0.7%) in the expectant management group received open label ibuprofen for three courses in total [2]. Additionally, no patient in the expectant management group underwent surgical or endovascular patent ductus arteriosus (PDA) closure prior to discharge home. As stated, we deliberately did not design a placebo-controlled trial. In fact, we randomized treatment intention, which might have contributed to this low open label treatment percentage.

As per study protocol, no co-interventions were allowed with the intention to close the PDA. If paracetamol was given, it was given in an analgesic dosage (20 to 40 mg/kg/day), rather than the advised higher dose of 60 mg/kg/day generally used to induce PDA closure [3]. In fact, we think that the absolute risk difference of -13.0% (95% CI -23.9 to -2.0) in paracetamol exposure might be driven by our treatment intention randomization strategy and our endeavor to refrain from (co-)interventions in the expectant management group. This might have led to a higher threshold to start paracetamol in these patients, even in the analgesic dosage. Apart from the early ibuprofen treatment, the higher (co-) administration of paracetamol in the early pharmacological treatment group might have additional injurious effects on the developing lung, as has been suggested recently [4].

Regarding the daily fluid intake, we presented the intake on postnatal day 7 in the supplementary material. This did not differ significantly i.e., 162 (IQR 157-181) mL/kg/24 hour in the expectant management group vs 160 [IQR 150-184] mL/kg/24 hour in the early pharmacological treatment group [2]. Fluid restriction; although, commonly used as supportive care in infants with PDA, should, in our opinion, be avoided, since it has been association with reduced growth and probably worsened systemic hypoperfusion [5].

We are currently collecting neurodevelopmental outcome data assessed at two years corrected age. Furthermore, we are reassessing echocardiograms to further stratify those patients with a high transductal shunt volume at enrollment and analyze whether our primary hypothesis of non-inferiority holds within this group. Although, many neonatologists, including ourselves, feel there might be a subgroup that would benefit from early pharmacological treatment, to date this has not been proven.

TIM HUNDSCHEID,* WILLEM P DE BOODE
Department of Pediatrics, Division of Neonatology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands.
**tim.hundscheid@radboudumc.nl*

REFERENCES

1. Gupta N. Is expectant management noninferior to early ibuprofen for patent ductus arteriosus?: neonatologist's view-point. Indian Pediatr.2023;60:489-90.
2. Hundscheid T, Onland W, Kooi EMW, et al. Expectant management or early ibuprofen for patent ductus arteriosus. N Engl J Med.2023;388:980-90.
3. Jasani B, Mitra S, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev.2022; 12:CD010061.
4. Wright CJ. Acetaminophen and the developing lung: could there be lifelong consequences? J Pediatr.2021;235:264-76.
5. De Buyst J, Rakza T, Pennaforte T, Johansson AB, Storme L. Hemodynamic effects of fluid restriction in preterm infants with significant patent ductus arteriosus. J Pediatr.2012; 161:404-8.

Isolated Decreased Platelets in a Child: Thinking Beyond Immune Thrombocytopenia

Immune thrombocytopenia is the commonest diagnosis in a previously healthy child with sudden onset muco-cutaneous bleeding and presence of isolated thrombocytopenia. However, subtle clues in history, examination and laboratory findings may help clinch an alternate diagnosis and hence a different treatment approach. We present the case of an 8-year-old girl, first born of a non-consanguineous couple; who was brought with complaints of four episodes of spontaneous profuse bilateral epistaxis since past 20 days. There was no history of preceding trauma, nose picking, nasal blockade, foreign body insertion, upper respiratory tract infection, sinusitis, allergy or fever. There was no bleeding from any other site. Child had no history of hypertension, chronic disease or chronic drug intake. Family history was unremarkable for any bleeding disorders. Antenatal and birth history were uneventful with no abnormal umbilical stump bleed. Child had mild pallor, bilateral nasal clots but no petechiae, bruises, rashes, lymphadenopathy, hepato-splenomegaly, joint swellings or dysmorphism. Anthropometry was age-appropriate. Hemogram with peripheral smear showed hemoglobin of 8.6 g/dL, total leucocyte count of 7.6 $\times 10^9$/L and platelets of 71×10^9/L, normocytic normochromic anemia, normal granulocytes and large platelet forms with normal platelet granularity. Mean platelet volume was 11.5 fL and platelet distribution width was 17.6 fL. Coagulation profile, and liver and kidney function tests were normal. Bone marrow aspirate revealed increased megakaryopoesis. Human immunodeficiency virus serology, Hepatitis B surface antigen, Anti-Hepatitis C antibody, anti-nuclear antibody, direct Coomb test were negative.

