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Editing the Academy's Journal in the Peri-COVID Era – A Different Ball Game Altogether!

Having been associated with *Indian Pediatrics* editorial board for more than 15 years, I complete my three-year tenure as editor-in-chief (EIC), and move on to the fourth year. This post was the culmination of a long academic journey, and was taken up with lofty ideals and a bunch of new ideas [1]. I find this an appropriate time to reflect on issues related to editing the journal of a professional society, especially in the coronavirus disease (COVID-19) times, and also touch upon the changes in the journal.

COVID-19 and the Journal

The effect of the COVID-19 pandemic on the publication of medical journals has not received as much interest, as the other effects of the epidemic. The intervening pandemic presented unique challenges to the publication of the journal. The COVID-induced lockdowns in the city forced the closure of the printing press, and also the journal office. However, the extensive support of the journal staff and the editorial board worked as a buttress to the publication process, which continued unhindered [2]. This led to the timely publication of all the online issues of the journal, which were later sent to the subscribers through the ever-reliable India Post, once the lockdown partially lifted.

The editorial response of the journal to the pandemic was also spot-on, with the first COVID-related guidelines to inform readers published on March 29, 2020 [3], within two months of the first case of the disease in India. One unintentional effect of the lockdown was the increased number of submissions to the journal (many of these COVID-related), and a very quick response from editors and reviewers. Later, this was reflected in the Journal Citation Report, 2022, when the journal's metrics had a major increase, a trend that was seen by many other journals [4].

New Sections

Quite a few innovations were thought-of and initiated, some of which succeeded and others fizzled out. A 'Pediatric subspecialties' section was introduced to promote publication of papers from the fields of pediatric radiology, pediatric dentistry, pediatric orthopedics and pediatric dermatology [1]. Despite wide publicity, hardly any submissions were received, and these too did not clear the peer-review process. On the other hand, 'Iconic pediatric institutions of India' section saw an enthusiastic response from the invited authors, and also received bouquets from the readers. This section was meant to provide a historical perspective on the development of child health in India, through the lens of the major institutions working in this field [1].

Journal ki baat, a monthly online discussion between authors, editors, and readers (one pediatrician in practice and one postgraduate pediatric resident from different regions of the country), was well received both by the panelists and the viewers. Having held 16 episodes till now [5], this platform, in addition to connecting the journal to the academy's members, also provides an important post-publication review for the authors. The whole-hearted involvement of the moderators Dr. Amit Upadhyay and Dr. Abhijit Saha remains the cornerstone of this activity.

Indian Pediatrics Case Reports (IPCaRes)

Initiated by Prof. Piyush Gupta, CIAP President, 2021, *IPCaRes* was started in 2021 by the journal to provide an avenue to the academy members to publish case reports, without strict restrictions on word count and numbers of figures/tables [6]. With eight issues published in the last two years, it continues to be a vibrant medium of scientific reporting and discussion, with additional content on soft skills like ethics and communication [7]. The journal is going from strength to strength under the tutelage of Dr. Sharmila M Bannerjee, and getting it indexed is the next activity scheduled.

Social Media Presence

The journal already had a Facebook page and was on Twitter since 2015. We debuted on Instagram in 2020 (*@indianpediatrics*) and on LinkedIn in 2021 (*www.linkedin.com/in/indian-pediatrics-342975218*). A team of young pediatricians were taken onboard to take up the responsibility of posting on these sites, under supervision of a designated editorial board member. Posting about important articles, and the early online articles, and

disseminating information about journal activities became easier and more effective through these platforms, and also increased the journal's reach to the younger generation of pediatricians.

Editorial Freedom

Editorial freedom, as per the World Association of Medical Journal Editors (WAME), is that the EIC has full authority over the entire editorial content of their journal, and the timing of publication of that content [8]. The International Committee of Medical Journal Editors additionally suggests that the EIC should have the final say in decisions about sponsored content/advertisements the journal carries [9]. Working with the office bearers and the executive board of Indian Academy of Pediatrics (IAP) over the last three years, I never found any of my editorial decisions hindered or 'influenced.'

Something New!

We plan to start a new section this year, '*Pediatric Subspecialties in India*.' This section will trace the growth of pediatric subspecialties in India, for the benefit of the younger generation of pediatricians, and will also showcase the contribution of many senior pediatricians, a few of whom remain unsung.

It was an exhilarating journey with many lessons learnt, but I end this tenure with the satisfaction that the journal remained a platform for debate on issues pertaining to child health as a whole, and not limited it self to being a journal just reporting on research alone. Ultimately, it is the readers and authors who are the final authority on the quality of a journal, and I feel that the journal scores highly with them.

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Diamonds are Forever!

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To all the readers of *Indian Pediatrics*, I wish you and your family a happy and healthy 2023. Over the last few months, the daily caseload of coronavirus disease (COVID-19) has been steadily declining in India, and we seem to be optimistically entering a post-pandemic era. It is time now to implement the numerous lessons learned over the last two years, as well as to reinvigorate pre-pandemic efforts to improve child health in India, which continues to be the core mandate of the Indian Academy of Pediatrics (IAP).

The IAP celebrates its Diamond Jubilee year this year, which is a good time to reflect on all that we have collectively achieved while reminding ourselves of all that is yet to be done. Milestones like the diamond jubilee year allow us to feel a sense of pride and appreciation for what our predecessors have achieved through the organization. In 1964, the organization pledged to raise the standards of the medical profession and medical education to provide quality care to every child in the country; to stimulate cordial relationships among all pediatricians and nurture the growth and diffusion of medical knowledge in every corner of the country. These founding tenets remain just as relevant in 2023, as IAP strives to achieve the best possible preventive and curative care for every child, irrespective of gender/region/socioeconomic strata/caste etc.

India still has a long way to go to ensure every child is adequately nourished and receives the right developmental environment to grow to her full potential. NFHS-5 data [1], released in the thick of the pandemic, exposed some worrying trends about the double threat of malnutrition in the country. On the one hand, the data shows an increase in severe wasting in children less than five years of age and only a marginal decrease in stunting. On the other hand, the survey made another startling revelation – an increasing number of under-five children are overweight. With rapid urbanization and easy access to "ordering in," we may be staring at the very real threat of childhood obesity and diabetes, something we thought (until very recently) is a public health challenge only in developed countries. These figures show that while one segment of society may not have access to essential nutrients, another segment is relying more and more on empty calories and junk food – both leading to the insidious outcome of child malnutrition. As a collective, IAP must step up our advocacy efforts to enhance policies that aim to improve nutritional outcomes in children. But we should also look for instances in our daily practice where we can monitor and track growth rates and identify danger signs early. Growth charts are simple but powerful tools that we are all equipped with, to identify children whose growth status is worrying and needs more attention. The child does not enter obesity without crossing over the overweight line and the same holds at the other extreme of undernutrition. Though, we all have the growth charts printed and attached to the patient record file, timely plotting on the chart is as important as documenting the immunization details. Weight for age is noted by most but somehow length/height for age and weight for length/height is overlooked when we very well know that stunting is almost irreversible after two years of age. I urge you all to use the IAP growth chart to track the growth of every child who comes to your clinic.

Secondly, we have made only marginal gains in breastfeeding practices in the country, over the last half-decade. The incidence of early initiation (within one hour of birth) has been almost stagnant since 2015. Every IAP member attending a delivery must ensure that every newborn baby is allowed direct skin to skin contact and thereby a chance to initiate breastfeeding within an hour after birth, whether in the labor room or OT. While the uptake of exclusive breastfeeding in the first six months has improved in this period (54.9% in 2015-16 to 63.7% in 2019-20), there is still a lot of scope to improve. For every challenge in the successful implementation of exclusive breastfeeding, there is a scientific and evidence-based solution that only needs our time and total commitment. Complementary feeding practice after the six-month mark has improved only slightly (42.7% in 2015-16 to 45.9% in 2019-20). Only 11.3% of children in the 6-23 month bracket

are receiving an adequate diet – which means only one in ten infants is obtaining sufficient nourishment. With all the discourse around early child development and the emphasis on the first 1,000 days of life, this finding serves as a rude reality check for all of us.

I would propose making the '6-month visit' a milestone pediatric check-up for the child, wherein we can use it as an opportunity to closely inspect the status of the child's growth while also counseling the parents on the importance of a minimum acceptable diet, dietary diversity and initiating complementary feeding while continuing breastfeeding. Spending time on this routine 6-month visit will surely pay rich dividends as it also allows the pediatrician to assess not only the gross and fine motor milestones but the social communication skills too, which can alert us for certain red flags.

Nurturing Care-Early Care Development (NC-ECD), the flagship program of IAP started in 2021, by the then President Dr. Piyush Gupta [2], has reached a milestone of hundred workshops conducted all over the country, and another hundred in the pipeline for 2023. Although, our workshops train the pediatricians, the ultimate goal is that this training reaches parents/caregivers, sensitizing them about the importance of NC-ECD during the 'well-child' visits and to bringing about a positive behavior change in them. We still need to ideate on simple, affordable and feasible methods to reach a maximum number of beneficiaries. Dr Nandita Chatterjee, from team Udbhaas CDC in collaboration with UNICEF Kolkata has published a novel idea of roping in frontline workers and young girls from the community itself, to further disseminate the merits of NC-ECD to new parents [3]. I hope that such voices from the field inspire more novel ideas, which is the need of the hour for the program to have a significant reach and impact.

Lastly, a word about strengthening our immunization practices. Towards the end of last year, we had an unexpected and unfortunate surge of measles in many areas of the country. It has taught us the lesson that 'not lowering the guard' was not meant only for COVID-19 but in fact for all infectious diseases. Let us ensure complete protection to every child from vaccine preventable diseases by advocating and offering age-appropriate vaccines.

As the largest body of pediatricians in the country, we can make a significant difference to child health in India by adopting these simple yet impactful measures in our day-to-day practice. In a post-pandemic world, children are looking at a dizzyingly fast-paced, virtual and compe-titive future, set in deteriorating climatic conditions, which brings along its own set of challenges to their mental and physical well-being. We are also witnessing the co-existence of contradictory public health challenges (e.g., rising number of overweight and underweight children). The time is now to go in with all guns blazing to advocate and act on early initiation of breast feeding, exclusive breast feeding for six months, timely introduction of complementary feeding, growth monitoring, strengthening our immunization practices, and finally empowering and guiding every parent/caregiver in applying principals of NC- ECD to prevent a cascade of more serious child health problems in the future.

When it is said that 'Diamonds are forever,' it actually means a diamond never loses its value. Similarly, in IAP's diamond jubilee year, let us all pledge to collectively work to overcome newer challenges for better health and wellbeing of our children, keeping our core values intact.

In all things that are purely social, we can be as separate as the fingers, yet one as the hand in all things essential to mutual progress.

– George Washington

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INVITED COMMENTARY

Measuring Overnutrition in Children: Do We Know Enough?

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Given the historical rarity of excess weight, assessment of pediatric weight status has long been focused on detecting and correcting growth faltering in children. However, since the mid-1970s, changes in dietary intake and energy expenditure that favor excess weight began to take hold the world over. This nutrition transition was first evident in the weight status of adults and in high-income settings, but it is increasingly manifest in the youngest ones even in low- and middle-income countries (LMIC). Available data suggest that roughly 6% of children in LMICs experience overweight, an average rise of one percentage point over the past two decades [1]. The nutrition transition has created a challenging panorama of child health promotion priorities in places like India, which simultaneously has among the largest absolute number of overweight and growth stunted children [1,2].

Despite the nutrition transition, there has been relatively limited discussion on the best measure for the classification of overnutrition compared with the extensive debate regarding best measures of child undernutrition, including short stature (low height for age), wasting (low weight for height), and underweight (low weight for age). Currently, the WHO-recommended weight for height index is the predominant measure of child overweight and obesity in global settings [3]. Some have questioned whether weight for height is the most appropriate index for overweight and obesity.

In their recent publication in *Indian Pediatrics*, Naga Rajeev, et al. [4] compare body mass index (BMI) thresholds to define overweight, and the prevalence of overweight obtained from applying weight for height versus BMI for age. Through examination of NFHS-4 data, the authors report that weight for height compared with BMI for age yielded higher estimates of prevalent overweight from birth to 6 months, but lower estimates of prevalent overweight in children ages 6 months to 5 years. Similarly, their simulation studies showed that in short populations, the BMI threshold for overnutrition was lower for weight for height compared with BMI for age from birth to 7-8 months, but higher thereafter [4]. The discrepancies are more impactful in scenarios where child height is much lower than the global mean. The authors conclude that BMI for age is preferable to weight for height for the classification of overweight due to its ability to produce estimates that are not sensitive to the age or mean height of the population [4]. The authors are to be commended for the thorough and detailed statistical considerations of applying one measure rather than the other. Here, we provide two additional considerations for discussion to advance the measurement of childhood overweight.

First, the ultimate goal of assessing overnutrition and excess weight is to gauge excess adiposity. In that regard, BMI stands above weight for height because it breaks the relationship between the index and height because of the height-squared adjustment in the denominator. BMI for age additionally accounts for changes in body size over time (age). In this sense, BMI for age conceptually is a better index to capture changes in excess weight (and adiposity) independent of height [5,6]. The importance of the independence of different indices of body size and composition from their denominators has been demonstrated in previous studies in LMICs, where individuals and populations face a double burden of malnutrition [7,8]. Nevertheless, from previous research in children, it is known that BMI is still an imperfect measure of body composition (adiposity) [9].

Second, both debated definitions of child overweight and obesity are statistical in nature. Akin to the approach for classifying undernutrition, overweight definitions are based on distributional thresholds anchored to a universal reference population. Whether a distributional threshold is the optimal approach to capture future metabolic risk is unclear. In adults, excess weight is defined so that it captures excess risk of health outcomes such as death and cardiovascular events, and the field may consider whether anchoring excess weight in children against metabolic

outcomes would add value. There is some evidence that shows that both BMI for age and weight for height in infants predict future health outcomes with comparable validity [10], yet additional systematic investigation is needed to resolve which measure is best at predicting metabolic risk. Furthermore, following on the lessons from adult anthropometry and metabolic risk, the appropriateness of universal versus population-specific thresholds can be explored. For example, the WHO recommends lower "action point" thresholds for overweight and obesity in Asian adults because of observed elevated risk of diabetes and cardiovascular disease even in the normal weight range [11]. A similar exercise may enhance our ability to appropriately classify excess weight in children.

In summary, a measure of overweight should not only be statistically robust but also appropriately identify, categorize, and rank children with respect to excess adiposity and risk of future adverse health outcomes. Considering the results of Naga Rajeev, et al. [4], BMI for age offers a statistical robustness across varying ages. Additionally, recognizing that BMI for age is an inexpen-sive and practical measure to assess weight status in community and clinical settings, that BMI measures excess weight for height independent of height, and that BMI correlates with metabolic outcomes in children, we concur with the authors that BMI for age is a preferred index to classify childhood overweight given present knowledge.

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INVITED COMMENTARY

Effect of Kangaroo Mother Care on Cerebral Hemodynamics in Preterm Infants

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Kangaroo mother care (KMC) has evolved as *sine qua non* intervention to meet the preterm baby's fundamental needs of warmth, nutrition, and protection from infection. KMC re-establishes the synchrony between mother and fetus interrupted by preterm birth. Maternal sensory inputs regulate the physiology of the newborn and attain homeostasis. Research suggests that for all mammals, the maternal environment is the primary requirement for regulation of all physiological needs (homeostasis), and maternal absence leads to dysregulation and adaptation to adversity. The cardio-respiratory instability seen in separated infants in the first 6 hours is consistent with mammalian "protest-despair" biology, and "hyper-arousal and dissociation" response patterns described in human infants. Thus, zero separation achieved with KMC facilitates normal biology and neurodevelopment [1].

Cerebral hemodynamics is very unique in preterm population – cerebral autoregulation and cerebral blood flow (CBF) being sensitive to the changes in the mean blood pressure (MBP), oxygenation, heart rate (HR) and carbon dioxide variability. Impaired cerebral auto-regulation, increasingly observed with decreasing gestational age and birth weight, results in pressure passive cerebral circulation and imbalance in the normal physiologic reflex worsens the possibility of neurologically intact outcomes. Immaturity of the autonomic nervous system, especially the parasympathetic control of CBF is particularly underdeveloped in preterm infants. Intact cerebrovascular autoregulation is found in clinically stable preterm infants, CBF being unaffected by fluctuations of MBP within the physiologic range of 25 to 60 mm Hg [2]. CBF autoregulation is functional in normotensive but not in hypotensive very low birth weight (VLBW) and extremely low birth weight (ELBW) infants in immediate neonatal period. Studies have shown that the ability of newborn brain to respond to changes in perfusion pressure is not only limited as compared to adults, its range is further quite diminished in sick and critically ill infants [2]. This creates an increased vulnerability to both ischemic and hemorrhagic brain injuries and increased risk of long term neurological insults. A fluctuating pattern of blood pressure, characterized by marked, continuous alterations in both systolic and diastolic flow velocities, are associated with similar trends in the CBF velocity tracings and a high risk of subsequent occurrence of intraventricular hemorrhage (IVH). Because of the pressure-passive cerebral circulation in sick premature infants, hypotension can lead to a parallel decrease in cerebral blood flow. It is important to note that carbon dioxide – CBF reactivity is more robust than pressure-flow reactivity. Moderate hypocarbia results in the reduction in CBF while moderate hypercarbia results in increase in CBF and also abolishes the autoregulatory response due to marked vasodilation resulting in ischemic brain injury.

The impact of KMC on cerebral hemodynamics in preterm neonates has been an area of research interest. The maintenance of normal temperature, heart rate, blood pressure, oxygen, carbon dioxide, and glucose are vitally important to maintain cerebral hemodynamics [3]. KMC stabilizes these cardiorespiratory parameters and positively influences the physiological stability. KMC in stable preterm infants has resulted in fewer bradycardic events, fewer desaturations and apneic events. The improvement in oxygenation can be attributed to the upright position of KMC which increases the efficiency of the diaphragm and pulmonary function [4]. The lesser variation of HR, respiratory rate, and stable oxygen saturation while in KMC contributes to the better hemodynamic stability and sudden fluctuations of blood pressure are prevented since there is positive regulation of serum cortisol and β-endorphins. KMC has also shown to improve the perfusion index and reduce HR variability [5,6]. KMC enhances peripheral perfusion through vaso-relaxation by releasing acetylcholine from parasympathetic nerves and induces vaso-relaxation by regulating the release of nitric oxide (NO) in arteries through M3 acetylcholine receptors on the

endothelium. Higher heart rate variability is a result of an immature autonomic nervous system and a dominant sympathetic nervous system in a preterm that tends to overshoot during auto-regulation and chronic exposure to stress. KMC is thought to enhance parasympathetic signaling by improving the myelination of the vagal branches leading to better regulation of HR, cardiac output and autonomic responses [7]. Near-infrared spectroscopy, before, during, and after KMC, have shown stable mean cerebral regional oxygen saturation (rSO2) throughout KMC duration [8].

Transcranial color Doppler sonography is a bed side tool for non-invasive real-time assessment of CBF in newborns. Color Doppler imaging of the middle cerebral artery (MCA) helps to evaluate alterations in CBF. The study by Chaudhari, et al. [9] in this issue of *Indian Pediatrics*, analyzed the impact of KMC on cerebral hemodynamics in hemodynamically stable preterm population. It was intriguing to find an improvement in CBF velocities along with an improvement in physiological stability after 60 minutes of KMC. This benefit of KMC on changing Doppler parameters in MCA can also be attributed human skin having slow conducting unmyelinated (type C) afferents that respond to touch and skin to skin contact during KMC. Activation of these fibers stimulates the insular cortex (limbic system) to produce mediators (endorphins, neuropeptide and calcitonin gene-related peptide), which in turn enhance postsynaptic NO synthase. Nitric oxide induces smooth muscle relaxation and plays a pivotal role in regulating blood flow in the microvasculature including the cerebral blood vessels of preterm neonate [10]. This recent study evaluating the impact on neonatal cerebral hemodynamics serves as a bridge to our understanding of the real-time impact of KMC on these long term scientifically docu-mented benefits [9].

On world prematurity day 2022, UNICEF is promoting KMC method under the theme – "A Parent's embrace: a powerful therapy, Enable skin to skin contact from the moment of birth." Hence the effect modification by immediate KMC on cerebral hemodynamic parameters that occur during the first 24 hours after birth in stable preterm infants as well as clinically unstable infants needs to be further explored along with subsequent long term neurodevelopment outcome to strengthen the evidence base for promoting KMC and protecting the vulnerable preterm brain.