Child required bilateral anterior nasal packing at admission. Continuing epistaxis after nasal pack removal warranted bilateral nasal endoscopy with cauterization. Supportive treatment with oral tranexamic acid and intranasal xylometazoline and hemocoagulase was given. Review of treatment in the previous two weeks showed that child had thrombocytopenia (50×10^9/L to 110×10^9/L), disproportionate to degree of bleed, with unusually large platelet forms on peripheral smear. Child was treated with platelet transfusions. No intravenous immunoglobulin or steroid was given. Differentials included immune thrombocytopenia (ITP), inherited thrombocytopathies with macrothrombocytopenia, and Von Willebrand disease (VWD). VWD assay was normal. Platelet aggregation study showed absent response to ristocetin and low expression of platelet surface GP1b/IX was seen on flow cytometry confirming Bernard-Soulier syndrome (BSS). Family screening of the parents for BSS was normal.

Inherited thrombocytopathies with macrothrombocytopenia are important differentials of ITP. These include BSS and Myosin Heavy Chain-9 (MYH9) anomalies [1]. Bleeding disproportionate to degree of thrombocytopenia, unusually large platelets on peripheral smear, sustained rise of platelet count after platelet transfusion in absence of ITP therapy, stoppage of bleeding after platelet transfusion, ITP refractory to standard treatment, family history of bleeding diathesis, consanguinity, and dysmorphic features should raise suspicion of an underlying inherited thrombocytopathy in a child suspected of ITP [2]. BSS is a rare inherited thrombocytopathy characterized by quantitative or qualitative defects of the platelet membrane glycoprotein (GP) Ib/IX/V complex [3]. Presentation as muco-cutaneous bleeding with variably associated thrombocytopenia and large platelets often leads to a misdiagnosis of ITP. Treatment of BSS includes antifibrinolytic agents, desmopressin, high-threshold platelet transfusion, recombinant factor VIIa and counselling.

Acknowledgements: Dr Prerna Arora, Professor, Department of Pathology, and Dr Ravi Meher, Professor of ENT, Maulana Azad Medical College, New Delhi, helped in the diagnosis and management of the patient.

SHELLY MITTAL, PUNEET KAUR SAHI*
Department of Pediatrics,
Maulana Azad Medical College and associated
Lok Nayak Hospital, New Delhi.
**puneetksahi@gmail.com*

REFERENCES

1. Holyome A, Cooper N, Qureshi A, Bain BJ. "ITP" is not always immune thrombocytopenia. Am J Hematol. 2020;95: 1614-5.
2. Kottayam R, Rozenberg G, Brighton T, Cohn RJ. Isolated thrombocytopenia in children: thinking beyond idiopathic thrombocytopenic purpura and leukaemia. J Paediatr Child Health. 2007;43:848-50.
3. Reisi N. Bernard-Soulier syndrome or idiopathic thrombocytopenic purpura: A case series. Caspian Journal of Internal Medicine. 2020;11:105-9.

Dabbling With Night Time Dribbling: Management of Nocturnal Enuresis

We congratulate the authors of the randomized controled trial on use of desmopressin plus tolterodine or desmopressin plus indomethacin in children with monosymptomatic nocturnal enuresis (MNE) or non-monosymptomatic nocturnal enuresis (NMNE) [1]. However, we would like to draw attention to following and seek issue relatd to the paper [1].

i) The authors have quoted the International Children's Continence Society (ICCS) recommendations for management, but the ICCS guidelines [2,3] have clearly stated that the first line therapy should be either alarm therapy or desmopressin, based on presence of nocturnal polyuria and maximum voided volumes (MVV). In children resistant to these therapies, a combination of both should be tried [2,3]. It is not clear from the study [1] whether combination of alarm therapy and desmopressin was tried before the use of the study drugs.

ii) Also the investigators have enrolled children with both NMNE and MNE in their study, with children with NMNE contributing significant proportion to both the groups. It may not be entirely justified to expose children with MNE to additional medications and their adverse effects as they are expected to have a more benign course and greater chance of resolution [4]. Previous studies have also demonstrated benefit of anticholinergics primarily in NMNE [5].

iii) Lastly, the goal of nocturnal enuresis management is not as so much about achieving dry nights as it is keeping the child dry at night, once the medications are off. Previous studies have reported high relapse rates when desmopressin or combination therapy of desmopressin with anticholinergics is stopped. Therefore, it would be prudent to comment on the efficacy of any drug combinations in nocturnal enuresis only in totality including the outcome of ability to sustain nocturnal continence after the drugs are withdrawn.