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INVITED COMMENTARY

Urgent Need of Research on Neurodevelopmental Outcome of Preterm/ Very Low Birth Weight Neonates From India

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Preterm birth varies from 8.7-13.4% globally and nearly 15 million preterm babies are born annually, of which 60% births are in Africa and South Asia [1]. India contributed about 3.1 million births in this cohort and which accounts to nearly 23.4% of global burden of preterm birth [2]. With improving facilities, training, infrastructure and newer technologies, there is increasing survival of preterm neonates across the globe including India which recorded a 40-60% reduction in preterm mortality between 1990 to 2019 [1].

These preterm neonates are at high risk of neurodevelopmental disabilities, almost 5-10% of very low birth weight (VLBW) babies have major sequelae like cerebral palsy (CP) while 25-50% have various cognitive and behavioral issues and lower academic performance [3-6]. An Italian cohort of preterm VLBW infants showed normal neuro-developmental outcome in 75.3% and the rest had minor (13.9%) and major sequelae (10.8%) including 3.8% CP [3]. The Neuroprem study reported 12.5% severe disability and 4.5% cerebral palsy rate among preterm VLBW infants (23-33 weeks gestation) at 24 months corrected age [5]. Epipage-2 cohort of preterm babies had severe to moderate disabilities in 36% cases at 27-31 weeks gestation and in 34% at 32-34 weeks gestation. Behavior was a major concern for most parents [6].

With nearly 25 million births and approximately 13.6% (11.1-16.1%) prematurity rate in India, a large number of preterm babies are born every year who needs a very long-term neurodevelopmental follow up however there are very scanty reports from India. A systematic review from resource limited set ups reported 21.4% neurodevelopmental impairment, 16.3% cognitive im-pairment, and 11.2% CP among preterm/low birth weight and very low birth weight infants; however, it included only three studies from India [7]. Another meta-analysis and systematic review from South Asia among low birth weight children showed significantly lower motor and cognitive scores as compared to normal birth weight children. This study included ten studies from India, but they included mostly low birth weight children and who were less than 2 kg [8].

We reported 3% CP, 11% gross motor delay and 8% language delay among our VLBW (≤1500 g) and preterm (≤34 week gestation) cohort at 18 months corrected age. In this cohort, 17% had a score of less than 70 in MeDQ and 25.7% in MoDQ and 84% had high behavioral scores [9].

Preterm small for gestational age (SGA) children are more at risk of neurodevelopmental disabilities due to double whammy of prematurity and growth retardation. In our country nearly 30% are LBW and some are preterm too. Murki, et al. [10] reported neuro-development at 12-18 months of corrected age among preterm (<35 week) small for gestational age (SGA) infants and found higher incidence of motor and mental delay as compared to preterm appropriate for age (AGA) infants. We also observed 24% had low DQ (<90) and 74% had average and above average DQ (>90) among ≤1250 grams cohort at CA 18 months. SGA infants had significantly higher risk of low scores [11]. Sacchi, et al. [12] also reported in a systematic review and meta-analysis, higher cognitive impairments among the children who were preterm and SGA. Gupta, et al. [13], in this issue of *Indian Pediatrics*, report neurodevelopmental disabilities and growth failure in VLBW neonates at 1 year CA, thereby highlighting the need for long-term follow up.

Hence, VLBW infants (AGA and SGA both) need long-term follow up for early detection of neurodevelopmental disabilities including hearing screening and ophthalmological evaluation and early intervention by a team of multispeciality experts. There is a need for a collaborative and systematic data collection from various NICUs as well as from SNCUs in our country, and assessments should be carried out with standardized scales so that uniformity of data can be maintained. Adequate and appropriate data collection and reporting will help to compare the data over the years and quality of care can be improved accordingly.

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RESEARCH PAPER

Comparison of Weight for Height and BMI for Age for Estimating Overnutrition Burden in Under-Five Populations With High Stunting Prevalence

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Background: Overnourished under-five children are anthropometrically classified as either being at possible risk of overweight, overweight or obese and defined so, when either weight for height or body mass index for age (BMI-for-age) are >1SD to 2SD, >2SD to 3SD and >3SD, respectively of the analogous World Health Organization standards.

Aim: To compare weight for height and BMI for age definitions for quantifying overnutrition burden.

Methods: Theoretical consequences of ignoring age were evaluated by comparing, at varying height for age *z*-scores, the age- and sex-specific cutoffs of BMI that would define overnutrition with these two metrics. Overnutrition prevalence was then compared in simulated populations (short, intermediate and tall) and real-life datasets from India.

Results: In short (-2SD) children, the BMI cutoffs with weight for height criteria were lower in comparison to BMI for age till 7-8 months, but higher at later ages. In National Family Health Survey-4, India dataset (short population), overnutrition (>1SD) prevalence with weight for height was higher from 0-0.5 years (exclusive breastfeeding age), but lower at subsequent ages. The prevalence difference (weight for height - BMI for age) in 0.5-5 years was -2.26% (6.57% vs 8.83%); this attenuated in 0-5 years (-1.55%; 7.23% vs 8.78%). The discrepancy was maximal for stunted children and was lower in girls. A similar pattern, of lower magnitude, was observed for overweight (>2SD) comparison. In intermediate and tall populations, there were no meaningful differences.

Conclusion: The two definitions produce cutoffs, and hence estimates of overnutrition, that differ with the age, sex, and height of under-five children. The relative invariance, with age and height, of BMI for age, favors its use.

Keywords: *Anthropometric indicators, Growth assessment, Overnutrition, Overweight,*

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Globally, an estimated 5.7% or 38.9 million under-five children, almost half in Asia and a quarter in Africa, were affected by overweight in 2020 [1]. Since overweight and obesity in childhood and adolescence are associated with adverse health consequences later in life, their prevention and control are important. Focusing on under-five children is an important component of this strategy [2]. Indeed, prevalence of overweight in under-five children is one of the Sustainable Development Goals (SDGs). The global nutrition targets endorsed by the World Health Assembly include: *i*) no increase in childhood overweight prevalence as target for 2025; and *ii*) reduce and maintain childhood overweight to below 3% as target for 2030 [1]. An accurate and bias free quantification of overnutrition burden is, therefore, crucial both at the individual and population level.

Overnutrition in under-five children can be identified by either of the two anthropometric indices: *a*) Weight for height, and *b*) Body mass index for age (BMI for age). Overnourished individuals are categorized as either obese, overweight or at possible risk of overweight, if these indices are >3SD, between >2SD and 3SD, and between >1SD and 2SD, respectively of the World Health Organization (WHO) growth references [3,4]. Currently, there is no

Invited Commentary: Pages 11-12.

unanimity regarding the preferred index among these two, to diagnose overnutrition in public health settings. Weight for height ignores the physiological changes in ponderosity with age, whereas by construct BMI for age accounts for such alterations [4,5]. Further, for a given weight and height at a particular age, the WHO SD (or *z*) scores of the two indices could also differ. We recently demonstrated that

these incongruencies resulted in appreciable and systematic differences in thinness estimates of populations [5]. A similar phenomenon is likely for overnutrition. Following the introduction of the WHO growth charts, only few studies from HICs have partially explored this possibility [6-9]. However, there is no detailed and systematic evaluation from low and middle income country (LMIC) settings, in which the children are generally shorter and thinner, but the double burden of malnutrition is now assuming alarming proportions [2]. We, therefore, compared these two indices for diagnosing overnutrition in under-five children, in populations with different heights, through theoretical considerations, simulation, and real-life data sets from research and survey settings in India.

METHODS

An ethical clearance for the study was not required as it deals with hypothetical considerations, simulations [4,10-13], and the real-life analyses of secondary datasets for which the consent was taken from the parents of the participants and the ethical clearance was obtained from the respective institutional boards [10,14-15].

The two metrics (weight for height and BMI for age) were compared independently for both the sexes (boys and girls) at monthly intervals from 0 to 60 months. We considered the values ht(t,z), bmi(t,z), and wt(t,z), respectively at age t where ht, bmi, and wt are height, BMI, weight (at height ht(t,z)) and *z* is the WHO standard score of height, BMI, and weight for height [4]. The plots were made for bmi (t,+2) and wt(t,+2)/ht^2(t,z) against age t (0 to 60 months), where *z* = -2, 0, +2 (short, intermediate, and tall), respectively. Further, at fixed weight for age with fixed height for age (both at 0SD, +1SD, and +2SD), we compared the SD scores of weight for height and BMI for age in both sexes, from 0 to 60 months, respectively.

The artificial datasets were constructed independently for boys and girls to study the effects of choice of metric on overnutrition estimates, in short: National Family Health Survey-4 (NFHS-4) [10], intermediate: WHO [4], and tall: National Health and Nutrition Examination Survey, USA (NHANES), Greenland and Poland populations [11-13]. In six-monthly age-group intervals from 0-5 years, 100,000 subjects were generated homogeneously and indepen-dently for both the sexes. The WHO *z*-scores of heights and weights were generated through bivariate distribution with respect to their mean, SD, and correlations (**Table I**). The height and weight were back calculated by using the LMS parameters of the WHO reference [4].

Three real-life datasets were used for the analyses:

a) the Meerut study, which was designed to assess the prevalence of severe acute malnutrition and to propose mid-arm circumference substitutes for the weight for height cutoffs [14]. This cross sectional, community-based study was conducted between September, 2012 and October, 2013 in the district of Meerut, Uttar Pradesh, India. Two adjoining rural blocks were identified, and their 70 contiguous villages were selected. The inclusion criteria were children aged between 6-59 months residing permanently in the study area, who had no severe ailments or physical deformities (*n*=18,463). The research team members were trained in recording anthropometry by standard techniques, assessment of age and examination for severe visible thinness and bipedal oedema. Length for the children below 24 months of age was measured using SECA 417 infantometer and for 24-59 months of age, SECA 213 stadiometer was used to measure the height with a minimal count of 0.1cm. Weight was recorded using SECA 383 digital weighing scale

Table I Details of Anthropometric Parameters Used for Creating the Simulated Populations

Simulated population, country	*Height for age z-score*		*Weight for age z-score*		*Correlation*
	Mean	*SD*	*Mean*	*SD*	
Short (National Family Health Survey-4), India [15]	-1.89 to -0.44	1.28 to 1.92	-1.69 to 1.11	1.07 to 1.39	0.55 to 0.69
Intermediate [7]	0	1	0	1	0.72
Tall					
National Health and Nutrition Examination Survey, USA [16]	-0.18 to 0.29	0.96 to 1.32	0.21 to 0.58	0.94 to 1.26	0.63 to 0.75
Greenland [17]	0.80 to 0.83	1.17 to 1.18	0.80 to 0.83	0.98 to 1.07	0.72
Poland [18]	0.28 to 0.40	0.98 to 1.00	0.36 to 0.45	1.03 to 1.12	0.72

The values under various columns depict either a single value (if applicable) or a range for the stratified six-monthly age groups from birth to five years of age. Reference numbers of studies from where these anthropometric details were collected for creating the synthetic populations are provided in square parenthesis.

closest to 10g. Inter-observer and intra-observer technical errors of measurements were <2% [14].

b) NFHS-4 is the cross-sectional Demographic Health Survey conducted between 2015-2016. Data was collected on 241,531 children throughout India between 0-5 years age [10]. A two-stage stratified sampling was done in which the primary sampling units (PSUs) were villages in rural areas and census enumeration blocks (CEBs) in urban areas. The final sample PSUs were selected with the probability proportional to the size (PPS) sampling. In every selected rural and urban PSU, households and individuals were selected using a well-defined process. Weights were measured using the SECA 874 digital weighing scale. Length was measured using SECA 417 infantometer for infants below 24 months of age and SECA 213 stadiometer was used to measure the height of children between 24-59 months of age. The least count and technical errors of measurements are not mentioned in the report. However, in this demographic survey, we expect more measurement errors.

c) The Comprehensive National Nutrition Survey (CNNS) was a cross-sectional nutritional survey conducted between 2016-2018. The data were collected on 38,060 children in India between 0-5 years of age by following the standard procedures [15]. Multi-stage stratified sampling was used in the survey with PSUs for villages in the rural areas and CEBs in the urban areas. The final selection of the PSUs was done by using the PPS sampling. Families and individuals were selected by a well-defined procedure from each of the chosen rural and urban PSUs. The weight of the children and adults was measured using SECA digital weighing scale and the length/height was measured using the three-piece wooden board. Children younger than two years of age, were measured lying down while older subjects were measured standing. In this survey, we expect less errors as the measurements, except weight, were conducted in duplicate with quality control procedures in place.

We noted discrepancies between the *z*-scores of various indices available in the NFHS-4 dataset and the *z*-scores calculated from the raw weights and lengths/heights. Thus, we used the calculated WHO *z*-scores using the macro syntax for STATA [4]. WHO criteria were followed to set the missing values (*z*-scores): length/height for age <-6 or >6, weight for age <-6 or >5, weight for-height <-5 or >5, and BMI for age <-5 or >5. Using these filters, 2,07,364 subjects were available for the analysis (**Web Fig. 1** and **2**). In the CNNS dataset, 3,162 subjects were excluded using the same filters and thus 34,898 subjects were available for the analysis. In Meerut study, we considered missing values below -7z for height-for-age, weight-for-age, and weight-for-height, as seemingly aberrant measurements had been reverified in the field. Using this filter, 11 subjects were excluded, and 18,452 subjects were available for the analysis. Age categories were divided into ten six-monthly intervals between 0-5 years age.

Statistical analysis: The proportions that were classified as overnourished with weight for height (>1 SD or >2 SD) metric but not with BMI for age for the corresponding cut-off, and vice versa, were estimated from 2×2 tables. The prevalence of overnutrition with both metrics, including for stratified ages, sex and height for age categories, was compared using the McNemar test. Correlation between the two metrics was computed using Pearson correlation coefficient. Agreement between weight for height and BMI for age was examined by using Bland-Altman analyses with 95% limits of agreement.

The statistical analyses were done using STATA 16.0 version and the graphs were made using R software 4.0.2 version (R Core Team, 2020, *www.R-project.org*/) and STATA 16.0 version (StataCorp LLC).

RESULTS

The absolute BMI cutoffs for defining overweight (>2SD) according to weight for height and BMI for age criteria are compared in **Web Fig. 3.** In short children (-2 SD), the cutoffs with weight for height were lower till 7-8 months and after 48 and 54 months in girls and boys, respectively, but were higher in between these ages. The two cutoffs were broadly similar at median height (0SD). In tall children (+2 SD), the cut-offs with weight for height were higher till 5-6 months and after 36 and 39 months in boys and girls, respectively, but were lower in between these ages.

For a given weight for age (0, +1 and +2SD), the *z*-scores for weight for height and BMI for age were similar in children with median height for age (**Web Fig. 4**). However, in children with height for age at -2SD, the weight for height *z*-scores were higher than BMI for age *z*-scores till 6 months of age and lower subsequently till 42-60 months of age. A reverse pattern was observed in tall children (height for age +2SD).

Fig. 1 compares the prevalence of possible risk of overweight (>1 SD) using the two metrics in simulated short, intermediate, and tall populations. The overall (0-5 years) prevalence with weight for height was lower in comparison to BMI for age in short populations. However, the prevalence was higher with weight for height criterion

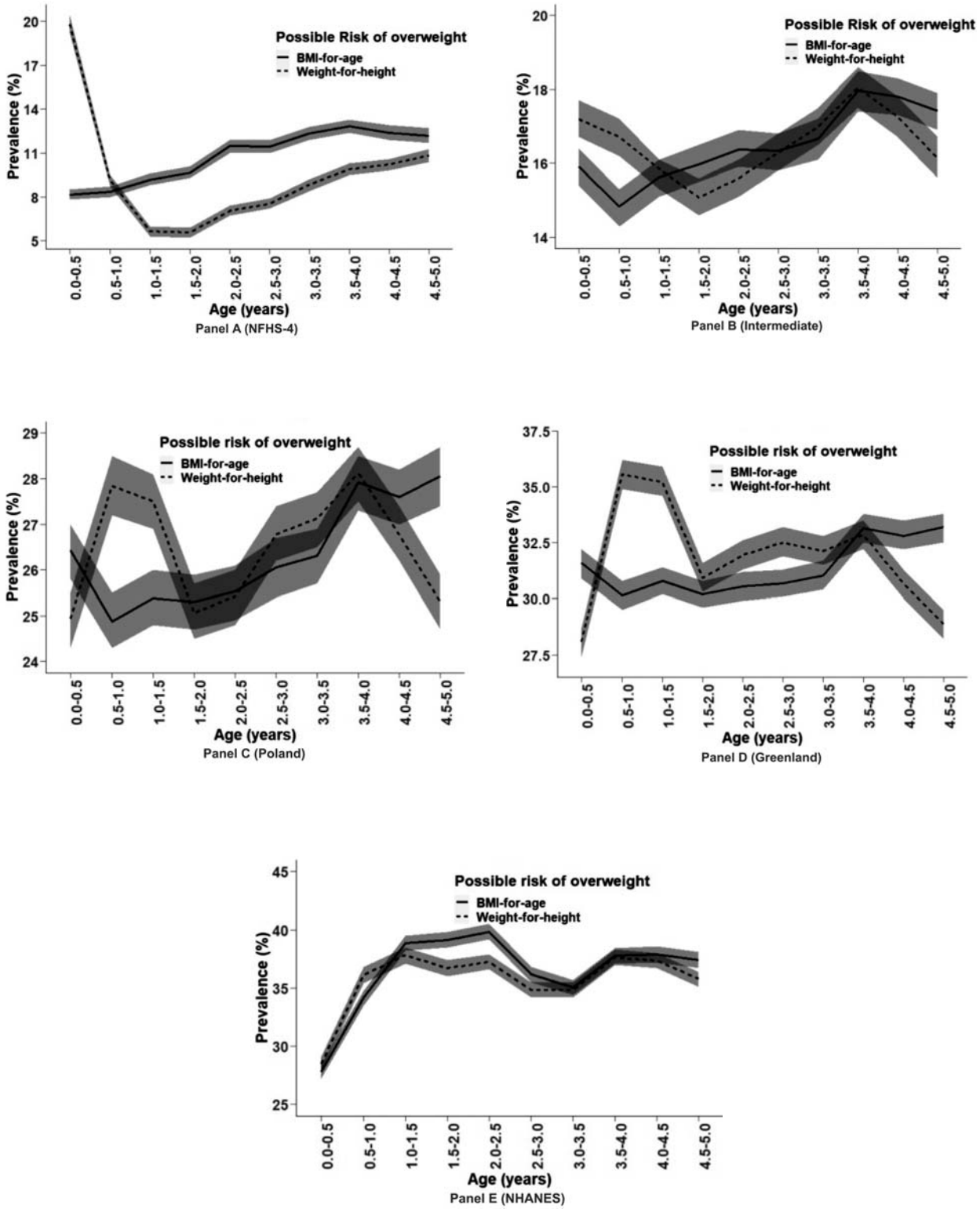

Fig. 1 Comparison of estimated prevalence and 95% confidence intervals of possible risk of overweight (>1SD) using weight for height and body mass index for age criteria on simulated populations. Panel A - short, based on the National Family Health Survey-4, India data [15]; Panel B - intermediate [7]; Panels C, D and E - tall, based on Poland [18], Greenland [17] and the National Health and Nutrition Examination Survey, USA [16] data, respectively.

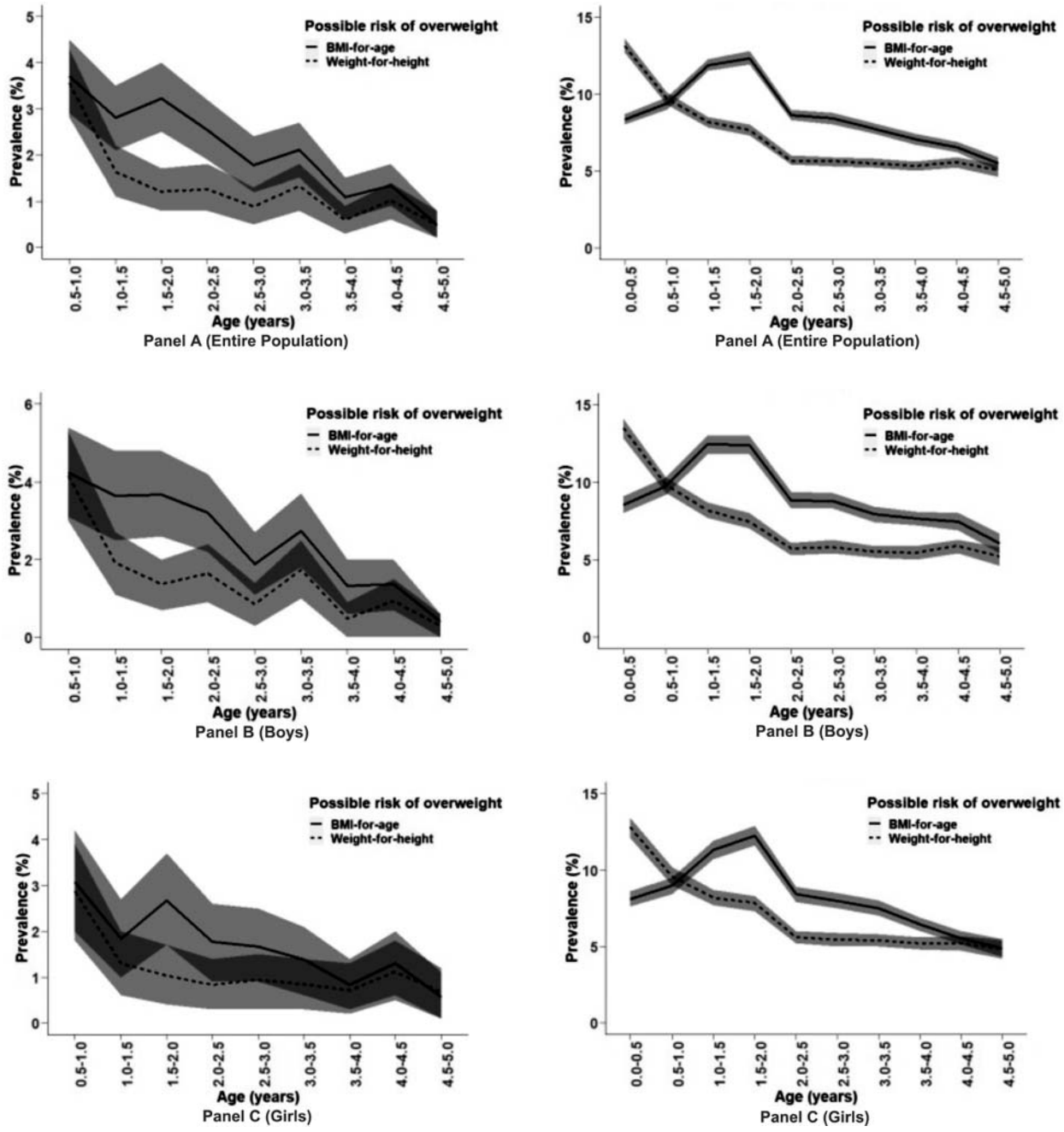

Fig. 2 Comparison of estimated prevalence and 95% confidence intervals of possible risk of overweight (>1SD) using weight for height and body mass index for age criteria in Meerut [14] (left) and National Family Health Survey-4 [15] (right), India datasets. Panel A – Entire population, Panel B – Boys, and Panel C – Girls.

in 0 to 0.5 years (19.8% vs 8.1%) and lower in 0.5 to 5 years (8.3% vs 11.1%). A reverse pattern was observed in tall populations, except for the USA dataset where the overall prevalence with weight for height was marginally lower (35.7% vs 36.4%). In intermediate population, the 0-5 years and 0.5-5 years prevalence estimates were similar with b oth metrics, whereas the 0-0.5 years prevalence was slightly higher with weight for height criterion (17.2% vs 15.9%). A similar pattern, but with lower magnitude, was evident for overweight (>2SD) comparison in short population (**Web Fig. 5**). No differences were observed for the intermediate population. In the tall populations from

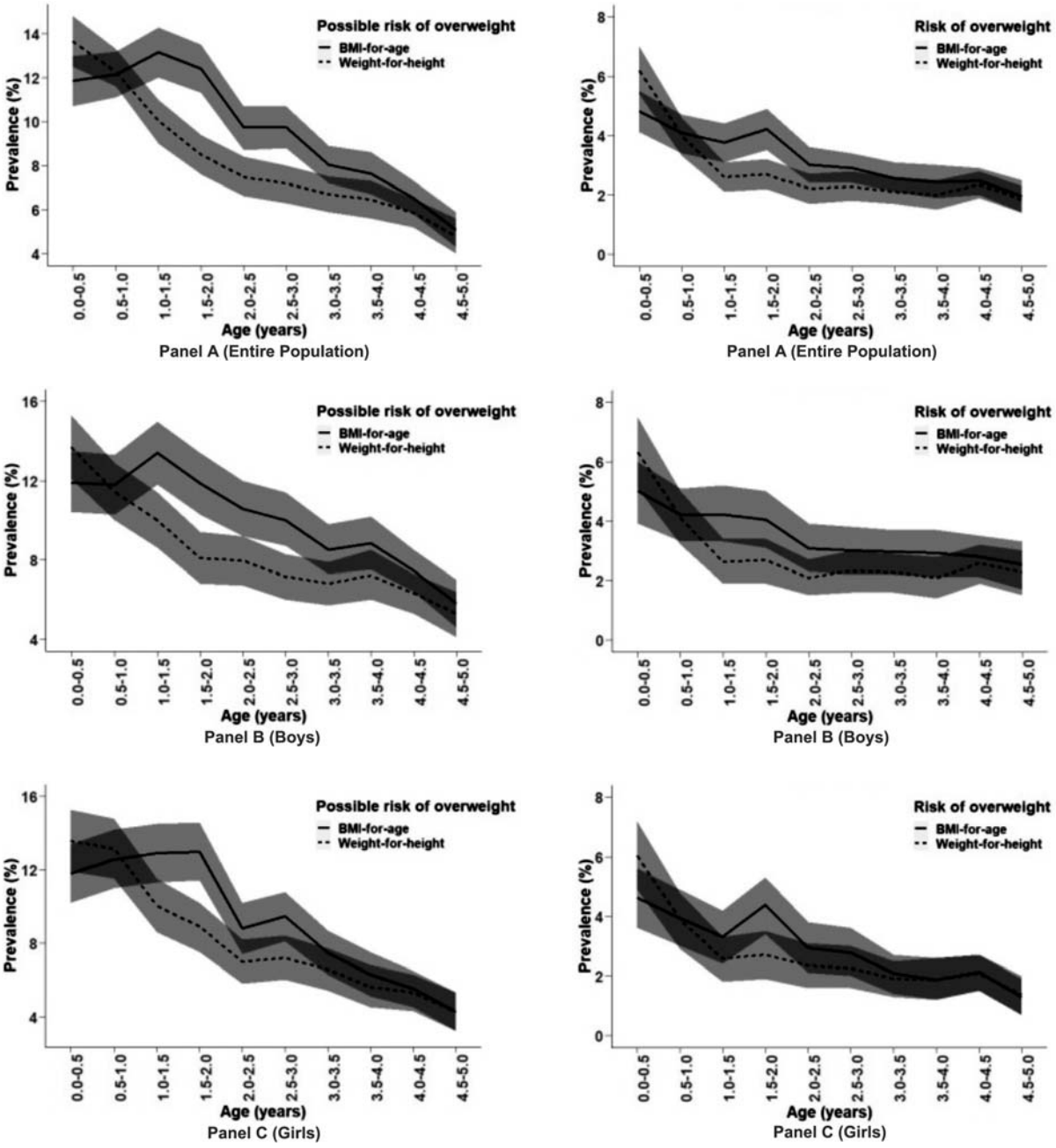

Fig. 3 Comparison of estimated prevalence and 95% confidence intervals of possible risk of overweight (>1 SD, left) and overweight (>2 SD, right) using weight for height and body mass index for age criteria in Comprehensive National Nutrition Survey, India datasets. Panel A – Entire population. Panel B – Boys, and Panel C – Girls.

Poland and Greenland databases, the weight for height estimates were slightly lower from 0-0.5 years, but comparable thereafter and for overall prevalence. In the USA dataset, the overall and 0.5-5 years prevalence was marginally lower with weight for height.

The mean (SD) age (months), height for age, weight for height, and BMI for age (*z*-scores) of the Meerut study were 32.6 (15.5), -1.87 (1.22), -1.11 (0.94), and -0.91 (0.94), respectively. Boys constituted 53% of the sample. Risk of overweight (>1SD) was lower with weight for height from 2-3 years and for overall (1.35% vs 2.15%) prevalence (**Fig. 2**). The difference was higher in stunted children and decreased with increasing stature. The discrepancy was more in boys. No significant differences were apparent for

Table II Bivariate Pearson Correlation Coefficients Between Weight for Height and Body Mass Index for Age (BMI for Age)

Datasets	*N*	*Correlation coefficients (P values)*	*Weight for height; [95% CI]*			*BMI-for-age; [95% CI]*			*Whether stunted; [95% CI]*	
			<-2 SD (n)	*≥-2 SD to ≥+2 SD (n)*	*> +2 SD (n)*	*<-2 SD (n)*	*≥-2 SD to ≥+2 SD (n)*	*> +2 SD (n)*	*Yes (n)*	*No (n)*
Simulated populations										
Short (NFHS-4)	200000	0.968 (<0.001)	0.93 (44437); [0.92, 0.93]	0.93 (150236); [0.92, 0.93]	0.37 (4627); [0.34, 0.39]	0.91 (42417); [0.90, 0.91]	0.93 (151539); [0.92, 0.93]	0.71 (5344); [0.69, 0.72]	0.93 (74083); [0.92, 0.93]	0.99 (125217); [0.98, 0.99]
Intermediate	200000	0.988 (<0.001)	0.87 (5764); [0.86, 0.87]	0.99 (189105); [0.98, 0.99]	0.92 (4991); [0.91, 0.92]	0.90 (5907); [0.89, 0.90]	0.99 (188874); [0.98, 0.99]	0.91 (5079); [0.90, 0.91]	0.93 (4611); [0.92, 0.93]	0.99 (195249); [0.98, 0.99]
Tall										
Poland	200000	0.990 (<0.001)	0.87 (4461); [0.86, 0.87]	0.99 (182644); [0.98, 0.99]	0.94 (12598); [0.93, 0.94]	0.92 (4770); [0.91, 0.92]	0.99 (182392); [0.98, 0.99]	0.91 (12541); [0.90, 0.91]	0.94 (1788); [0.93, 0.95]	0.99 (197915); [0.98, 0.99]
Greenland	200000	0.982 (<0.001)	0.58 (1923); [0.55, 0.61]	0.98 (181618); [0.97, 0.98]	0.92 (14905); [0.91, 0.92]	0.87 (2131); [0.85, 0.88]	0.98 (181554); [0.97, 0.98]	0.89 (14761); [0.88, 0.89]	0.93 (1576); [0.92, 0.93]	0.98 (196870); [0.97, 0.98]
NHANES	200000	0.987 (<0.001)	0.78 (2453); [0.76, 0.80]	0.98 (177011); [0.97, 0.98]	0.94 (20379); [0.93, 0.94]	0.89 (2344); [0.88, 0.90]	0.98 (176385); [0.97, 0.98]	0.94 (8741); [0.93, 0.94]	0.93 (6236); [0.92, 0.93]	0.99 (193607); [0.98, 0.99]
Meerut Study	18452	0.974 (<0.001)	0.89 (2930); [0.88, 0.89]	0.96 (15490); [0.95, 0.96]	0.91 (32); [0.82, 0.95]	0.89 (2087); [0.88, 0.89]	0.96 (16323); [0.95, 0.96]	0.90 (40); [0.82, 0.95]	0.97 (8379); [0.96, 0.97]	0.99 (10073); [0.98, 0.99]
NFHS-4	207364	0.971 (<0.001)	0.90 (41761); [0.89, 0.90]	0.94 (160553); [0.93, 0.94]	0.58 (5050); [0.56, 0.60]	0.88 (37871); [0.87, 0.88]	0.94 (163858); [0.93, 0.94]	0.77 (5635); [0.76, 0.78]	0.95 (79053); [0.94, 0.95]	0.99 (128311); [0.98, 0.99]
CNNS	34898	0.979 (<0.001)	0.90 (4850); [0.89, 0.91]	0.96 (29066); [0.96, 0.97]	0.76 (982); [0.73, 0.78]	0.89 (4251); [0.88, 0.90]	0.96 (29529); [0.96, 0.96]	0.82 (1122); [0.80, 0.84]	0.93 (1024); [0.92, 0.94]	0.98 (33874); [0.98, 0.98]

overweight (>2SD), but the overall prevalence was only 0.17%-0.22% (**Web Fig. 6**).

The mean (SD) age (months), height for age, weight for height, and BMI for age (*z*-scores) in the NFHS-4 survey were 28.3 (16.2), -1.46 (1.7), -0.93 (1.4), and -0.81 (1.4), respectively. Boys constituted 52% of the sample. The prevalence of possible risk of overweight with weight for height metric was higher in 0-0.5 years, but lower in 0.5-5 and 0-5 years (**Fig. 2**). The absolute differences in 0.5-5 years and overall sample were 2.26% (6.57% vs 8.83%) and 1.56% (7.23% vs 8.78%). In severely and moderately stunted children, the difference was much higher in 0-0.5 years (53.9% vs 11.6% and 39.1% vs 19.8%, respectively) in comparison to 0.5-5 years (11.9% vs 18.2% and 8.1% vs 12.5%, respectively). The differences decreased with increasing stature. The discrepancy was higher in boys. Similar patterns were evident for overweight (>2SD), but with a smaller magnitude of overall prevalence and absolute differences (**Web Fig. 6**). Kernel density plots confirmed a shift in the entire distribution, which was in opposite direction in 0-6 months and 6-59 months and of a greater magnitude in the stunted subjects (**Web Fig.7**).

The mean (SD) age (months), height for age, weight for height, and BMI for age (*z*-scores) of the CNNS dataset were 30.53 (16.8), -1.15 (1.5), -0.72 (1.3), and -0.60 (1.3), respectively. Boys comprised 52% of the sample. Patterns similar to NFHS were documented for both the possible risk of overweight (>1SD) and overweight (>2SD) and the kernel density plots; however, the magnitude of overall prevalence and differences was lower and not statistically significant at more time intervals (**Fig. 3**, and **Web Fig. 8**).

Misclassification occurred in both directions, being more evident in short populations (**Web Tables I** and **II**). In 0-0.5 years, children classified as overnourished by weight for height and not by BMI for age was more frequent than opposite misclassification. The reverse pattern was observed in 0.5-5 years, except for the Poland and Greenland simulated datasets.

The Bland-Altman analyses varied with age for the simulated short population. In the 0-6 months age group, thinner infants had lower

weight for height *z*-scores whereas obese infants had lower BMI for age *z*-scores (positive association between the difference and average of weight for height and BMI for age *z*-scores). An opposite but milder association was evident for 6-59 months. A similar but relatively milder pattern was seen in other data sets (**Web Table III**).

There was an excellent correlation between the two metrics in all data sets (r= 0.97–0.99; r^2 =0.94–0.98) (**Table II**). In general, in thin and overweight subjects, the correlation coefficients were significantly lower (non-overlapping 95% confidence intervals) than in those classified as normal with either the weight for height or BMI for age criteria. In the NFHS-4 and CNNS population, the correlation was weaker for obese subjects in comparison to thin subjects, whereas the converse was true for the tall populations. Further, the correlations were significantly, but slightly, weaker in stunted participants.

DISCUSSION

In under-five children, overnutrition definitions based on WHO's weight for height and BMI for age standards produced cutoffs, and hence prevalence estimates, that differed with the age, sex and height of subjects. Also, for a given height and weight, these characteristics were associated with subtle variations in the computed *z*-scores for these two metrics. Consequently, in Indian real-life datasets, representative of a short population, prevalence with weight for height was higher from 0-0.5 years (exclusive breastfeeding age), but lower for 0.5-5 years. The discrepancy was lower in girls and maximal for stunted children. In simulated datasets from intermediate and tall populations, there were no meaningful or marginal differences. This study focuses on the systematic comparison of these two metrics, using the WHO standards, for defining various grades of overnutrition in a LMIC setting. Consonance between theoretical considerations, simulations and real-life data sets enhances confidence in the findings.

There is a paucity of published data from LMIC settings for comparison. Theoretically, Cole first demonstrated with the National Centre for Health Statistics (NCHS), USA standards, that short children above 6 months of age appear thinner based on weight for height [16]. He suggested that weight/height^2 should be the preferred index to prevent misleading assessments in tall or short under-five children. With NCHS standards, in 4348 children from USA, aged 2-5 years, overweight (≥85th percentile) prevalence by weight for height was lower (0.9%-6%) than by BMI for age with greater differences in shorter children and at 4 years age [17].

Using WHO standards, in 547 diseased, 0-2 years old Canadian children, the prevalence of stunting was 23%. Their BMI for age and weight for length percentiles differed by >25 percentile points in ~9%, and ~16% in those below 6 months. Overweight (≥85th percentile) prevalence was higher with weight for length (21% vs 18.3%), with differences (18.2% vs 12.5%) in 0-6 months age, but comparable estimates (23.7% in both) for 6-24 months. Similar findings were evident for obesity (≥95th percentile; 12.2% vs 9.9%) [6]. In 0-2 years and under-five healthy children, from Canada [7] and USA [18], respectively, the prevalence of stunting was low. Weight for length and BMI for age demonstrated high agreement with comparable overweight prevalence. These findings are similar to our analyses, factoring for stunting prevalence and age strata. In an analysis on global prevalence and trends of overweight and obesity among preschool children, 450 nationally representative cross-sectional surveys from 144 countries were evaluated [19]. Both metrics yielded com-parable prevalence estimates in aggregated data from high income countries (HICs) (only graphical depiction), with similar results for other regions (text statement). In the absence of estimates related to stunting prevalence, age strata and sex, these findings cannot be compared with our analyses.

We depicted prevalence differences in under-five children with both 1SD and 2SD cutoffs. The former showed greater disagree-ment and are more relevant for LMICs, particularly India. First, this aligns the BMI for age cutoffs for defining overweight in under-five (currently 2SD) children and those aged 5-19 years (currently 1SD) [20], which allows pertinent comparisons across age ranges. Second, metabolic perturbations associated with increased ponderosity start manifesting at lower cutoffs in older children, adolescents and adults in India [21]. However, prevalence estimates based on arbitrary cutoffs (1SD or 2SD) may be of restricted utility, if the underlying process is continuous, and *z*-scores distribution could therefore be more meaning-ful for population monitoring [22]. We docu-mented a distributional shift too, compatible with the prevalence discrepancy. In the NFHS-4 survey, the mean *z*-scores differences ranged from 0.16 to 0.21, which are roughly comparable to effective interventions at population level [23]. The excellent correlations (r=0.97 to 0.99), observed by us and others [5-7, 17] summarize only the degree of linear relation between these two metrics and do not establish the interchangeability of the two stan-dards. The weaker correlations at the margins (>2SD or <-2SD), Bland-Altman analyses and 2×2 tabular depictions provide a deeper insight into the disagreement patterns.

Among limitations, real-life datasets from diverse settings of linear growth failure, and intermediate and tall

WHAT IS ALREADY KNOWN?

- Overnourished under-five children are anthropometrically classified as either being at possible risk of overweight, overweight or obese and defined so, when either weight for height or body mass index for age are >1SD to 2SD, >2SD to 3SD and >3SD, respectively of the analogous World Health Organization standards.

WHAT THIS STUDY ADDS?

- The two definitions produce cutoffs, and hence estimates of overnutrition, that differ with the age, sex, and height of under-five children.

populations were not evaluated; however, simulations partly address this gap. Also, biological outcomes were not studied for determining the comparative utility of these two metrics. Data from USA indicate that BMIZ and its change are better indicators of adiposity at 1 month age [8] and fat accrual during the first 5 postnatal months [24], respectively. However, analyses of USA and Belarus cohorts concluded that choice of weight for length vs BMI to define overweight during the first 2 years of life may not greatly affect the association with cardio-metabolic outcomes during early adolescence [9]. There is a paucity of similar studies from LMIC settings.