Thus, it is probably prudent to be more parsimonious in prescribing medications including desmopressin to children with nocturnal enuresis, especially to those with MSNE. These children should undergo careful evaluation to rule out comorbidities leading to failure of alarm therapy and/or desmopressin and all attempts should be made to identify subgroup of children most likely to respond to anticholinergics or other add on medications.

SUPRITA KALRA
Department of Pediatrics,
Command Hospital, New Delhi
kalrasuprita@gmail.com

REFERENCES

1. Esteghamati M, Mousavi SE, Zoghi G. Desmopressin plus tolterodine vs desmopressin plus indomethacin for refractory pediatric enuresis: An open-label randomized controlled trial. Indian Pediatr. 2023;60:447-51.
2. Franco I, von Gontard A, De Gennaro M. International Childrens's Continence Society. Evaluation and Treatment of Nonmonosymptomatic Nocturnal Enuresis: A Standardization Document from the International Children's Continence Society. J Pediatr Urol. 2013;9:234-43.
3. Nevéus T, Fonseca E, Franco I, et al. Management and Treatment of Nocturnal Enuresis-an Updated Standardization Document From the International Children's Continence Society. J Pediatr Urol. 2020;16:10-19.
4. Feehan M, McGee R, Stanton W, Silva PA. A 6-year-follow-up of childhood enuresis: prevalence in adolescence and consequences for mental health. J Pediatr Child Health. 1990; 26:75-9.
5. Song P, Huang C, Wang Y, et al. Comparison of desmopressin, alarm, desmopressin plus alarm, and desmopressin plus anticholinergic agents in the management of paediatric monosymptomatic nocturnal enuresis: a network meta-analysis. BJU Int. 2019;123:388-400.

Editor's Note: The authors of the concerned article did not respond to requests for response to the reader's comments.

Stress during Minimally Invasive Surfactant Treatment in Very Preterm Infants

We read with interest the article on minimally invasive surfactant therapy (MIST) in preterm infants [1]. We would like to highlight certain aspects of the study and seek clarifications.

Most of the published literature has used Poractant for MIST [2]. The authors in their study have used Beractant, and the volume being higher than poractant, it is likely to take more time in administration, have more chances of spillage, and more chances of bradycardia and desaturation while administration. It is logical that the amount of stress and pain for the neonate during MIST will dependon the duration of time of administration, thus poractant would actually be the surfactant of choice for MIST, volume being lesser than beractant.

Nowadays, Surfcath (Vygon) is available, which is best suited for MIST, as the device is firm enough to navigate and small caliber enough to allow spontaneously breathing in a baby. It may actually be less stressful for the baby as the useof this device is far easier than maneuvering a feeding tube. Lastly, the amount of pain during the procedure may also be expertise dependent, as the level of experience of the operator remains a critical determinant of success [3]. The operator handling of laryngoscope and the entire procedure may be different in hands of an expert and a novice. The chances of failure of MIST and need of second attempt for MIST may also be less in hands of an expert [4]. It is also worth mentioning that all babies undergoing MIST should at least receive non-pharmacological analgesia, such as swaddling, facilitated tucking, holding, or 24% sucrose analgesia, if not pharmacological analgesia and sedation.

DIVYANSHI, SUBHASH CHANDRA SHAW*
Department of Pediatrics, Army Hospital (R&R), Delhi.
**drscshaw@rediffmail.com*

REFERENCES

1. Sawant T, Manerkar S, Patra S, Kalamdani P, Kalathingal T, Mondkar J. Pain and physiological stress during minimally invasive surfactant therapy (MIST) in very preterm infants. Indian Pediatr. 2023;60:557-560.
2. Kribs A. Minimally invasive surfactant therapy and noninvasive respiratory support. ClinPerinatol. 2016;43: 755-71.
3. Foglia EE, Ades A, Sawyer T, et al; NEAR4NEOS Investigators. Neonatal intubation practice and outcomes: an international registry study. Pediatrics. 2019;143:e20180902.
4. Pichler K, Kuehne B, Dekker J, et al. Assessment of comfort during less invasive surfactant administration in very preterm infants: a multicenter study. Neonatology. 2023;120:473-81.