There are potential policy implications of these findings. In contrast to intermediate or tall populations, in nations with substantial stunting, weight for height compared with BMI for age, inflates the undernutrition burden [5] and simultaneously deflates the overnutrition estimates, especially in children aged 6-59 months. This magnifies the gap between the HICs and LMICs for 'malnutrition' (combined under- and over-nutrition) burden, and distorts the ranking and progress of nations in achieving the related SDGs. In routine Demographic National Surveys conducted in LMICs, the discrepancies in absolute prevalence may appear small. Nevertheless, with relatively lower overnutrition prevalence currently, these differences assume importance for urgently influencing investments and policy. The disagreements are likely to be larger and more relevant for granular planning, with over one-third of districts in India having stunting prevalence above 40% [25]. The misclassification will assume prominence for identifying eligible individuals in public health programmes. BMI for age offers an additional advantage of using a uniform metric from birth till adulthood for identifying both thinness and obesity. Unlike weight for height, BMI for age like height or weight for age, requires an accurate evaluation of age, which could rarely become a limitation. Global stakeholders' decision to replace or complement the weight for height indicator with BMI for age, for national, sub-national and individual use, should therefore be based on evidence-based consideration of potential benefits, harms and costs (financial and logistic) involved, including for potential biological outcomes like adiposity and cardiometabolic risk factors in later life.

In conclusion, weight for height and BMI for age definitions produce estimates of overnutrition, which vary with the age, sex and height of children. In populations with substantial stunting, in under-five children and especially those aged 6-59 months, overnutrition estimates are lower with weight-for-height criterion, but there are no meaningful differences in intermediate or tall populations. The relative invariance of BMI for age with age and stature, and establishment of a uniform metric definition from birth to adulthood, justifies its preference for classifying overnutrition in under-five children.

Ethics clearance: Authors confirm that such approval is not needed for these theoretical simulations and secondary analyses of data from other studies for which the requisite ethical permissions had been obtained. Authors declare that the study procedures conform to the principles laid down in the Declaration of Helsinki.

Contributors: HSS: conceptualized the study; LNR: primary analyses and interpretation under the supervision of MS, CO and HSS; LNR,HSS: drafted the initial manuscript. All authors provided critical inputs into revision of the article and are willing to be accountable for all aspects of the study.

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

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Web Table I Summary of Disagreement in Possible Risk of Overweight (>1 SD) Classification

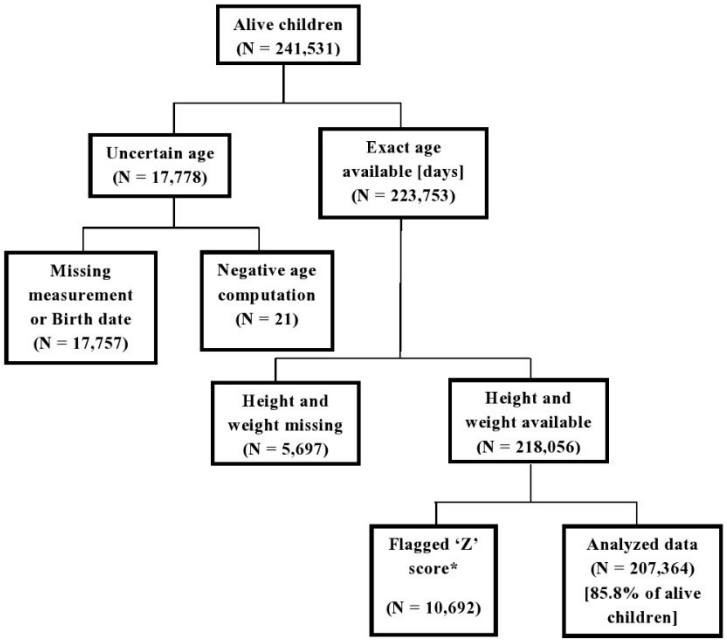
Datasets	*Age-groups (years)*							
	0.0-0.5				*0.5 - 5.0*			
	Overweight by weight-for-height but not by BMI-for-age (%) (a)	*Not overweight by weight-for-height but by BMI-for-age (%) (b)*	*Total (a+b)*	*Ratio (a/b)*	*Overweight by weight-for-height but not by BMI-for-age (%) (c)*	*Not overweight by weight-for-height but by BMI-for-age (%) (d)*	*Total (c+d)*	*Ratio (c/d)*
Short simulated from NFHS-4	11.9	0.2	12.1	54.0	0.3	3.1	3.3	0.1
Intermediate Population	3.4	2.1	5.4	1.6	1.0	1.1	2.1	0.9
Tall population simulated from								
Poland	2.3	3.8	6.2	0.6	1.5	1.1	2.6	1.3
Greenland	2.3	5.8	8.2	0.4	2.5	1.4	3.9	1.8
NHANES	4.3	3.6	7.9	1.2	1.2	2.1	3.3	0.6
Real-life datasets								
Meerut study	Not sampled	Not sampled	Not sampled	Not sampled	0.0	0.8	0.9	0.0
NFHS-4	5.2	0.4	5.6	14.0	0.2	2.4	2.6	0.1
CNNS	2.8	1.1	4.0	2.6	0.2	1.9	2.1	0.1

Web Table II Summary of Disagreement in Overweight (>2SD) Classification

Datasets	*Age-groups (years)*							
	0.0-0.5				*0.5 - 5.0*			
	Overweight by weight-for-height but not by BMI-for-age (%) (a)	*Not overweight by weight-for-height but by BMI-for-age (%) (b)*	*Total (a+b)*	*Ratio (a/b)*	*Overweight by weight-for-height but not by BMI-for-age (%) (c)*	*Not overweight by weight-for-height but by BMI-for-age (%) (d)*	*Total (c+d)*	*Ratio (c/d)*
Short simulated from NFHS-4	5.30	0.03	5.33	176.67	0.13	1.06	1.19	0.12
Intermediate Population	0.53	0.63	1.16	0.84	0.21	0.25	0.46	0.84
Tall population simulated from								
Poland	0.54	1.82	2.36	0.30	0.58	0.46	1.04	1.26
Greenland	0.78	2.41	3.19	0.32	0.82	0.64	1.46	1.28
NHANES	1.53	1.65	3.18	0.93	0.57	1.00	1.57	0.57
Real-life datasets								
Meerut study	Not sampled	Not sampled	Not sampled	Not sampled	0.05	0.17	0.22	0.29
NFHS-4	3.57	0.13	3.70	27.46	0.08	0.77	0.85	0.10
CNNS	1.67	0.30	1.97	5.57	0.06	0.64	0.70	0.09

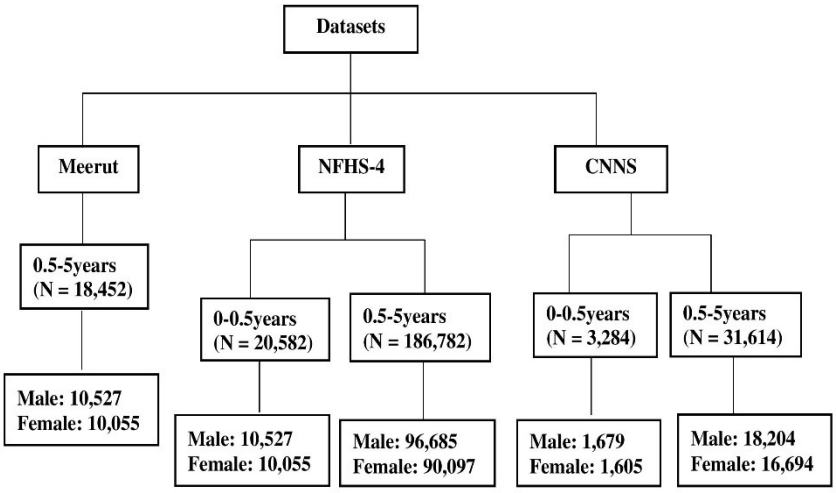
Web Table III Regression Coefficients Between the Difference and Average of Weight-for-height and Body-Mass-Index-for-Age *Z*-scores in Various Datasets

Datasets	*β coefficient (SE); P value*			
	Male		*Female*	
	0-6 months	*6-59 months*	*0-6 months*	*6-59 months*
Simulated Populations				
Short (NFHS-4)	0.2 (0.0); *<0.0001*	-0.1 (0.0); *<0.0001*	0.2 (0.0); *<0.0001*	-0.1 (0.0); *<0.0001*
Intermediate Population	0.0 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0);*<0.0001*
Tall				
Greenland	0.1 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*
NHANES	0.1 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.0 (0.0); <0.0001
Real-life datasets				
Meerut Study	Not sampled	0.0 (0.0); *0.314*	Not sampled	-0.1 (0.0); *<0.0001*
NFHS-4	0.2 (0.0); *<0.0001*	0.1 (0.0); *<0.0001*	0.2 (0.0); *<0.0001*	-0.1 (0.0); *<0.0001*
CNNS	0.1 (0.0); *<0.0001*	0.0 (0.0); *<0.0001*	0.1 (0.0); *<0.0001*	-0.2 (0.0); *<0.0001*

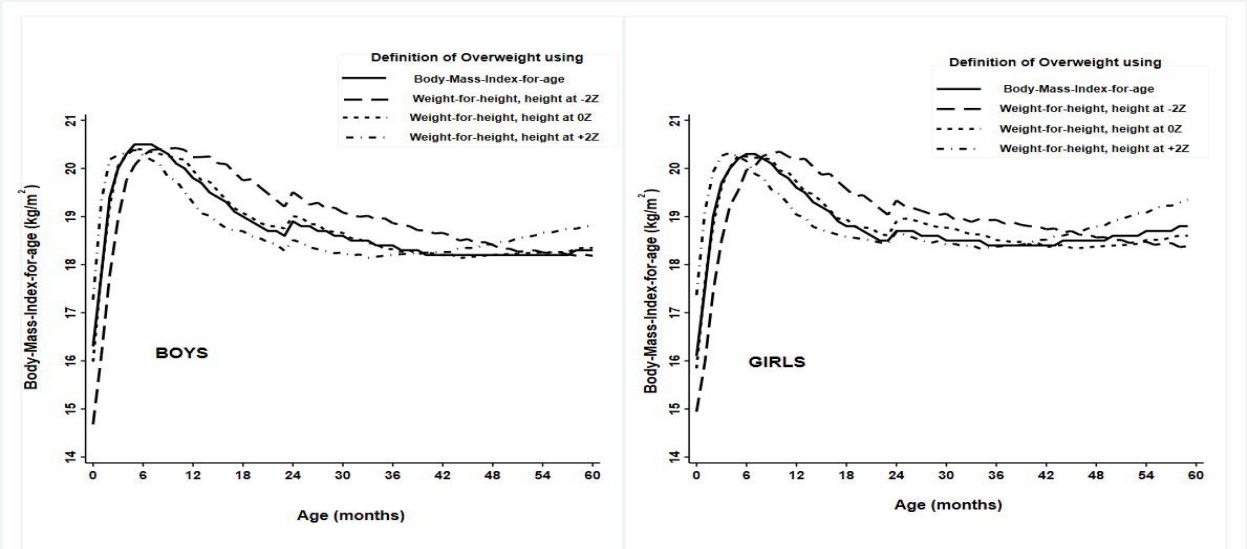


* *Weight-for-age z-score <-6 or >5; Length/Height-for-age z-score <-6 or >6; BMI-for-age z-score <-5 or >5; Weight-for-length/height z-score <-5 or >5*

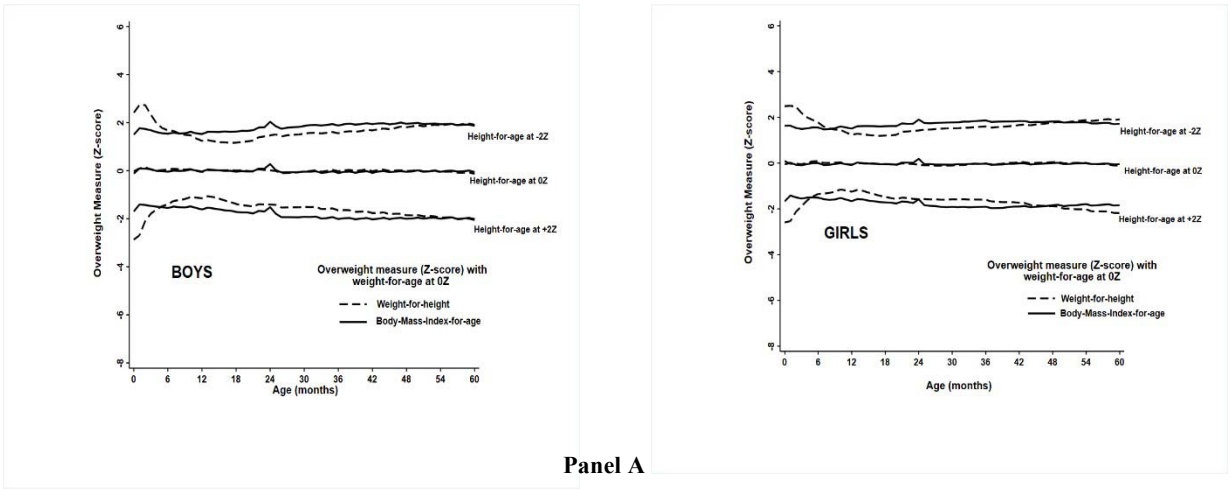
Web Fig. 1 Flowchart for arriving at the analytic sample in NFHS-4 dataset.



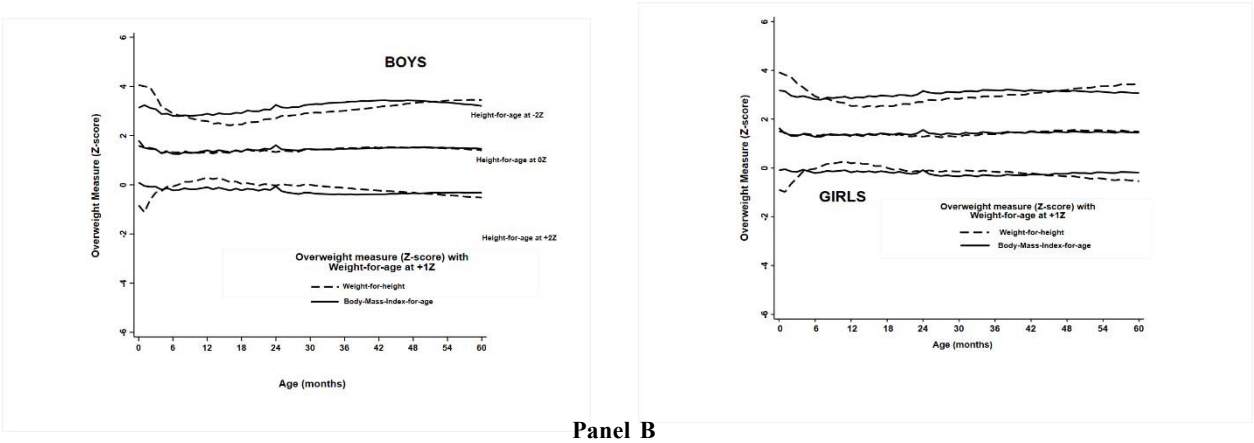
Web Fig. 2 Flowchart for Showing the Details of Children (age-wise and gender-wise) in Each of the Datasets



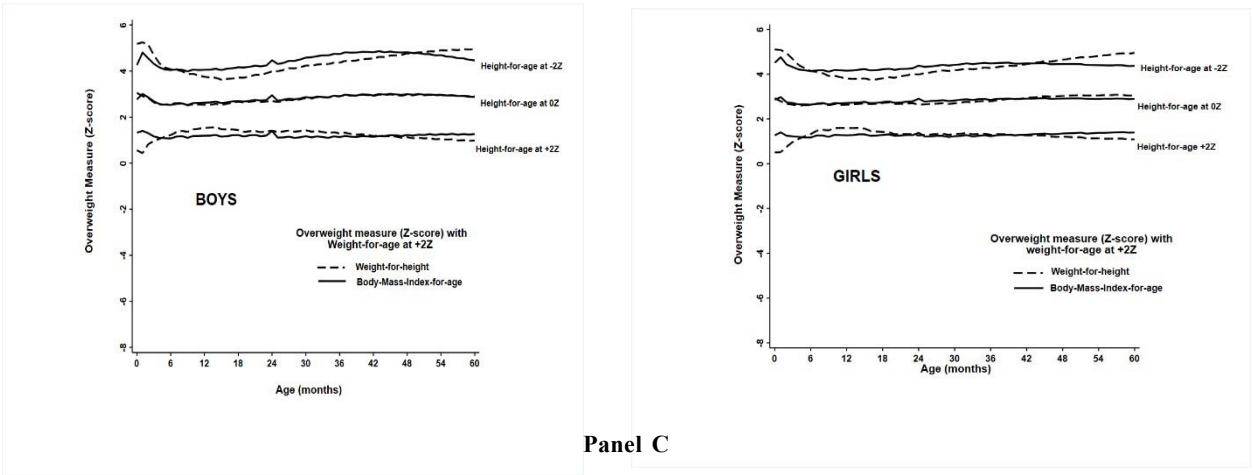
Web Fig. 3 Comparison of absolute Body-Mass-Index cut-offs for defining overweight (>2SD) according to weight-for-height and Body-Mass-Index-for-age criteria in boys (left side) and girls (right side) whose height is at -2SD, 0SD and +2SD of World Health Organization growth standards.



Panel A

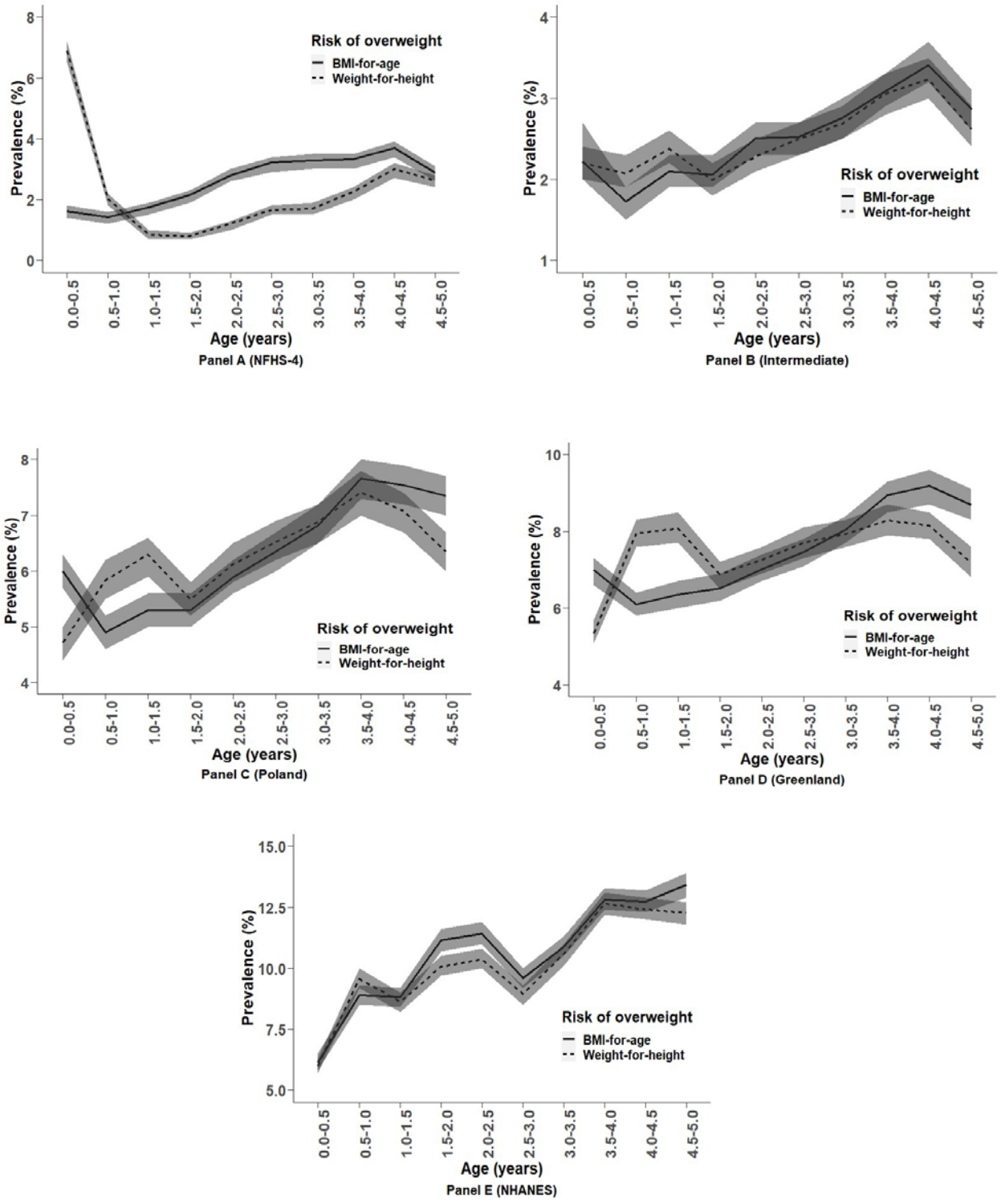


Panel B

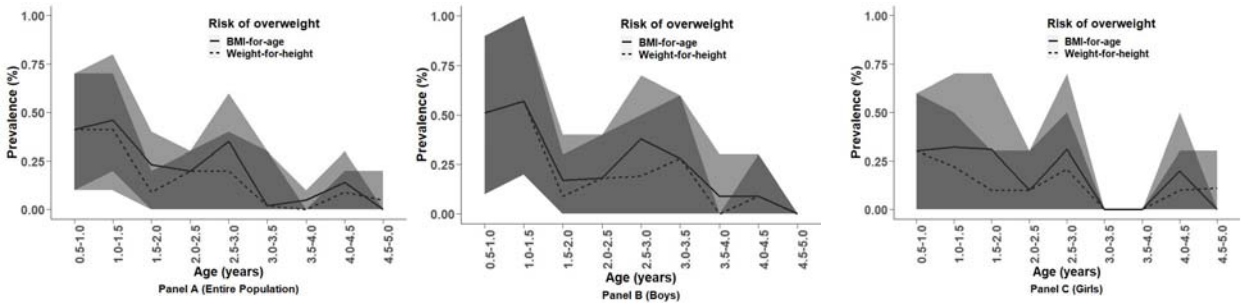


Panel C

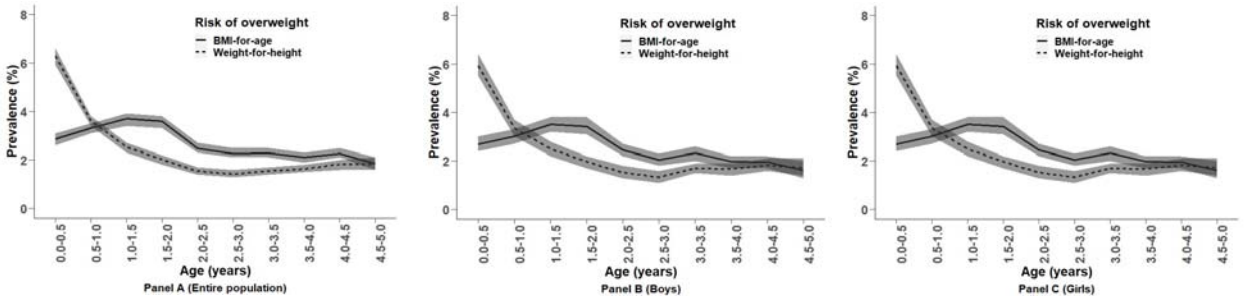
Web Fig. 4 Comparison of z-scores of weight-for-height and Body-Mass-Index-for-age for a fixed height-for-age (-2SD, 0SD, and +2SD) in boys (left side) and girls (right side) whose weight-for-age is at 0SD (Panel A), +1SD (Panel B) and +2SD (Panel C) of WHO growth



Web Fig. 5 Comparison of estimated prevalence and 95% confidence intervals of risk of overweight (>2SD) using weight-for-height and Body-Mass-Index-for-age criteria on simulated populations: Panel A - short based on the National Family Health Survey-4, India data; Panel B - intermediate; Panels C, D and E - tall based on Poland, Greenland and the National Health and Nutrition Examination Survey, USA data, respectively.

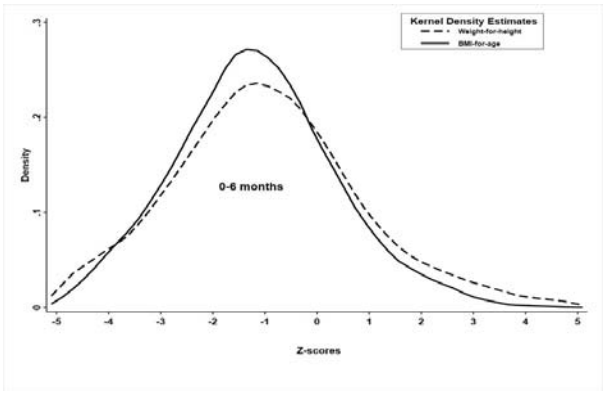


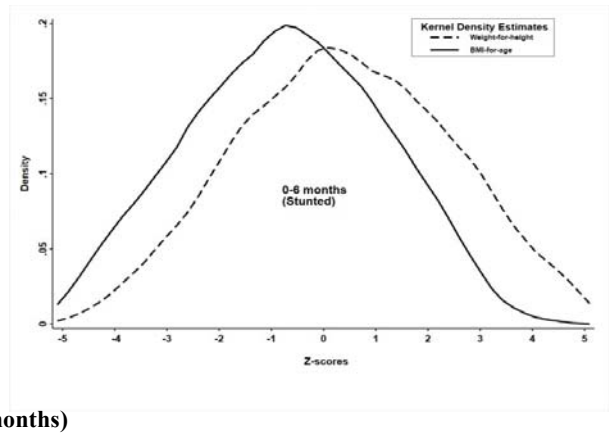
Meerut Study



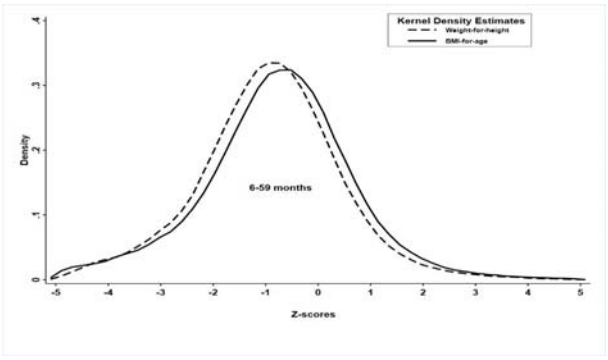
NFHS-4

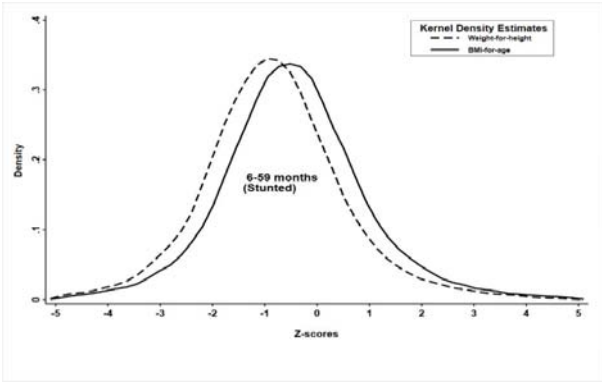
Web Fig. 6 Comparison of estimated prevalence and 95% confidence intervals of overweight (>2SD) using weight-for-height and Body-Mass-Index-for-age criteria in Meerut (above) and National Family Health Survey-4 (below), India datasets: Panel A – Entire population, Panel B – Boys, and Panel C – Girls.





(0-6 months)

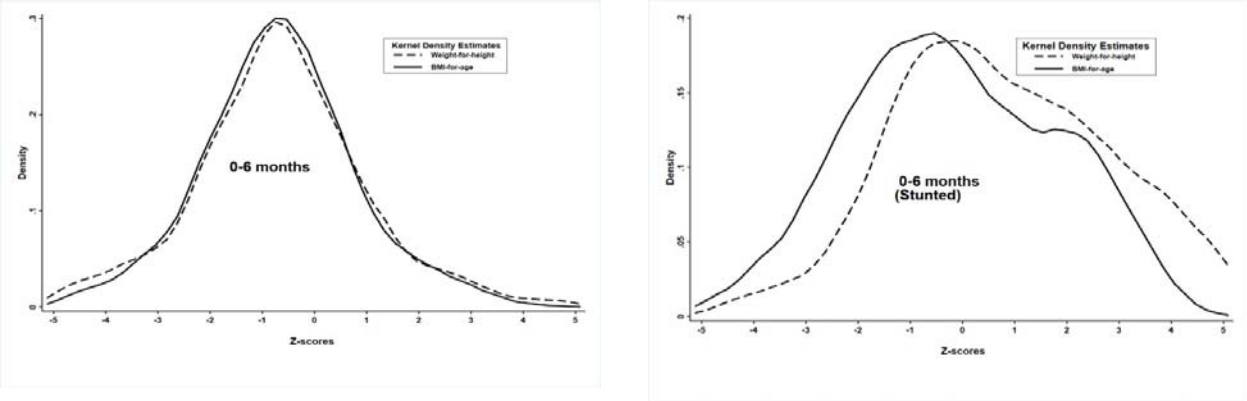




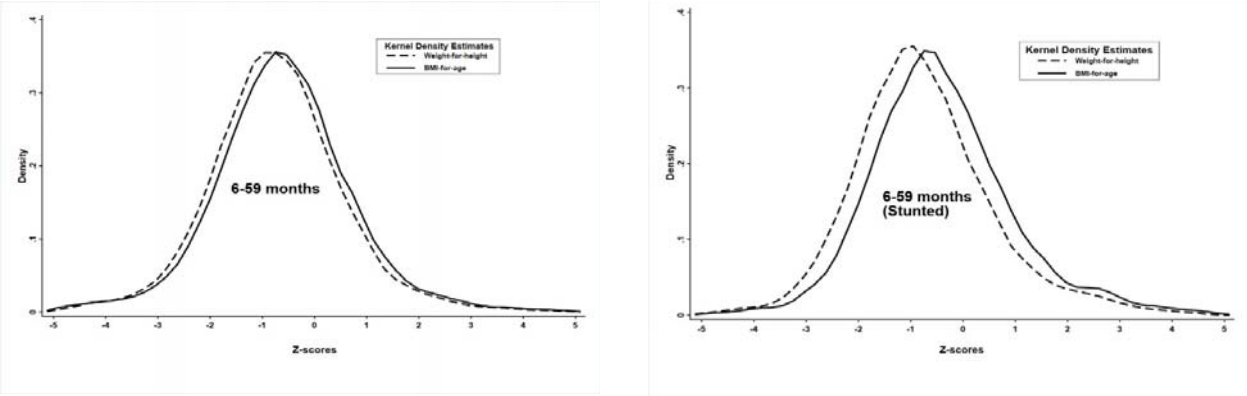
(6-59 months)

Panel A **Panel B**

Web Fig 7 Kernel density estimates for z-scores of Weight-for-height and Body-Mass-Index-for-age in NFHS 4 dataset: Panel A: Overall and Panel B: Stunted.



(0-6 months)



(6-59 months)

Panel A **Panel B**

Web Fig. 8 Kernel density estimates for z-scores of weight-for-height and Body-Mass-Index-for-age in Comprehensive National Nutrition Survey dataset: Panel A: Overall and Panel B: Stunted.

RESEARCH PAPER

Effect of Kangaroo Mother Care on Cerebral Hemodynamics in Preterm Neonates Assessed by Transcranial Doppler Sonography in Middle Cerebral Artery

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Objective: To study the effect of KMC in premature newborns on cerebral hemodynamics in the middle cerebral artery (MCA) using transcranial doppler sonography.

Methods: In this descriptive study, 40 clinically stable preterm neonates admitted to the neonatal intensive care unit of our institute and undergoing Kangaroo mother care (KMC) were enrolled. Physiological and cerebral blood flow parameters of MCA were obtained by using transcranial doppler sonography at baseline, at 60 minutes of KMC, and after 60 minutes of stopping KMC.

Results: Of the 40 enrolled neonates (24 males), the mean (SD) birth weight, gestation age, and postnatal age were 1698.25 (495.44) g, 33.00 (1.67) wk, and 6.80 (4.51) days, respectively. The mean (SD) cerebral blood flow velocities increased (peak systolic velocity (PSV), *P*=0.03; end diastolic velocity, *P*<0.001; mean velocity, *P*<0.001) and doppler indices decreased (resistive index, *P*=0.001; pulsatility index, *P*<0.001) significantly; whereas, heart rate (*P*<0.001) decreased but SpO2 (*P*=0.001) and mean blood pressure (*P*=0.003) increased significantly at 60 minutes of KMC as compared to baseline. Sixty minutes after stopping KMC, all parameters (except PSV) were higher than baseline, indicating post KMC effect.

Conclusion: KMC improves cerebral hemodynamics in clinically stable preterm neonates.

Keywords: *Benefit, Cerebral blood flow, Neonatal care, Outcome*.

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Premature neonates, born across the globe, spend their first few weeks of life in the neonatal intensive care unit (NICU) [1], where they are subjected to an abnormal environment and multiple invasive procedures. The neonatal period is the critical period of brain development and maturation [2]. Preterm neonates are especially susceptible to brain injury as they have immature cerebral vasculature and ineffective cerebral autoregulation, leading to the marked fluctuation in cerebral blood flow [3,4]. This results in cerebrovascular events like intraventricular hemorrhage and ischemic injury to periventricular white matter, which have long-term adverse neurodevelopmental problems in cognitive, motor, and behavioral domains [5].

Globally, during the last two decades, there has been significant improvement in the survival of extremely preterm neonates due to advanced perinatal and neonatal intensive care practices. Increased survival has also resulted in increased neuro-morbidity among the survivors. Hence, neuroprotective strategies are required to improve cerebral hemodynamics [6]. Kangaroo mother care (KMC), an evidence-based standard of care for preterm neonates [7-10], positively influences the premature brain networks, facilitates the formation of neural connections, and leads to better long-term neurodevelopmental outcomes [11].

Invited Commentary: Pages 13-14

Most studies on KMC have focused on thermoregulation, pain control intervention, physical growth, mortality and sepsis reduction, success with breastfeeding, and improvement in cardiorespiratory parameters. However, the effect of KMC on cerebral blood flow and its dynamics in preterm has not been studied well. Transcranial color Doppler sonography is an excellent, non-invasive modality for real-time assessment of cerebral blood flow in newborns [12]. Color Doppler imaging of the middle cerebral artery (MCA) displays various cerebral blood flow parameters, which helps to evaluate alterations in cerebral hemodynamics [13]. The current study aims to evaluate the changes in cerebral blood flow patterns and velocities in MCA by using transcranial color Doppler before and after KMC in clinically and hemodynamically stable preterm neonates.

METHODS

A single- arm interventional study was conducted between September, 2020 to May, 2021 at Level 3 NICU in a Medical college in Anand, Gujarat, India, enrolling all clinically and hemodynamically stable preterm neonates (28 0/7 to 36 6/7 weeks gestational age) admitted to NICU or KMC ward. Exclusion criteria were neurological impairment (perinatal depression and hypoxic-ischemic encephalopathy, intra-ventricular hemorrhage, hydrocephalus, stroke, seizure or congenital malformation of the central nervous system), congenital heart disease, critical illness rendering the babies unstable (needing invasive mechanical ventilation and/or inotropes), administration of pain control/sedative medications within 24 hours before study interventions, and neonatal abstinence syndrome.

In the absence of any regional estimates of the standard deviation of outcome variables, it was not possible to calculate the exact sample size. The study period was planned for around nine months expecting to enrol around 35 participants.

After obtaining written informed consent from parents, the baseline physiological parameters [heart rate (HR), oxygen saturation (SpO_2), and blood pressure (BP)] and cerebral blood flow parameters of MCA were obtained by using transcranial color Doppler ultrasonography in a supine position under a radiant warmer. After that, neonates were given KMC for the first time as per standard positioning technique, for a minimum of 60 minutes. All cerebral blood flow parameters and physiological parameters were obtained at 60 min of KMC and 60 minutes after stopping KMC. All neonates were examined in a calm and resting state without any sedation. Cerebral blood flow parameters were obtained by Doppler imaging evaluation of the middle cerebral artery using Transcranial color Doppler (TCD) ultrasonography machine (Sonosite, Model-EDGE-Fifth generation portable ultrasound, Sr. no-03P565) with a high resolution phased array transducer (Model P10x) of 8-4 MHz. All cranial ultrasound examinations were performed by a Neonatology fellow having expertise in neonatal cranial ultrasound. Color Doppler imaging with pulsed wave Doppler (PWD) was used to identify MCA from the temporal window. The cerebral blood flow velocities (CBFVs) and Doppler indices (RI and PI) measured included *i*) Peak systolic velocity (PSV): Highest velocity in the cardiac cycle; *ii*) End diastolic velocity (EDV): Lowest velocity at the end of the cardiac cycle; *iii*) Mean velocity (MV): Calculated over a series of cardiac cycles; *iv*) Resistive Index (RI): (PSV-EDV)/PSV; and *v*) Pulsatility index (PI): (PSV-EDV)/MV.

Statistical analysis: Paired *t* test was used to compare physiological and cerebral blood flow Doppler parameters at baseline (before KMC), at 60 min KMC and after 60 min of KMC. Pearson correlation coefficient was used to correlate cerebral blood flow parameters with gestational age and birth weight. The analysis was performed using STATA (14.2). A *P* value of less than 0.05 was considered significant.

RESULTS

Of a total of 152 preterm neonates admitted in NICU, 93 neonates did not meet the inclusion criteria, mothers of 15 eligible neonates were not available to provide KMC as they were COVID-19 positive and sick, and mothers of four neonates refused to participate. So, 40 (24 (60%) males) clinically stable preterm neonates were enrolled in the study, with 27(67.5%), 11(27.5%) and 24 (60%) being appropriate for gestation age (AGA), small for gestation age (SGA) and late preterm babies, respectively. The mean (SD) gestational age, birth weight, and postnatal age of the participants was 33.05 (1.68) weeks, 1698.25 (495.44) g, and 6.8 (4.52) days, respectively.

All the mean cerebral blood flow parameters of MCA Doppler viz., PSV, EDV, MV, RI and PI improved significantly at 60 minutes of KMC compared to baseline

Table I Cerebral Blood Flow Parameters of Middle Cerebral Artery Doppler at Different Durations of Kangaroo Mother Care (KMC) (*N*=40)

Parameters	*Before KMC (Baseline)*	*At 60 min of KMC*	*MD (95% CI)[a]; P value*	*60 min after stopping KMC*	*MD (95% CI)[b]; P value*
PSV (cm/s)	43.9 (3.76)	44.8 (3.94)	-0.90 (-1.70,-0.90); 0.030	43.8 (3.45)	0.12 (-0.59,0.82); 0.74
EDV (cm/s)	10.8 (1.30)	11.8 (1.33)	-0.97 (-1.41,-0.54); <0.001	11.4 (1.1)	-0.66 (-0.96,-0.36); <0.001
MV (cm/s)	21.8 (1.90)	22.8 (1.91)	-0.92 (-1.39,-0.46); <0.001	22.2 (1.64)	-0.38 (-0.73,-0.03); 0.032
RI	0.7 (0.02)	0.7 (0.03)	0.02 (0.01,0.03); 0.001	0.7 (0.023)	0.16 (0.01, 0.020); <0.001
PI	1.5 (0.09)	1.4 (0.11)	0.07 (0.03,0.11); <0.001	1.4 (0.09)	0.06 (0.04,0.09); <0.001

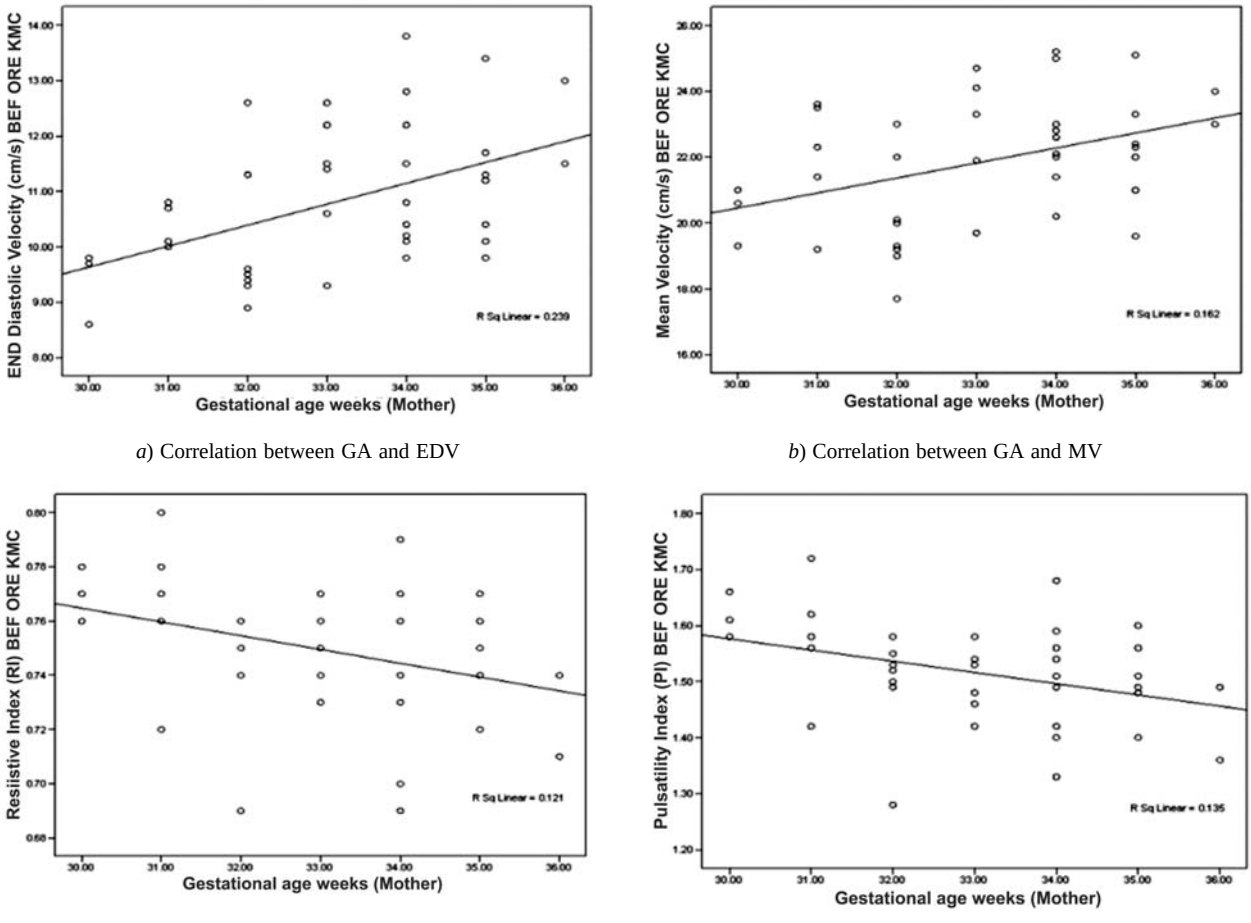
All values in mean (SD). MD-mean difference. [a]before KMC–at 60 min of KMC. [b]before KMC–60 min after stopping KMC. SpO2-oxygen saturation; BP-blood pressure; PSV-peak systolic velocity; EDV-end diastolic velocity; MV-mean velocity; RI- resistive index; PI-pulsatility index.

values. The values were higher than baseline at 60 minutes after stopping KMC except for PSV (**Table I**). Similarly, the physiological parameters viz. SpO2, heart rate, and mean blood pressure showed significant improvement at 60 minutes of KMC from baseline, whereas systolic and diastolic blood pressure remained similar. The effect was sustained only for mean blood pressure after 60 minutes of stopping KMC (**Table II**).