AUTHORS' REPLY

We are thankful to the readers for their interest in the article [1]. Our responses are detailed below.

Though several published studies have used Poractant for MIST, emerging evidence is also available to support the use of Beractant, despite its high volume, with LISA/MIST based both on short-term and long-term outcomes [2-4]. Most clinicians, especially in the public sector, do not have a choice of surfactant, and have to use the one provided by the institution [2]. Beractant is easily available and used more commonly. It is possible that high volume surfactants like beractant might cause greater stress and pain while administration, and that was exactly what we have tried to observe in this study. Though most of the pain and discomfort is attributed to laryngoscopy, more studies are required comparing the pain and discomfort between low volume and high volume surfactants used for LISA/MIST.

Surfcath (Vygon) seems to be a promising option for surfactant administration, but easy availability and cost can be limiting factors. Also, there is limited evidence comparing the safety and efficacyof flexible versus stiff catheters. Bhattacharya, et al. [5] showed that there was no difference between flexible and stiff catheters in the rate of procedural success during LISA/MIST. Though, an in vitro study comparing different catheters in a mannequin model did show that stiff catheter insertion is quicker and easier compared to flexible catheters [6]. Due to the paucity of data, we feel that there is a need to generate more evidence in this regard.

In our study, trained senior residents (post MD) administered surfactant by MIST. We provided non-pharmacologic pain relieving measures to every infant, as also mentioned in the methods section of the publication [1]; however, no premedication was provided. There are no clear answers about the best procedural analgesia for LISA/MIST, and therefore we need more studies to guide us about the best analgesia during MIST/LISA to make the procedure more comfortable for tiny preterm babies.

SWATI MANERKAR,* JAYASHREE MONDKAR
Department of Neonatology,
LokmanyaTilak Municipal Medical
College and General Hospital, Sion,
Mumbai, Maharashtra.
**drswatimanerkar@gmail.com*

REFERENCES

1. Sawant T, Manerkar S, Patra S, Kalamdani P, Kalathingal T, Mondkar J. Pain and physiological stress during minimally invasive surfactant therapy (MIST) in very preterm infants.

Indian Pediatr. 2023;60:557-60.
2. Sanchez Luna M, Unnebrink K, Martinez-Tristani M, Ramos Navarro C. Less invasive surfactant administration: a review of current evidence of clinical outcomes with beractant. Cureus. 2022;14:e30223.
3. Bhattacharya S, Read B, McGovern E, da Silva O. High-volume surfactant administration using a minimally invasive technique: Experience from a Canadian neonatal intensive care unit. Paediatr Child Health. 2019;24:313-7.
4. Ramos-Navarro C, Sánchez-Luna M, Zeballos-Sarrato S, González-Pacheco N. Three-year perinatal outcomes of less invasive beractant administration in preterm infants with respiratory distress syndrome. J Matern Fetal Neonatal Med. 2020;33:2704-10.
5. Bhattacharya S, Read B, Miller M, da Silva O. Impact of catheter choice on procedural success of minimally invasive surfactant therapy. Am J Perinatol. 2023;40:1202-7.
6. Rigo V, Debauche C, Maton P, Broux I, Van Laere D. Rigid catheters reduced duration of less invasive surfactant therapy procedures in manikins. Acta Paediatr. 2017;106:1091-6.

Transient Hypothyroidism Due to Accidental Ingestion of Povidone-Iodine Solution in a Preschooler

Povidone-iodine solutions are widely used as an antiseptic medication for treating and preventing wound infections. We herein report a child who presented with transient hypothyroidism after accidental ingestion of this solution.

A 4-year-5-month-old girl was brought with an alleged history of ingesting 5 mL of povidone-iodine solution (date of drug expiry one year prior to the incident) instead of cough syrup. She developed abdominal pain and an episode of vomiting following the ingestion, which subsided with conservative treatment. Physical examination and vital signs were normal. Starchy food with bread and medications for gastro-protection were initiated. Initial investigations showed elevated thyroid stimulating hormone (TSH) level of 10.54 µIU/mL (normal range: 0.5-6 µIU/mL), normal free T4, 1.62 ng/dL (normal range: 0.7-2.0 ng/dL), and normal free T3, 5.03 pg/mL (normal: 2.4-5.6 pg/mL). Renal function tests and serum electrolytes were normal. Iodine concentration in the urine sample was elevated (198 µg/dL) (normal <100 µg/dL). The urine output and repeat renal function tests were normal, with no evidence of acute kidney injury. She was discharged after 48 hours with health education to parents regarding child proofing at home. She was reviewed after seven days and repeat thyroid functions (TSH: 0.97 µIU/mL, free T4: 1.48 ng/dL, and free T3: 3.93 pg/mL) were within normal limits.

Iodine-based mouth gargling solutions containing povidone-iodine are in use for disinfection of the oral cavity. Despite its common use, poisoning is unusual and previously reported effects are mainly complications of topical usage during surgical procedures [1]. Iodine is an essential element for thyroid hormone synthesis [2]. However, excess iodine levels may cause a transient decrease in thyroid hormone production by inhibiting the organification of iodine, resulting in hypothyroidism, which is known as the acute Wolff-Chaikoff effect [3]. This inhibition serves as a temporary protection against hyperthyroidism. Early administration of starch-containing food is suggested to convert iodine to the much less toxic iodide [4]. As it was transient hypothyroidism, we did not administer levothyroxine to our patient.

Accidental ingestion of drugs resulting in poisoning and adverse drug effects is increasing all over the world with parent's medication administration error as an important factor [5]. Educating parents about intensified child supervision, safe storage of drugs, and proper drug dosage and administration will go a long way to prevent poisoning incidents.

Acknowledgements: Dr Suresh Panchanathan, Professor and Head of the Department, for his guidance.

BALAJI SWAMINATHAN, PEDIREDLA KARUNAKAR*
Department of Pediatrics,
Melmaruvathur Adhiparasakthi Institute of
Medical Sciences and Research (MAPIMS),
Melmaruvathur, Tamil Nadu.
**karunakar.pediredla@gmail.com*

REFERENCES

1. Bigliardi PL, Alsagoff SA, El-Kafrawi HY, et al. Povidone iodine in wound healing: A review of current concepts and practices. Int J Surg. 2017;44:260-68.
2. Leung A, Pearce EN, Braverman LE. Role of iodine in thyroid physiology. Expert Rev Endocrinol Metab. 2010; 5:593-602.
3. Bürgi H. Iodine excess. Best Pract Res Clin Endocrinol Metab. 2010;24:107-15.
4. Wax PM. Antiseptics, disinfectants, and sterilants. *In*: Nelson LS, Lewin NA, Howland MA, Hoffman RS, et al, editors. Goldfrank's Toxicologic Emergencies, 9th ed. McGraw-Hill; 2011. p. 1345-57.
5. D'Errico S, Zanon M, Radaelli D, et al. Medication errors in pediatrics: proposals to improve the quality and safety of care through clinical risk management. Front Med (Lausanne). 2022;8:814100.

NEWS IN BRIEF

Water to Prevent Childhood Overweight

Over the last five decades the incidence of childhood overweight and obesity has increased drastically not only in high-income countries but also in low- and middle-income countries, especially in the urban population. According to WHO in 2020, globally ~ 39 million children under the age of 5 years were overweight or obese, and almost half of these were from Asia. Early onset of obesity is associated with multiple problems like breathing difficulties, increased risk of fractures, insulin resis-tance and psychological effects along with increased higher chances of obesity, premature death and disability in adulthood. Measures like limited energy intake, increase consumption of fruit and vegetables, and regular physical activity have been suggested to reduce the development of overweight and obesity in children.