Table II Physiological Parameters of Middle Cerebral Artery Doppler at Different Durations of Kangaroo Mother Care (*N*=40)

Parameters	*Before KMC (Baseline)*	*At 60 min of KMC*	*MD (95% CI)[a]; P value*	*60 min after stopping KMC*	*MD (95% CI)[b]; P value*
Heart rate (per min)	148.8 (10.42)	143.6 (11.24)	5.23 (2.95,7.50); <0.001	146.1 (10.55)	2.65 (-0.05, 5.35); 0.05
SpO2 (%)	95.7 (1.40)	96.5 (1.50)	-0.88 (-1.38,-0.37); 0.001	95.8 (1.82)	-0.18 (-0.76, 0.41); 0.55
Systolic BP(mmHg)	64.0 (7.81)	64.6 (8.73)	-0.63 (-1.84, 0.59); 0.31	63.9 (8.38)	0.05 (-1.34, 1.44); 0.94
Diastolic BP (mmHg)	42.2 (6.96)	43.3 (6.75)	-1.05 (-2.44, 0.34); 0.14	43.3 (6.83)	-1.08 (-2.69, 0.54); 0.19
Mean BP (mmHg)	45.1 (7.59)	46.9 (8.32)	-1.73 (-2.81,-0.64); 0.003	47.1 (7.81)	-1.93 (-3.11,-0.74); 0.002

All values in mean (SD). KMC-kangaroo mother care; MD-mean difference, [a]before KMC–at 60 min of KMC, [b]before KMC–60 min after stopping KMC. SpO2-oxygen saturation; BP-blood pressure.



a) Correlation between GA and EDV

b) Correlation between GA and MV

c) Correlation between GA and RI

d) Correlation between GA and PI

EDV: end diastolic velocity, MV: mean velocity, RI: resistive index, PI: pulsatility index.

Fig. 1 Correlation between gestational age (GA) and cerebral blood flow (CBF) parameters in preterm infants undergoing kangaroo mother care (KMC).

Table III Correlation Between Birth Weight and Cerebral Blood Flow (CBF) Parameters of Middle Cerebral Artery Doppler at Baseline Before Kangaroo Mother Care (*N*=40)

CBF parameters	*Correlation coefficient*	*P value*
PSV	0.362	0.022
EDV	0.552	<0.001
MV	0.505	0.001
RI	-0.324	0.042
PI	-0.361	0.022

PSV: peak systolic velocity; EDV: end diastolic velocity; MV: mean velocity; RI: resistive index; PI: pulsatility index.

On evaluating the correlation between cerebral blood flow parameters of MCA Doppler at baseline and gestation age (**Fig.1**) and birth weight (**Table III**), it was seen that while EDV (r=0.49) and MV (r= 0.40) were significantly positively correlated with gestation age, RI (r = -0.35) and PI (r = -0.37) were significantly negatively correlated with gestation age. Although, PSV (r=0.26) had a positive correlation with gestation age, it was not statistically significant. The correlation between cerebral blood flow parameters of MCA Doppler and gestational age are shown in **Fig. 1**.

DISCUSSION

The current study determined the impact of KMC on cerebral hemodynamics in MCA and physiological parameters. There was a statistically significant improvement in all CBF parameters at 60 minutes of KMC compared to baseline. However, these changes in CBF parameters were within the normal range. The trend of improving CBF parameters was still evident at 60 minutes of stopping KMC except for the PSV, which was closer to the baseline values. As this effect of KMC was studied only up to 60 minutes after stopping KMC, the effect after that is unknown. We also found significant correlation between CBF parameters at baseline and gestation age and birth weight. Further, this study showed a positive impact of KMC on cardiorespiratory parameters, the effect was sustained only for mean blood pressure post 60 minutes of stopping KMC.

KMC has emerged as a safe, feasible, and low-cost intervention for neonates, with significant benefits [14,15]. The beneficial effects of KMC on cerebral hemodynamics in preterm neonates are yet to be fully explored. Neurophysiological effects of KMC might mediate improvement in cerebral blood flow. Skin-to-skin care by the mother provides multisensory stimulation, including tactile, auditory, and olfactory. All these may have a tranquilizing effect on the baby, allowing physiological parameters to stabilize, facilitating neural connections, enhancing synaptic efficacy and connectivity of cerebral motor pathways. It also enables better quality of quiet sleep and induces non-chaotic sleep patterns and normal sleep cycling [9]. Nelson and Panksept's brain opioid theory of social attachment, based on animal experimentation, postulates that maternal touch, smell, and milk release endogenous opiates, which are known to promote affiliative behavior [16]. Oxytocin is the primary hormone promoting affiliation and appears to have anti-nociceptive effects. Activation of slow-conducting unmyelinated afferents by pleasant touch stimulates the cortex to produce various vasodilatory mediators and induces nitric oxide-mediated smooth muscle relaxation of cerebral microvasculature [17,18]. Hence, KMC might positively influence cerebral hemodynamics in the preterm brain by these various proposed mechanisms.

Korraa, et al. [19], in a similar study in Egypt, recruited 60 clinically stable preterms and measured CBF parameters in MCA before and after 30 min of KMC. This study demonstrated a significant increase in CBFVs (EDV and MV) and a significant decrease in Doppler indices (RI and PI) after 30 minutes of KMC, indicating improvement in CBF following KMC application. Other authors [20-22] also observed a correlation between all CBFVs and gestational age. Thus, the current study results are concordant with these previously published studies.

Similar to the study by Seibert, et al. [23], Doppler indices (RI and PI) showed a significant decrease with increasing gestational age in the current study. Nourian, et al. [24] suggested that the effect of KMC on the physiological parameters remains sustained. Azeez, et al. [25] also found that the majority of babies who received KMC showed significant improvement in vital parameters. Pezzati, et al. [22] generated normal reference data for MCA CBF parameters in preterm infants and demonstrated association with GA and BW. The current study additionally helped in the establishment of a normative database for MCA cerebral Doppler measurements in stable preterm infants.

The residual effect on many parameters even after 60 minutes suggests that KMC may be working through the release of various hormones or neurotransmitters which have a half-life of more than 60 minutes. As KMC is a multimodal intervention and achieves its actions through various mechanisms, it is difficult to isolate a single or few hormones/neurotransmitters that are responsible for it. Duration of KMC has a dose-relation-ship effect on the size of the grey matter, especially the left caudate nucleus, as shown by a 20-year follow-up study [11]. We now have some evidence that KMC alters circulatory flow in the

WHAT IS ALREADY KNOWN?

- Most of the studies on Kangaroo Mother Care have focused on thermoregulation, pain control intervention, physical growth, breastfeeding, mortality, and sepsis reduction.

WHAT THIS STUDY ADDS?

- KMC improves cerebral hemodynamics response by improving cerebral blood flow in hemodynamically stable preterm neonates.

brain, which might ensure appropriate growth of neurons and thus their function [26]. The residual effect following stopping KMC, as shown in the current study, suggests that short breaks between KMC sessions due to change in KMC providers/KMC provider fatigue may not deprive preterm neonates of the beneficial effects of KMC. A recently published i-KMC trial showed that low birth weight babies who were provided continuous KMC initiated immediately after birth experience a reduced risk of mortality compared with a similar group in whom KMC is initiated only after clinical stabilization [27].

The pre-requisite of enrolling only hemodynamically stable newborns in this study limited the application of KMC to other newborns. The sample size was also small across gestations, and we do not have data on the long-term neurodevelopmental follow up.

The current study showed a positive impact of KMC on cerebral hemodynamic response by improving cerebral blood flow in hemodynamically stable preterm neonates. It also shows it stabilized cardiorespiratory para-meters and thus positively influences the physiological stability of preterm neonates**.** Further research could compare cerebral blood flow Doppler parameters between babies who were initiated on KMC after birth and those in whom KMC is initiated after clinical stabilization.

Ethics clearance: IEC, HM Patel Centre for Medical Care and Education; No. IEC/HMPCMCE/123/Faculty/2/246120, dated Oct 22, 2020.
Contributors: AC: conceptualized and designed the study, undertook data collection, and reviewed and revised the manuscript; SN: conceptualized and designed the study, coordinated and supervised the analysis, and substantially reviewed and revised the manuscript; DP: conceptualized the study, contributed to the data collection, and reviewed and revised the manuscript; AP: conceptualized the study, conducted the analysis, and reviewed the manuscript for important intellectual content. 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.

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RESEARCH PAPER

Growth and Neurodevelopmental Outcomes of Very Low Birth Weight Infants From Southern India at Corrected Age of One Year

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Objective: To assess the growth and neurodevelopmental outcome of very low birth weight (VLBW) infants at corrected age of one year. **Methods:** This prospective cohort study enrolled VLBW infants delivered in a tertiary care hospital, and followed up till one-year corrected age. The WHO Anthropo version 3.2.2 software was used to calculate weight for age, length for age, and head circumference *z*-score during follow up. Neuro-developmental assessment was done using Developmental Assessment Scale for Indian Infants (DASII) at the age of one year. **Results:** The mean (SD) *z*-scores at one-year for weight for age, length for age and head circumference were -2.1 (1.1), -1.4 (1.03) and -2.2 (1.2), respectively. The mean (SD) DASII motor and mental scores were 90.8 (13.4) and 96.5 (13.2), respectively. Major and minor developmental abnormalities were noted in 9.4% and 18.2%, infants, respectively. Cerebral palsy was noted in 5.8% infants. **Conclusion:** VLBW infants showed impaired growth and significant developmental abnormalities at the corrected age of one year.

Keywords: *Cerebral palsy, Development quotient, High risk follow up*.

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VLBW neonates contribute to 1.4- 2.1% of total live births [1,2]. With an increase in the incidence of prematurity and better neonatal care, the number of very low birth weight (VLBW) survivors is increasing, who are prone to short term adverse outcomes and long-term neurodevelop-mental problems [3]. In the earlier Pune study [4], preterm small for gestational age infants and VLBW infants had the poorest cognition at the age of 12 years. There is paucity of literature from southern India related to long-term out-comes of VLBW infants. This study was done to assess the growth and neurodevelopmental outcomes of VLBW infants at corrected age (CA) of one-year.

METHODS

This prospective cohort study was conducted at a tertiary care teaching hospital in southern India from January, 2017 to December, 2018 after approval from institutional ethics committee. All VLBW inborn neonates delivered in the hospital during the study period were enrolled after obtaining informed consent from the parents. Neonates with one or more of the following were excluded: *i*) birth weight <500 g and/or gestational age (GA) less than 25 weeks; *ii*) presence of lethal congenital malformations, and *iii*) death within 6 hours of life. All neonates were managed as per standard neonatal intensive care unit (NICU) protocols.

Relevant antepartum and intrapartum details including mother's age, parity, associated medical or pregnancy related complications, ultrasound findings, antenatal steroid use, fetal distress, and mode of delivery were recorded from maternal case records on a pre-structured form. Gestational age was determined by first trimester scan findings or new Ballad score. In case of discrepancy between these two methods, first trimester scan findings were preferred. Neonatal data including gender, birth weight, resuscitation details and Apgar scores were recorded. Co-morbidities observed during the NICU stay were also recorded. Enrolled infants were assessed within 24 hours of birth, at discharge, 40 weeks of CA, and subsequently at CA of 3, 6, 9 and 12 months with time tolerance limit of ± 7 days on the day of assessment at high risk follow up clinic.

Invited Commentary: Pages 15-16.

At each visit to the clinic, the infant was evaluated for anthropometric measurements, clinical assessment of vision and hearing, neurological examination and develop-mental assessment. Vision was assessed by the ability to fix and follow a target and hearing was checked using a bell. Screening for retinopathy of prematurity (ROP) was done first at 3 weeks of CA in eligible neonates and was classified according to the International Classification of

Retinopathy of Prematurity (ICROP) [5]. Hearing screening was done by oto-acoustic emission (OAE) (Interacoustics Titan TEOAE 440) at 34 weeks of gestation or prior to discharge, whichever was later. Infants who failed on OAE were further assessed by brain evoked response auditory (BERA) in the Ear Nose and Throat (ENT) department of the Institute. Cranial ultrasonography was done as per the unit protocol.

Weight, length and head circumference were measured using infant weighing scale, infantometer and non-stretchable tape, respectively. All equipment were calibrated and standard precautions were taken during measurements by the first author. Growth was assessed by measuring weight for age, length for age and head circumference for age. Growth was plotted on Fenton charts for boys and girls till 40 weeks of CA, after which WHO child growth standards were used till one-year CA. Growth parameters were entered in WHO Anthropo version 3.2.2 to calculate the *z*-score. A single trained researcher carried out all the neurological and anthropometric evaluations.

The neurodevelopmental assessment was done at one-year CA using Developmental Assessment Scale for Indian Infants (DASII), which is an Indian adaptation of Bayley scales of infant development (BSID) [6]. Development score less than 70 was considered as severe delay [7]. Major neurodevelopmental abnormality was defined if at least one of the following was present *i*) Cerebral palsy, *ii*) development quotient less than 70% in DASII (either mental or motor assessment), *iii*) vision impairment, or *iv*) hearing impairment. The motor ability of infants with cerebral palsy was graded using the Gross Motor Function Classification System (GMFCS). A GMFCS level ≥II was considered as functionally impaired. Visual impairment was defined as blindness with no functional vision in at least one eye [8]. Hearing impairment was defined as the need for sound amplification. Hearing loss was defined as hearing loss greater than 30 dB in the better hearing ear [9]. Minor neurodevelopmental abnormality was defined as the presence of any morbidity less than that classified as major neurodevelopmental abnormality. Intraventricular hemorrhage (IVH) was detected by ultrasonography, and graded according to Papile classification.

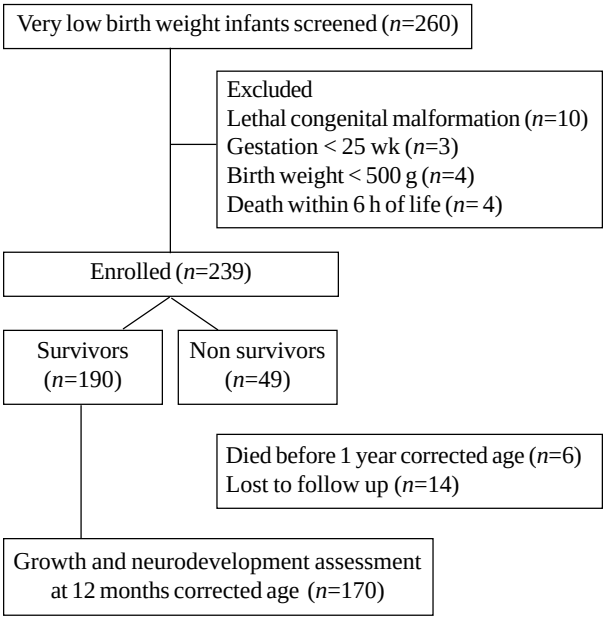

Fig. 1 Flow of participants in the study.

Statistical analysis: Comparisons were made using independent *t* test, paired *t* test and repeated measure ANOVA, and chi-square test as applicable. Statistical analysis was done using Stata version 14. A value of $P<0.05$ was considered statistically significant.

RESULTS

A total of 260 VLBW infants were screened for eligibility at the time of birth and 170 infants were included in the final analysis (**Fig.1**). The baseline characteristics and morbidity profile of the VLBW cohort is described in **Table I**. The mean (SD) motor and mental scores of the babies were 90.8 (13.4) and 96.5 (13.2), respectively. A DASII score below 70% (borderline intellectual functioning) was seen in 13 (7.6%) and 10 (5.8%) babies for the motor and mental domain, respectively. The serial anthropometric parameters and neurodevelopmental parameters at one-year CA are shown in **Table II**.

Major and minor developmental abnormalities were found in 16 (9.4%) and 31(18.2%) infants, respectively. Ten (5.8%) infants developed cerebral palsy at follow up. One infant was diagnosed to have moderate to severe hearing impairment. No infant was noted to have vision loss.

Table I Baseline Characteristics of Very Low Birth Weight Infants Enrolled in the Study (*N*=170)

Variables	*Value*
Birthweight (g) [a]	1253 (170)
Gestational age (wk) [a]	32.1 (2)
Small for gestational age	107 (62.5)
Male gender	83 (48.8)
Sepsis	52 (30.5)
Intraventricular hemorrhage	18 (10.5)
Bronchopulmonary dysplasia	8 (4.7)
Hemodynamically significant PDA	24 (14.1)
Retinopathy of prematurity	7 (4.1)

Data expressed as no.(%) or [a]mean (SD). PDA-patent ductus arteriosus.

WHAT THIS STUDY ADDS?

- Very low birth weight infants have impaired growth and significant developmental abnormalities, at one-year corrected age.

Table II Anthropometric Parameters at Different Time-points in Very Low Birth Weight Infants (*N*=170)

Timing of assessment	*WFA z-score*	*LFA z-score*	*HCFA z-score*
Birth	-1.6 (1.3)	-1.2 (1.6)	-1.5 (1.3)
At discharge[a]	-2.7 (1.1)	-1.8 (1.3)	-1.7 (1.0)
Chronological age			
3 mo	-2.9 (1.3)	-2.3 (1.3)	-2.3 (1.3)
6 mo	-2.4 (1.08)	-1.6 (1.2)	-2.5 (1.1)
9 mo	-2.2 (1.09)	-1.3 (1.0)	-2.5 (1.1)
12 mo	-2.1 (1.1)	-1.4 (1.03)	-2.2 (1.2)

Data expressed as mean (SD). [a]measurements at discharge from neonatal intensive care unit. WFA-weight for age; LFA-length for age; HCFA-head circumference for age.

DISCUSSION

The present study reported growth and neurodevelopmental outcomes of VLBW infant at one-year CA. The anthropometry showed growth impairment and a significant proportion of infants had neurodevelopmental abnormality.

The high rates of neurological and developmental problems reported among VLBW infants are of concern. Birth weight, gestational age, sex, multiple births, antenatal corticosteroid administration, neonatal infection, necrotizing enterocolitis, periventricular leukomalacia and IVH are some of the risk factors that influence both short- and long-term outcomes [11]. Local NICU data on expected mortality and adverse long-term outcomes may be useful to counsel parents of VLBW neonates. The birth weight and gestation of our cohort was comparable to other Indian studies [12,13]. VLBW mortality rate was 20% in the population studied. A birth weight <1000 g, severe grade of IVH, hyperglycemia, and respiratory distress syndrome requiring surfactant therapy were the significant predictors of mortality among VLBW neonates [14].

The mean *z*-scores at one-year CA were below the corresponding *z*-scores at birth. The mean *z*-scores of weight and length were below and farthest from the population median at 3 months CA, and subsequently improved. However, head circumference *z*-scores improved only after 9 months CA. This may suggest that somatic growth in VLBW infants recovers earlier than the neural growth. These findings are similar to an earlier Indian study [12], except that the improvement in *z*- scores for weight and length were noted after three months in our cohort. Although, our study had a larger sample size compared to the earlier Indian studies [6,7,12,13], the results are similar.

According to the Neuroprem 2 study [15], among 502 VLBW survivors who completed 24-month follow up, severe functional disability, and cerebral palsy were seen in 9.6% and 5.4%, respectively. The rates of severe functional disability and cerebral palsy were higher in neonates with a lower gestational age. In our study, the proportion of developmental abnormalities and cerebral palsy were similar. On comparing our data with the Western data, ethnicity and development assessment tools used may have affected the outcome assessment. Extra-uterine nutrition and comorbidities at birth could have influenced both growth and development of the cohort studied.

To conclude, at one-year CA, VLBW infants showed impaired growth and significant developmental abnormalities in this study. Appropriate nutritional and follow-up strategies should be implemented so that these vulnerable infants achieve optimum growth and development.

Ethics clearance: IEC (Human studies), JIPMER, Puducherry; No. JIP/IEC/2016/1145, dated Feb 16, 2017.
Contributors: SG: collected and analyzed data and drafted manuscript; AB: designed the study, reviewed data analysis and edited the manuscript; VB, NM: supervized clinical work and provided critical inputs. All authors have seen and approved the submission of this manuscript and take full responsibility for the manuscript.
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RESEARCH PAPER

LATCH Score for Identification and Correction of Breastfeeding Problems - *A Prospective Observational Study*

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Objective: To determine early breastfeeding problems using LATCH tool, and analyze the impact of breastfeeding supportive measures in improving LATCH score. **Methods**: This prospective study included all inborn term neonates born at our center between September, 2019 and March, 2020. Breastfeeding problems were identified by LATCH score at 6-12h after birth, and were addressed by the study team providing breastfeeding support, education and training to mothers. LATCH scores were reassessed at 24-48h. **Results**: Among 400 mother-infant dyads, 399 (99.7%) required support to position the neonate, 190 (47.5%) had poor latch and 52 (13%) had nipple problems during initial assessment. Breastfeeding supportive measures improved the LATCH score [median (IQR) 7 (5,8) vs 8 (8,8) at 6-12 and 24-48 hours, respectively; *P* <0.001], and reduced the number of mothers with LATCH score <8 [288 (72%) vs 63 (15.8%); *P* <0.001]. **Conclusion**: LATCH is a comprehensive yet simple tool to identify breastfeeding problems. Given the high incidence of breastfeeding problems during early postpartum period, systematic assessment of breastfeeding related problems using LATCH tool can help timely intervention and improvement in the breastfeeding technique.

Key words: *Breastfeeding support, Counselling, Latching, Neonatal feeding.*

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Breastfeeding is considered an important intervention to reduce infant and under-5 mortality [1,2]. Though breastfeeding is a natural process, some mother-infant dyads may have problems in breastfeeding, particularly during the initial days after childbirth [3,4]. Improper breastfeeding technique may result in inadequate feeds leading to excessive weight loss, hypernatremic dehydration, jaundice and re-hospitalization. Evidence suggests that early initiation of breastfeeding and exclusive breastfeeding at hospital discharge are associated with improved rates of exclusive breastfeeding until six months and increased duration of breastfeeding [5].

As we ardently promote institutional deliveries, the initial hospitalization period is a good opportunity for health care workers to assess breastfeeding, educate mothers on correct breastfeeding techniques, and boost their confidence in breastfeeding before discharge from hospital. There is a need for a systematic way to evaluate the breastfeeding technique, identify problems related to breastfeeding and take appropriate corrective actions in a timely manner. In this study, we aimed to determine the incidence and nature of early breastfeeding problems using LATCH tool [6], and to analyze the impact of breastfeeding support in improving the LATCH score.

METHODS

This prospective observational study was conducted in a tertiary care neonatal centre from September, 2019 to March, 2020, including all inborn term neonates. The exclusion criteria were neonates who required neonatal intensive care unit (NICU) admission, multiple births and sick mothers where LATCH score could not be assessed within stipulated time. The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from the mother prior to recruitment.

LATCH is an acronym that stands for latch, audible swallowing, type of nipple, comfort and hold [6]. Each component is scored from 0-2 and the total score ranges from 0-10. A total score less than 8 is considered low/ unsatisfactory.

LATCH score was assessed at 6-12 hour after birth. The scoring was performed by a group of eight senior nurses (two in each postnatal ward), who had been trained in LATCH score assessment and breastfeeding support,

before commencing the study. The training was provided in multiple sessions using images and videos, and by hands-on training under direct observation by the study investigators. Depending on the problem in breastfeeding that was identified during the initial assessment, counselling, education and support were provided to the mothers by the study team. Mothers were trained in cradle or cross-cradle hold of the baby while breastfeeding. Mothers who had undergone caesarean delivery were taught breastfeeding in side-lying position. Signs of good attachment were explained to the mothers using visual aids. Mothers were encouraged to evaluate and correct the positioning and attachment of the baby by themselves during subsequent feeding sessions, which was supervised by the study team. Tactile stimulation and/or nipple pullers were prescribed to mothers with flat or inverted nipples. Following the interventions, LATCH scores were reassessed at 24-48 hour from the time of delivery. For most mother-infant dyads, both the initial assessment and post-inter-vention assessment were performed by the same nurse.

Demographic and clinical details of the mother and the baby were collected in a pretested study form. Sample size obtained was 400 mother-infant pairs, assuming a 50% incidence of breastfeeding problems in term neonates, taking precision of 5%.

Statistical analysis: Descriptive statistics are presented as median and interquartile range (IQR) or number and percentage, as appropriate. Chi-square test was used to compare categorical data between independent samples, McNemar test for categorical data between paired samples, and Wilcoxon signed rank test for ordinal data between paired samples. All statistical analyses were performed using SPSS 20.0. A *P* value <0.05 was considered statistically significant.

RESULTS

Among the 400 study neonates, 217 (54.2%) were boys and 19 (4.8%) had a birth weight <2500 g. Nearly half of the mothers (197, 49.2%) were primiparous, and 252 (63%) had delivery by cesarean section. Maternal age was <20, 20-30 and > 30 years in 4 (1%), 290 (72.5%) and 106 (26.5%), respectively. Of these, 29 (7.2%) mothers had high-school education, 342 (85.6%) were graduates and 29 (7.2%) were professionals.

During the initial assessment at 6-12 hour, 399 (99.7%) mothers required support to position the neonate, 190 (47.5%) mother-infant dyads had a poor latch with a score of 0 or 1, and 52 (13%) mothers had a flat or inverted nipple. While 288 (72%) mother-infant dyads had a LATCH score of < 8 at 6-12 hour after delivery, this reduced significantly to 63 (15.8%) at 24-48 hour after the breastfeeding support and training (*P*< 0.001). The median (IQR) LATCH scores also improved significantly [7 (5,8) vs 8 (8,8); *P*<0.001].

Table I Scores of Individual Components of LATCH scoring System at 6-12 Hour and 24-48 Hour After Delivery (*N*=400 Mother-Infant Dyads)

Component	*Score*		
	6-12 h	*24-48 h*	*P value*
Latch	2 (1, 2)	2 (2, 2)	< 0.001
Audible swallowing	1 (0, 1)	1 (1, 2)	< 0.001
Type of nipple	2 (2, 2)	2 (2, 2)	< 0.001
Comfort	2 (2, 2)	2 (2, 2)	0.121
Hold	1 (0, 1)	1 (1, 1)	< 0.001

Scores in median (IQR).

The scores of individual components are given in **Table I**. The 'latch' component improved significantly with 95.5% mother-infant pairs having a score of 2 at 24-48 hour. Though there was improvement in 'audible swallowing' and 'hold' components, the proportion of mother-infant pairs achieving a score of 2 was less even after the training. Most of the mothers had a score of 2 for 'comfort during breastfeeding.' Number of mothers who have a flat or an inverted nipple decreased from 13% to 2.7% after the intervention.

Table II Comparison of Low Scores (<8) Between Different Sub-groups of Mother-Infant Dyads

Mother-infant groups (n)	*LATCH score < 8*	
	At 6-12 h (n=288)	*At 24-48 h (n=63)*
Birthweight		
< 2500 g (*n*=19)	14 (73.7)	4 (21.1)
> 2500 g (*n*=381)	274 (71.9)	59 (21.5)
Delivery		
Cesarean (*n*=252)	223 (88.5)[a]	51 (20.2)[c]
Vaginal (*n*=148)	65 (43.9)	12 (8.1)
Parity		
Primipara (*n*=197)	161 (81.7)[a]	39 (19.8)[d]
Multipara (*n*=203)	127 (62.6)	24 (11.8)
Maternal age		
>30 y (*n*=106)	78 (73.6)	19 (17.9)
20-30 y (*n*=290)	206 (71)	42 ((14.5)
<20 y (*n*=4)	4 (100)	2 (50)
Mother's education		
High school (*n*=29)	23 (79.3)[b]	9 (31.0)[d]
Graduate (*n*=342)	239 (69.9)	46 (13.5)
Professional (*n*=29)	26 (89.6)	8 (27.6)

Values in no. (%). At 6-12 h, [a]P<0.001; [b]P<0.05; At 24-48 h, [c]P<0.001; [d]P<0.05.

WHAT THIS STUDY ADDS?

- Timely intervention, following early identification of breastfeeding related problems using the LATCH tool, help in significant reduction of such problems.

Analysis of the association between demographic characteristics and LATCH scores showed that caesarean delivery, primiparity and mother's education were risk factors for a lower LATCH score at 6-12 hours (**Table II**). Though, the scores improved significantly after breastfeeding support in all these subgroups, they had persistently lower scores at 24-48 hours when compared to their fellow groups.

DISCUSSION

Our study showed that almost all the mothers required assistance in positioning the neonate during breastfeeding and almost half of mother-infant dyads had problems related to latching, with 13% mothers having nipple issues soon after delivery. We found a significant reduction in breastfeeding problems with timely support, training and counselling of mothers.

LATCH score provides a systematic method to evaluate five key components of the breastfeeding technique [6]. It helps to identify the nature of the problem, so that appropriate corrective measures can be taken by counselling and training the mothers with simple visual aids. Improper latching and positioning of the neonate during breastfeeding may result in the baby sucking only on the nipple, which in turn will lead to inadequate feeds to the neonate and sore/cracked nipples and breast engorgement in the mother. We found a significant improvement in nipple problems such as flat or inverted nipples by 24 hours after delivery with simple interventions such as tactile stimulation or nipple puller.

The 'comfort' component had good scores at both 6-12 and 24-48 hours post-delivery, probably because problems causing discomfort while breastfeeding, such as breast engorgement or sore/cracked nipples usually develop later during the postpartum period. 'Audible swallowing' component scored low at both assessments and this is probably due to the less quantity of milk secreted by mothers on day 1 and 2 after delivery. The frequency of audible swallowing improves after the secondary lactogenesis, when mother starts secreting more milk [6].

Primipara mothers who have no previous experience with breastfeeding and mothers who have a caesarean delivery and hence have pain and cannot sit up are more likely to have problems in breastfeeding, as shown by our study and previous studies [6,7]. These subgroups of mothers would require more support to establish breastfeeding.

Better LATCH scores in the early postnatal period were shown to correlate positively with exclusive breastfeeding rates at discharge and at 6-8 weeks of life [8-10]. Hence, we are of the view that systematic assessment of breastfeeding using the LATCH tool and timely initiation of appropriate measures to address the problems that are identified will help to improve exclusive breastfeeding rates at and after hospital discharge.

The study has some limitations. We did not follow the mother-infant pairs beyond 48 hours. Hence, several problems related to breastfeeding that appear later were not assessed. We did not include neonates who required NICU admission and late preterm neonates, who may be at greater risk of improper breastfeeding. We did not assess inter-observer agreement in assessment of the LATCH score among the study nurses. Finally, other factors could also have contributed to the improvement in the LATCH score. Nevertheless, identifying the nature of breastfeeding problem in each mother-infant dyad and addressing the problem through breastfeeding counselling, education and support was undeniably a major factor contributing to the improvement in the scores.

To conclude, the incidence of problems related to breastfeeding is high during the initial days after child birth. LATCH is a comprehensive, yet simple and easy to use tool to identify these problems and guide us to initiate appropriate intervention. Breastfeeding support, counselling and education during the postpartum hospital stay significantly reduce problems in breastfeeding.

Ethics clearance: Name of IEC: KMCH Ethics Committee; No. EC/AP/762/08/2019, dated August 24, 2019.
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RESEARCH PAPER

Six-Year Surveillance of Acquired Bloodstream Infection in a Pediatric Intensive Care Unit in Israel

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Objectives: We studied the profile of bloodstream infections (BSI) in the pediatric intensive care unit (PICU) and identified predictors of mortality. **Methods**: The study collected data from hospital records for children younger than 18-years who developed BSI during their PICU stay between 2014 and 2019. **Results**: In 114 patients, 136 PICU-acquired BSIs with 152 pathogens were documented. The incidence of BSI was 47.12/1000 PICU admissions and 7.95/1000 PICU hospital days. Gram-negative rods accounted for 75% of isolates, Gram-positive cocci accounted for 21.7% of isolates, and fungi accounted for 3.3% of isolated pathogens. ICU mortality was observed in 25 (21.9%) patients with a BSI compared to 94 (3.1%) patients without a BSI (P<0.001). Hemodynamic instability (P=0.014, OR 4.10, 95%CI 1.33-12.66), higher blood urea nitrogen (BUN) (P=0.044), and lower albumin levels (P=0.029) were associated with increased risk of ICU mortality. **Conclusion**: BSI in the PICU is associated with increased mortality. Early identification and management of risk factors independently associated with poor clinical outcomes in these patients should be aimed to ensure improved survival.

Keywords: *Hypoalbuminemia, Klebsiella spp, Mortality, Nosocomial infection*.

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Bloodstream infections (BSI) acquired in the pediatric intensive care unit (PICU) are the leading cause of hospital morbidity and mortality [1]. Mortality rates attributable to BSI range from 11% to 81.8% [1-3]. A few studies have addressed the epidemiology of BSI in pediatric patients admitted to PICU [1-5], but none of these studies have examined the predictors of mortality. Recognition and treatment of these predictors of mortality may lead to a reduction in the incidence, and consequently, the morbidity and mortality of BSI.

The aim of this study was to determine the characteristics and outcome of BSI in the PICU, and to identify predictors of mortality in these patients.

METHODS

We retrieved hospital records of children younger than 18 years who were admitted to the PICU of Rambam Health Care Campus between January, 2014 and December, 2019, and had acquired BSI. This is a tertiary, university-affliated hospital with a 15-bed PICU with an average of 520 annual PICU admissions, and facilities for respiratory and hemodynamic support, including extracorporeal membrane oxygenation. Cases were identified from monthly reports of positive blood cultures. Clinical and laboratory data of patients with positive blood cultures were obtained from the case sheets. The study was approved by the local ethics committee.

The Centers for Disease Control (CDC) guidelines were used for classification of BSI [6]: PICU-acquired BSI: BSI that occurred after the first 48 hours of hospital admission, when no evidence of infection was present on admission; Primary BSI: BSI that was not due to infection at another body site; Central line-associated BSI (CLABSI): BSI in which a central venous catheter (CVC) is present; Secondary BSI: BSI due to site-specific infection; and, Mucosal barrier injury (MBI): BSI in neutropenic patients or oncologic patients with diarrhea. Hemodynamic instability was defined as need for fluid resuscitation and/or vasopressors, and respiratory deterioration was defined as worsening respiratory status. PICU associated mortality was defined as mortality occurring during the stay in PICU.

Coagulase-negative staphylococci (CoNS) and other commensal bacteria were considered true pathogens only if patients had at least two positive cultures or, alternatively, clinical signs of sepsis and had received targeted antibiotic treatment [6].

Statistical analysis: Data were analyzed using SPSS software (version 26). Univariate analyses were performed using chi square test for categorical variables and independent *t* test for continuous variables. All tests were two-tailed, and $P<0.05$ was considered statistically significant. A binomial regression model was fitted for potential predictors of mortality during PICU stay. In this model, only the last sepsis episode of each patient was considered. Variables were included if the *P* value in the univariate analysis was <0.1; variables with $P<0.05$ were retained.

RESULTS

Over the six-year study period, 114 patients [61 males; median (IQR) age, 0.92 (0.12,11.53) years] were diagnosed with 136 episodes of BSI, with isolation of 152 pathogens (**Web Fig. 1**). The BSI incidence rate in the PICU was 47.12 per thousand PICU admissions, and 7.95 per thousand PICU hospitalization days (**Fig. 1**).

About half of the patients with BSI were younger than 1 year, compared with 29.1% of all patients admitted to the PICU during the study period ($P<0.001$). A CVC was documented in 99 (72.8%) cases, and 60 (60.6%) episodes of these were defined as CLABSI. Mean (SD) time from CVC insertion to BSI in patients with CLABSI was 14.45 (13.08) days (**Table I**).

A total of 152 isolates were identified from blood cultures. Most, 114 (75%), were Gram-negative rods (GNR).

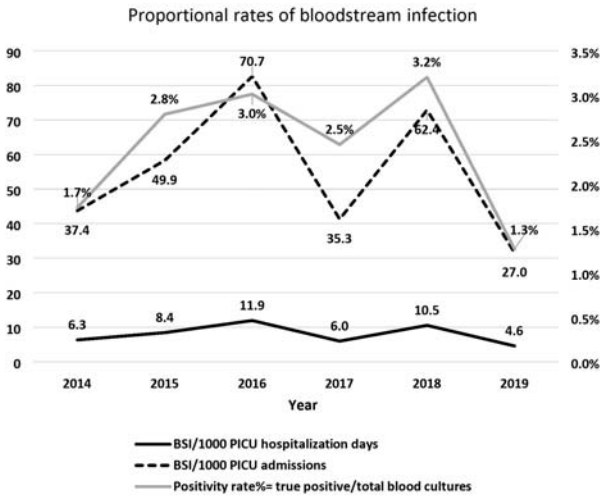

Fig. 1 Rates of bloodstream infections in children in a pediatric intensive care unit in Haifa, Israel (2014-2019).