In a recent study from Stanford University, researchers evaluated the effect of drinking water on maintaining the body weight in school children. Students of 56 fourth-grade classes in 18 elementary schools belonging to low-income minority families were evaluated. Under the "Water First" program - drinking tapwater stations were established and water promotion was done as an intervention in nine schools (remaining nine schools were taken as control). In total, 1249 students were evaluated at baseline, 7 and 15 months during the intervention. At the end of study period, students from intervention group had significantly lower change in overweight prevalence (0.5%) compared to students from control group (3.7%). There was no effect of intervention on the prevalence of obesity. Findings of the study suggests an easy, cheap intervention to contain an emerging epidemic. (*Pediatrics 07 August, 2023*)

Targeted Next Generation Sequencing for TB

Reports suggests that the number cases with Isoniazid resistant TB is more than two times higher than the RR-TB and approximately one-fifth of MDR/RR-TB cases also have fluoroquinolone resistance. Only one third of people with MDR/RR-TB were known to have been diagnosed and enrolled on treatment. Recent approval of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) treatment regimens has shortened the treatment duration and improves the outcomes of MDR/RR-TB cases.

In order to achieve the target of elimination of TB by 2030 and address the increasing concern about the risk of resistance to bedaquiline and linezolid in near future, recently WHO has released a communication for the participating countries. In this WHO has emphasised the need of rapid diagnosis of drug resistant TB and the modification of regimens according to the available sensitivity pattern. For this, all the stakeholders were requested to consider the use of targeted next-generation sequencing (NGS) technology. By including the newly added drugs in the test and identifying the specific mutations associated with resistance, NGS provides an option for rapid and accurate identification of mutations associated with drug resistance, and guiding the treatment regimens. (*WHO.int July 25, 2023*)

Healthy Sleep Routine of Mothers and Their Infants

Duration of infant sleep plays a critical role during early childhood development as it has been associated with physical health, cognitive, and psychosocial development.Shorter sleep duration in infants is found to be associated with poor growth, increased risk for injuries, higher BMI and poor cognitive development. On the other side parenting stress, infant sleep duration and feeding patterns influence the maternal sleep duration which can have negative impact on mother's physical and mental health, ultimately affecting her child and family.

In a recent study, 464 participants of STRONG Kids 2 birth cohort were studied to find a relationship between the sleeping patterns of infants and their mothers during first 2 years of life.Participants were followed at 3, 12, 18, and 24 months of age and details about bedtime routines, their child's sleep duration, nighttime waking, and sleep problems were noted. Two sleep patterns were noted among the mothers – low maternal sleep pattern group (getting 5-6 hour's sleep/night) and average maternal sleep pattern group (getting 7-8 hour's sleep/night). Infants in low maternal sleep pattern group had shorter duration of sleep compared to those in average sleep pattern group. In this study consistent sleep routines and earlier bedtime are important factors found to be associated with better sleep patterns in both infants and their mothers. Simple measure like early bedtime routine can improve sleep duration and reduce various sleep related problems, thus helps in improving the neurocognitive outcomes and health in children. (*Journal of Developmental & Behavioral Pediatrics 22 July, 2023*)

RAJESH KUMAR MEENA
raj.mamc@gmail.com

CLIPPINGS

PEDIATRIC GASTROENTEROLOGY

Bilirubin-displacing effect of ceftriaxone in infants with unconjugated hyperbilirubinemia born at term (J Pediatr. 2023;254:91-5)

This prospective study was conducted with the aim to evaluate the effect of intravenous (IV) ceftriaxone on free bilirubin concentrations in infants with unconjugated hyperbiliru-binemia born at term. They included 27 infants born at term <7 days old with sepsis and receiving IV antibiotics for >3 days and resolving hyperbilirubinemia with total serum bilirubin levels between 6 and 12 mg/dL by day 4 of life. Free bilirubin was assessed before (baseline) and at follow-up, 15 minutes after IV ceftriaxone administration on postnatal days 4 to 6. The bilirubin-albumin binding affinity, Ka (L/mmoL) was measured as: total serum bilirubin - free bilirubin/free bilirubin (albumin - total serum bilirubin + free bilirubin). An auditory brainstem-evoked response was measured at follow-up. The free bilirubin after ceftriaxone administration/free bilirubin at baseline before initiating the ceftriaxone ratio, an index of displacing effect was 0.58 (95% CI 0.30-0.86) with zone fluidics device. There were no significant differences in the Ka between follow-up and baseline. The mean difference (SD) between follow-up Ka and baseline Ka was 19.7 (63) L/mmoL, suggesting no worsening of Ka after administration of ceftriaxone. All infants passed the automated auditory brainstem-evoked response test performed within 6 hours of IV ceftriaxone administration. The author concluded that ceftriaxone was not associated with a bilirubin-displacing effect in infants with mild unconjugated hyperbilirubinemia.

Efficacy of oral psyllium in pediatric irritable bowel syndrome (J Pediatr Gastroenterol Nutr. 2023;76:14-9)

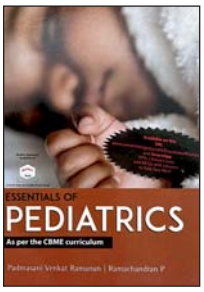
Due to changes in lifestyle, pediatric IBS is becoming increasingly common in office practice. Psyllium is a relatively inert substance and is a useful alternative as compared to other pharmacotherapies that have cholinergic and anticholingeric mismatches. This double blind randomized controlled trial (RCT) evaluated the efficacy of psyllium husk as compared to placebo in pediatric IBS patients. In this trial, 43 children were assigned to psyllium arm (Group A) and 38 into placebo (maltodextrin) arm (Group B). Both psyllium and maltodextrin were administered in powder form and subjects were asked to ingest it after mixing with plain water, twice a day. Both powders were administered in the form of radio-opaque sachets, with each sachet containing 3 g of either of the material, to ensure double blinding. Patients between 6 and 12 years of age were given 6 g per day and those in the 13-18 year age group were given 12 g per day in two daily divided doses. Severity is assessed at baseline and after 4 weeks of treatment using IBS severity scoring scale (IBS-SSS) and classified into mild, moderate, and severe categories. Mean ages (SD) of Groups A and B were 9.87 (2.7) and 9.82 (3.17) years, respectively, with median duration of illness of 12 months. At baseline, type, severity, and IBS-SSS parameters were equally distributed in two groups. There was a significant reduction in median (IQR) of total IBS-SSS in psyllium vs placebo [75 (42.5-140) vs 225 (185-270); P <0.001] at 4 weeks. Similarly 43.9% in Group A vs 9.7% in Group B attained remission [IBS-SSS < 75 (P< 0.001)]. The mean difference in IBS-SSS between Group A and Group B was -122.85 with risk ratio of 0.64 (95% CI; 0.42-0.83; P = 0.001) and absolute risk reduction of 32% (NNT = 3). The authors concluded that psyllium husk is effective for the therapy of pediatric IBS when compared with placebo in short-term.

Long-term outcome of necrotizing enterocolitis and spontaneous intestinal perforation (Pediatrics. 2022; 150:e2022056445)

ELGAN-ECHO (Extremely low gestational age newborns-Environmental influences on Child Health Outcomes) study group prospectively assessed the outcome of necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) survivors over a span of 10-15 years for growth and neurodevelopmental (ND) outcomes. They compared children with medical NEC vs surgical NEC vs surgical SIP vs neither NEC, nor SIP (controls). SIP was defined as an isolated gastrointestinal perforation on radiograph and managed by exploratory laparotomy or an abdominal drain (without surgery) in the absence of other corroborative features of NEC. The authors assessed anthropometrics, neurocognition, attention-deficit/hyperactivity disorder, epilepsy, and gross motor function. Children with medical NEC had similar weight, body mass index (BMI), height, and head circumference when compared with controls at 10 and 15 years. At 15 years, children with surgical NEC had lower weight z score (adjusted β: -0.75, 95% confidence interval [CI]: -1.25 to -0.25), lower BMI z score (adjusted β: -0.55, 95% CI: -1.09 to -0.01), and lower height z score (adjusted β: -0.65, 95% CI: -1.16 to -0.14). Children with SIP had lower weight and height z-scores at baseline when adjusted for sample attrition, but these differences were not significant when adjusted for confounders. They did not observe any differences in long-term ND outcomes between the groups. Authors concluded that surgical NEC- and SIP-associated growth impairment may persist through late childhood. ND outcomes among school-aged children born extremely preterm with NEC/SIP are no different from children without NEC or SIP.

MOINAK SEN SARMA
moinaksen@yahoo.com

BOOK REVIEWS



Essentials of Pediatrics

PADMASANI VR, RAMACHANDRAN P
Universities Press
Pages: 724; Price: Rs. 1575/-

This book covers the very relevant and pertinent area of undergraduate medical education in a background of changing concept, based on Competency based medical education (CBME). The book contains 35 chapters, with use of colored charts, tables, figures and photographs. In just 724 pages, it addresses different aspects of pediatrics including normal physiological and pathological concepts of diseases, contributed by 54 authors and edited by eminent teachers.

Each chapter begins with a listing of learning objectives and sum up with key points, self-assessment and case scenarios. The book covers the subject in such a way as to set off a new and stimulating train of thought in the mind of a student who is curious. The chapters include all systemic diseases along with systematic approach for management.

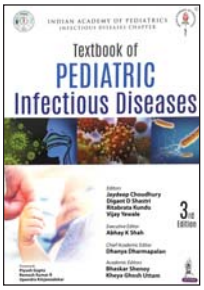
The section on growth and development is made easy to understand with use of pictorial illustrations, tables and tools of measurements. A simplified approach to deal with pediatric emergencies at first point of contact shall not only help the student to learn but also to improve the outcome. Separate section on IMNCI approach shall boost the confidence of student to provide care at community level.

Each section of this book delivers numerous clinical algorithms as one practical, portable resource. The book also includes abundant quick reference tables for diseases and conditions commonly seen in hospitalized children, providing rapid access to bedside information when decisions need to be made quickly. Sections with tables of drug dosages are very useful for students.

The book includes latest updates and clinical developments in pediatric medicine, which truly makes it easy to find what you need at the point of care. The easy-to-navigate chapters cover signs and symptoms, differential diagnosis and pediatric laboratory reference values, related to specific diseases, medical emergencies, and care of the hospitalized patient, with a particular emphasis on recent treatment guidelines.

This book is written in a simple and easy to understand language, and is able to create interest among readers. In addition, a focused approach and portability makes it a most suitable book for all undergraduate medical students for training, case management and preparation for final examination. The pediatricians, residents and faculty too would find this book as a useful resource to their practice and teaching-learning activities. As intended, it fulfils all the qualities of a textbook of pediatrics.

VIRENDRA KUMAR
Maulana Azad Medical College, Delhi
drvkumar1@gmail.com



Textbook of Pediatric Infectious Diseases
Third Edition

JAYDEEP CHOUDHARY, DIGANT D SHASTRI, RITABRATA KUNDU, VIJAY YEWALE
Jaypee Brothers Medical Publishers (P). Ltd,
Pages: 900, Price: Rs. 2495/-

The updated 3rd Edition of IAP Textbook of Pediatrics Infectious Diseases is the outcome of the learned and experienced team of the Infectious Diseases Chapter compiled and edited, experts of infectious diseases in children. Infectious diseases often present as complex and challenging clinical situations for practicing pediatricians. The book lays emphasis on the practical understanding to manage as relevant towards the patient care with the inclusion of topics of current and future relevance.

It constitutes 88 chapters with the contributions from more than 100 authors. There is addition of new chapters related to common and not so common infections. The book has sections on general topics related to pediatric infectious diseases, principles of management of infections and approach to varied presentations of common infections. The book dwells on systemic infections with their etiological basis covering the whole gamut of microbes incorporating the diagnostics, their relevance in clinical practice along with the management algorithms and treatment protocols. There is a section on vaccine preventable diseases, vaccines and immunization, rational drug therapy, and drug dosages etc.

This third edition, in its revised and updated version, is vastly covering all the infections and is also country-specific. Indeed a very useful book for the Residents and Practicing Pediatricians.

SANGITA YADAV
Deparment of Pediatrics, HIMSR & HAHC, New Delhi.
sangeetayadava@gmail.com

Printed and published by Dr Devendra Mishra on behalf of Indian Academy of Pediatrics and printed at Cambridge Press, Kashmere Gate, Delhi-110006 and published at 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049. Editor: Dr Devendra Mishra

Mankind
Serving Life

THE RARE PROBIOTIC

Entromax

2 Billion *Bacillus Clausii* Spores

Suspension

- **R** Reliable
- **A** Affordable
- **R** Rapid Action
- **E** Efficacy & Safety

In
- Infectious Diarrhea
- Antibiotic Associated Diarrhea (AAD)

For Billion Smiles

ASSURED GOODNESS

Gudcef-100

Cefpodoxime 100mg / 5ml

Dry Syrup

Good @ Efficacy
Micronised Cefpodoxime

Good @ Compliance
Palatable Orange Flavour

Good @ Affordability

In RTIs • Acute Otitis Media • Typhoid Fever

Orangilicious Choice for Kids