Table I Characteristics of Children With Bloodstream Infection in the Pediatric Intensive Care Unit (*N*=114)

Characteristic	*Number (%)*
Age	
0-28 d	22 (19.3)
29 d - 1 y	36 (31.6)
1-5 y	19 (16.7)
>5 y	37 (32.5)
Jewish ethnicity	35 (30.7)
Diagnosis on admission	
Medical	73 (64)
Surgical	25 (21.9)
Trauma/burns	15 (13.2)
Underlying condition	
No underlying condition	25 (21.9)
Cardiac	33 (28.9)
Genetic/metabolic	15 (13.2)
Neurologic	11 (9.6)
Oncologic/immune deficiency	11 (9.6)
Renal	6 (5.3)
Gastrointestinal	6 (5.3)
Prematurity	4 (3.5)
Pulmonary	3 (2.6)
Carriage of multidrug resistant organisms at time of BSI[a]	
Extended spectrum beta-lactamases	45 (39.5)
Enterobacteriaceae	
Methicillin-resistant *Staphylococcus aureus*	8 (7)
Vancomycin resistant *Enterococcus*	3 (2.6)
Clinical presentation	
Fever	99 (72.8)
Hemodynamic instability	35 (25.7)
Respiratory deterioration	53 (39)
Acute renal failure	20 (14.7)
CVC type (>2 d)	
No CVC	37 (27.2)
Subclavian	11 (8.1)
Femoral	30 (22.1)
Jugular	35 (25.7)
Multiple	23 (16.9)
Classification	
CLABSI	60 (44.1)
Secondary BSI	42 (30.9)
Primary BSI	29 (21.3)
Mucosal barrier injury BSI	5 (3.7)
Secondary BSI	
PVAP/PNEU	24 (57.1)
Surgical site infection	6 (14.3)
CAUTI/SUTI	8 (19)
Other sources	4 (9.6)

Values in no. (%) [a]*One child had carbapenem resistant Acinetobacter. CVC-central venous catheter, CLABSI-central line associated blood stream infection, BSI-bloodstream infection, PVAP/PNEU-ventilator associated pneumonia, CAUTI/SUTI-catheter associated urinary tract infection.*

Table II Predictive Factors for Mortality in the Intensive Care Unit (ICU) in Children With Bloodstream Infection

Factors	*ICU survivors (n=89)*	*ICU non-survivors (n=25)*
Age (y)[a]	4.82 (6.16)	5.43 (6.94)
Male gender	50 (56.2)	11 (44)
Arab ethnicity	60 (67.4)	19 (76)
Admission cause		
Medical	55 (62.5)	18 (72)
Surgical	20 (22.7)	5 (20.0)
Trauma/burns	13 (14.8)	2 (8.0)
Associated serious comorbid condition[c]	65 (73.0)	23 (92.0)
Hemodynamically unstable[c]	19 (21.3)	12 (48.0)
Consciousness deterioration	6 (6.8)	2 (8)
Acute kidney injury	12 (13.6)	6 (24)
Laboratory		
White blood count (10^9/L)[a]	14.07 (11.56)	15.96 (15.44)
Hemoglubin (g/dL)[a]	10.22 (2.69)	10.35 (2.26)
Albumin (g/dL)[a,c]	2.75 (0.69)	2.43 (0.54)
CRP (mg/dL)[a]	0.53 (0.41)	0.74 (0.72)
Lactate (mmol/L)[a]	1.56 (0.64)	2.68 (1.41)
Creatinine (mg/dL)[a]	0.53 (0.42)	0.74 (0.72)
BUN (mg/dL)[a,c]	17.9 (14.2)	34.87 (29.39)
Gram-positive organisms	23 (26.7)	5 (20.8)
CLABSI	38 (42.7)	12 (48.0)
ICU stay before BSI (d)[a]	17.9 (15.42)	17.60 (17.26)
ICU stay after BSI (d)[a]	25.1 (28.93)	21.08 (31.40)
Carriage of resistant bacteria[b]	43 (48.3)	15 (60.0)
Carriage of ESBL	31 (34.8)	14 (56.0)
Inappropriate empiric antibiotics	13 (12)	5 (11.6)

All values in no. (%) or [a]mean (SD). [b]Resistant bacteria-ESBL, CRE, MRSA, VRE or CRAB. CLABSI-central line-associated bloodstream infection, ESBL-extended-spectrum beta-lactamase Enterobacteriaceae, CRE-carbapenem resistant enterobacteriaceae, MRSA-methicillin resistant staphylococcus, VRE-vancomycin resistant enterococcus, CRAB-carbapenem resistant Acinetobacter baumani. [c]P<0.05.

Klebsiella spp. were most frequently identified in 37 (24.3%) cultures. Gram-positive cocci (GPC) were detected in 33 (21.7%) cultures. *Staphylococcus aureus* was most frequently isolated GPC in 13 (8.6%) cultures.

Fifty-eight (50.9%) patients were carriers of multi-drug resistant organisms (MDRO) at the time of bacteremia, detected by screening or clinical specimens. ESBL producing enterobacteriaceae were isolated from blood cultures of 36 (31.6%) patients and MRSA was isolated from blood cultures of 4 (3.5%) patients. Carbapenem-resistant enterobacteriaceae (CRE) were not detected during the study period. GNR resistance to amikacin was detected in 6 (5.8%), to piperacillin-tazobactam in 20 (20.6%) and to ceftazidime in 36 (40.9%) patients (**Table I**).

Mortality occurred during stay at PICU was documented in 25 (21.9%) patients with BSI compared with 94 (3.1%) patients without BSI. Mean age, sex, and ethnicity were similar in survivors and non-survivors. Bacteria group (GNR vs GPC) was not associated with higher mortality (P=0.557). Inappropriate empiric antibiotic treatment administered within 2 hours of clinical or laboratory evidence of bacteremia occurred in 12% of survivors and 11.6% of non-survivors (P=0.944) (**Table II**).

In univariate analysis, presence of serious comorbid condition, hemodynamic instability, low albumin level and higher blood urea nitrogen (BUN) levels were significantly more prevalent in non-survivors (P=0.046, 0.008, 0.035 and 0.010, respectively). These variables were included in the multivariate analysis in addition to carriage of ESBL (P=0.056). In the multivariate analysis, hemodynamic instability resulted in a 4-fold increase in ICU mortality. Each one-unit increase in BUN level was associated with a 1.026-fold increase in ICU mortality, whereas each one-unit decrease in albumin level was associated with a 2.6-fold increase in ICU mortality (**Table II**). The logistic regression model was statistically significant (P<0.001), and fitted the data well, as shown by Hosmer and Lemeshow test (P=0.317).

DISCUSSION

We found a high proportion of BSI among children in PICU, comparable to rates of 56 and 63/1,000 PICU admissions [2,3] and to 7 and 31.2/1,000 patient days [2,5]. During the study period, the incidence of BSI varied between 27 and 70.7/1,000 PICU admissions. This change in incidence may be related to the changing workload and intermittent reinforcement of infection prevention measures taken to reduce BSI in ICUs, such as reimplementation of CVC insertion and maintenance policies, surveillance of BSI, and debriefing of BSI events. The significant proportion of patients younger than one year and patients with complicated underlying diseases may explain the broad use of invasive devices, such as a CVC in this cohort.

The ICU mortality rate in patients who developed BSI was consistent with that reported by Gray, et al. [7], but significantly lower than in previous studies (40.7 -55.9%) [2,3]. In the current study and in another Israeli study [3], ICU mortality was 7-fold higher in patients with BSI than in patients without BSI. This difference in ICU mortality was less pronounced in other studies worldwide [5,7].

Hemodynamic instability, as also noted by Pillon, et al. [8], increased BUN, and decreased albumin levels were identified as predictors of PICU-associated mortality. Diagnostic tools based on biomarkers such as albumin and urea have been successfully used to predict mortality

WHAT THIS STUDY ADDS?

- Profile of bloodstream infections and associated factors of mortality in the pediatric intensive care unit are presented.

[9,10]. Critical illness often results in altered cellular energy metabolism and protein catabolism. Whether albumin levels or nutritional status have a direct adverse effect on survival or reflect severe disease and catabolic state remains to be determined [11]. The predictors of ICU mortality found in this study may reflect in some way the severity of illness at the onset of bacteremia and the compromise to vital organs.

Similar to previous studies [2,3,5], GNR pathogens were responsible for the majority of BSI events [2,3,5], but they were not associated with greater mortality. We found a much lower rate of fungemia in this study, compared to 7.8-15% in previous studies [3,5].

The main limitation of the study was its retrospective design, which may affect the quality of the data and follow-up. However, most of the data were collected as part of a national monthly surveillance of BSI in intensive care units in Israel, which masks this limitation. Although, a single study, it was conducted in a large referral center that enrolls patients with complicated conditions, which may mitigate this limitation and even overestimate the mortality rate. Although data on comorbidities and disease severity parameters were presented in the current study, no well-known disease severity scores were used to standardize severity, and no severity data were collected from patients who were admitted to the PICU but had not developed BSI, making it difficult to determine whether patients with BSI had higher severity compared with patients without BSI. Moreover, the fact that low albumin levels were associated with mortality makes it necessary to assess overall nutritional status in future studies.

In conclusion, the high incidence of BSI, the high mortality in patients with BSI, and the uncontrolled factors predicting mortality found in this study underscore the need for continuous surveillance and infection prevention interventions to all patients to reduce the incidence of BSI. These predictors may indicate severe disease and catabolic state, and clinicians should be aware of these predictors and provide optimal supportive and nutritional care.

Ethics clearance: Local Ethics Committee; No.0053-19-RMB, dated Jan 24, 2019.
Contributors: HDY,IK,KH: designed the study, analyzed the data and edited the manuscript; MA,RDS: gathered the data and reviewed the manuscript; JBA,AH, YSM,TA: helped in gathering the data and revising the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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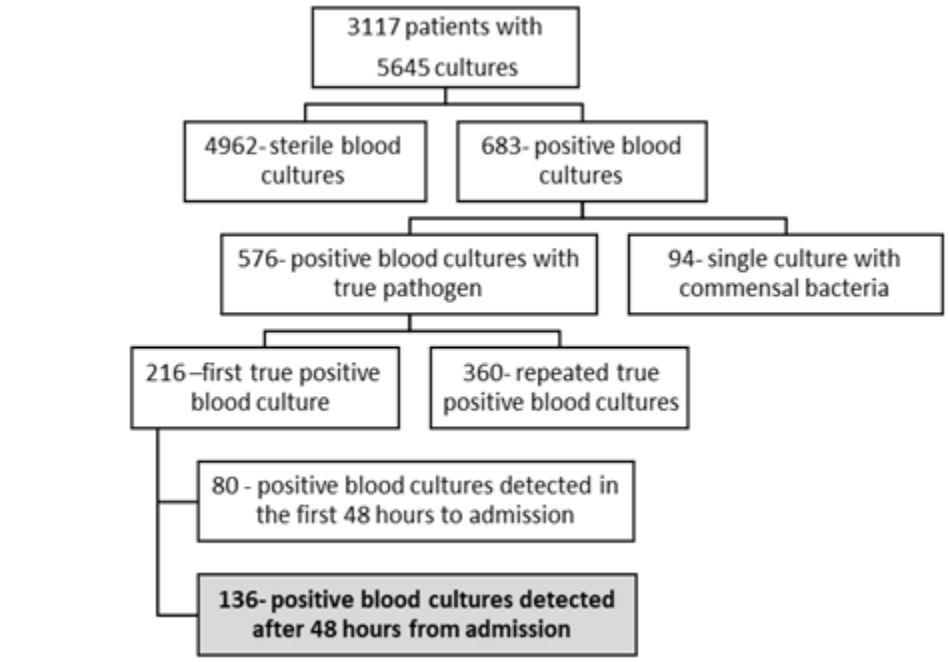

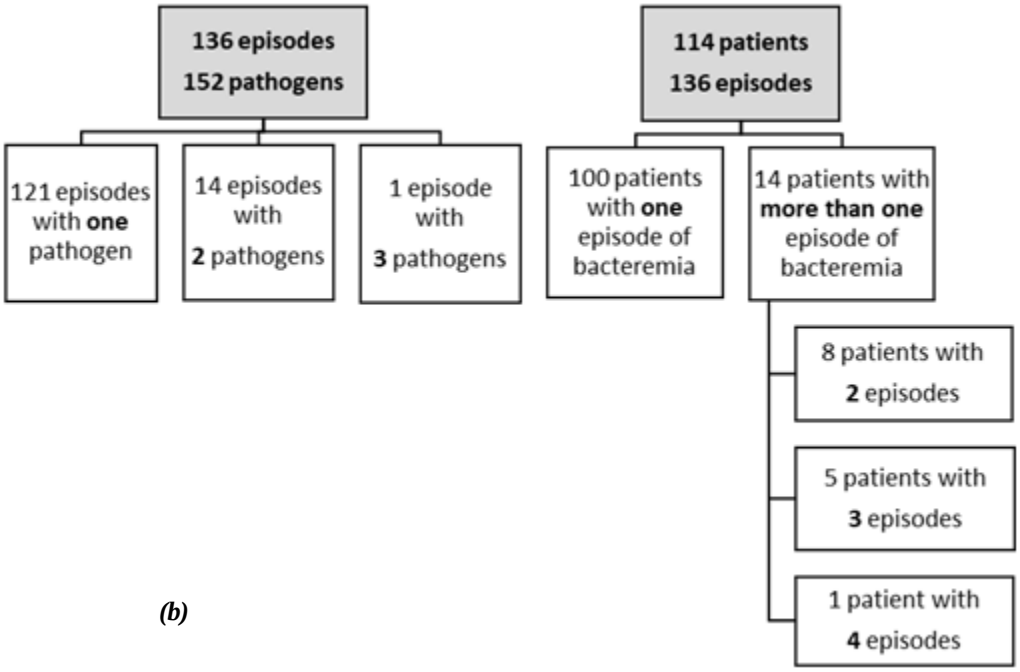

Web Fig. 1. (*a*) The total number of patients and blood cultures identified in the study. (*b*) Flowchart of patients, episodes and pathogens included in the study.

RESEARCH PAPER

Evaluation of AIIMS Modified INCLEN Tool for Diagnosis of Epilepsy

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Objectives: To evaluate the AIIMS Modified INCLEN tool for the diagnosis of epilepsy. **Methods:** This cross-sectional study enrolled 250 children aged 1 month to 18 years presenting with complaints of abnormal body movements to either the pediatric or neurology outpatient departments in our institution between October 1, 2018 and June 30, 2020. The All India Institute of Medical Sciences (AIIMS) modified International Clinical Epidemiology Network (INCLEN) diagnostic tool for epilepsy (AIIMS modified INDT-EPI) was administered and a diagnosis was made, which was further verified by a pediatrician or a neurologist. Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. **Results:** The study tool had a sensitivity of 87.6% and specificity of 84.0%. The PPV and NPV of the study tool were 86.8% and 84.9%, respectively. **Conclusion:** The study tool has good psychometric properties for physician assessment with regard to diagnosis of epilepsy.

Keywords: *Diagnosis, Seizure, Sensitivity, Specificity*.

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Epilepsy accounts for 0.5% of the global disease burden [1]. The diagnosis of epilepsy is usually made on the basis of clinical history supported by brain imaging and electroencephalography (EEG). Misdiagnosis may occur in nearly one third of cases, even when physicians are involved [2-5]. Multiple possible reasons for epilepsy misdiagnosis have previously been reported [2,5,6]. Most health centers in our country do not have adequate resources or ready access to diagnostic facilities, which may contribute to misdiagnosis and increase in referral of several patients [7,8]. Approximately 80% of specialist physicians are practicing in urban India. In this scenario, primary health center (PHC) based care can be essential to decrease treatment gap [6].

Questionnaires that are inexpensive, freely available, and easy to use by a general pediatrician can aid in correct management of epilepsy in children. The International Clinical Epidemiology Network (INCLEN) developed a simple questionnaire-based tool in multiple Indian languages for epilepsy diagnosis in the community (INDT-EPI), which had good psychometric properties [9]. This was subsequently modified as the AIIMS Modified INCLEN diagnostic tool for epilepsy (AIIMS Modified INDT-EPI) [10]. This study was planned to evaluate the diagnostic accuracy of the AIIMS Modified INDT-EPI tool for epilepsy.

METHODS

This cross sectional study was conducted in the outpatient clinics of pediatric and neurology department in a tertiary level healthcare institution in Northern India from October 1, 2018 to June 30, 2020. Ethical approval was obtained from the institutional ethics committee. A written informed consent was obtained from the primary caregiver, and written assent was obtained from children between 12 and 18 years. Children aged one month to 18 years present-ing with abnormal body movements or seizures were enrolled. Children with severe acute illness, which required hospital admission, were excluded from the study.

Demographic details and pre-diagnosed comorbid neurodevelopmental disorders (NDDs) were recorded. AIIMS Modified INDT-EPI 10-item questionnaire [11] was administered to primary caregivers, and the diagnosis of "epilepsy", "No epilepsy", "single seizure" or "indeterminate" was made after assessing as per the scoring mentioned in the INCLEN tool. The diagnosis of epilepsy was further verified by either a pediatrician or a neurologist (labelled as 'experts'), who were blinded to the scoring on the tool. Diagnosis of "epilepsy" or "No epilepsy" made by the expert was considered as the gold standard.

Statistical analysis: The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were expressed as percentages with 95% CI. Cohen

Kappa test was used to compare diagnosis by study tool and the gold standard. The data of indeterminate category patients were excluded from statistical analysis while comparing the study tool with the experts' diagnosis.

RESULTS

Clinico-demographic profile of the enrolled 250 children is illustrated in **Table I**. As per gold standard, 138 children were diagnosed as epilepsy. Seizures were found secondary to underlying etiologies in 80.3% (*n*=90) of children diagnosed with 'No epilepsy' and most common etiology was febrile seizures (*n*=44, 48.8%), followed by toxic and metabolic causes (*n*=21, 23.3%). As per the study tool, 114 (45.6%) children had epilepsy, 93 (37.2%) children did not have epilepsy and rest 43 (17.2%) children were classified as indeterminate.

There was substantial agreement between physician diagnosis and study tool diagnosis (κ=0.717, *P*<0.001). The sensitivity, specificity, PPV and NPV of the study tool were >80% (**Table II**). The study tool showed maximum sensitivity and NPV among age group of 1 month-2 years, whereas maximum specificity and PPV was found among age group of 2-5 years. However, this tool showed least accuracy with least specificity among age group of 5-18 years as compared to other age groups (**Table II**).

Table I Clinico-demographic Characteristics of Children With Abnormal Movements Assessed for Epilepsy (*N*=250)

Characteristics	*Value*
Males	161 (64.4)
Age group	
1 mo-2 y	70 (28)
2 y-5 y	64 (25.6)
5-18 y	116 (46.4)
Urban residence	194 (77.6)
Comorbid NDDs	88 (35.2)
Intellectual disability	42 (47.7)
Neuromotor disability	34 (38.6)
Behavioral disorder	12 (13.6)

Values in no. (%). NDDs-neurodevelopmental disorders.

DISCUSSION

Utility of pediatric management protocols such as Integrated management of neonatal and childhood illness (IMNCI) for management of common childhood illnesses have exemplified the importance and usefulness of simple management tools that can help a primary care physician in the peripheral settings to manage patients satisfactorily [12,13]. The present study demonstrates acceptable psychometric properties of the AIIMS modified INDT-EPI tool for diagnosis of epilepsy in children.

The psychometric properties of a questionnaire will help qualify their usefulness as a diagnostic screening tool in primary health care level where tertiary level diagnostic aids are not available. Earlier researchers have attempted to study the utility of questionnaire-based epilepsy diagnostic or screening tools. Most of the earlier screening questionnaires for epilepsy concentrated on diagnosis of only tonic clonic seizures [14]. However, the AIIMS Modified INDT-EPI includes questions to detect various seizure types, including myoclonic seizures, epileptic spasms, atonic seizures, absence seizures and focal seizures [10,11].

Questionnaires for diagnosis of epilepsy used in the earlier studies were designed based on experience of experts rather than standard international definitions or classification of seizures. AIIMS Modified INDT-EPI is based on ILAE classification, which could be possible explanation for high sensitivity for this study tool as compared to most of the previous studied tools [14,15]. Second possible reason for high sensitivity in our study is

Table II Psychometric Properties of AIIMS Modified INDT-EPI in Various Age Groups (*N*=250)

Value	*1 mo-18 y (overall)*	*1 mo-2 y (n=70)*	*2 - 5 y (n=64)*	*5-18 y (n=116)*
Sensitivity	87.61% (80.09% to 93.06%)	94.44% (72.71% to 99.86%)	77.42% (58.90% to 90.41%)	90.62% (80.70% to 96.48%)
Specificity	84.04% (75.05% to 90.78%)	85.71% (71.46% to 94.57%)	96.00% (79.65% to 99.90%)	70.37% (49.82% to 86.25%)
Positive predictive value	86.84% (80.50% to 91.34%)	73.91% (57.25% to 85.70%)	96.00% (77.70% to 99.40%)	87.88% (80.13% to 92.87%)
Negative predictive value	84.95% (77.42% to 90.28%)	97.30% (84.22% to 99.59%)	77.42% (64.00% to 86.86%)	76.0% (58.72% to 87.57%)
Accuracy	85.99% (80.50% to 90.41%)	88.33% (77.43% to 95.18%)	85.71% (73.78% to 93.62%)	84.62% (75.54% to 91.33%)

AIIMS modified INDT-EPI - All India Institute of Medical Sciences (AIIMS) modified International Clinical Epidemiology Network (INCLEN) diagnostic tool for epilepsy.

WHAT THIS STUDY ADDS?

- The AIIMS Modified INDT-EPI tool has a good sensitivity and specificity, and can be used in the outpatient setting for a diagnosis of epilepsy or no epilepsy among children aged between 1 month and 18 years.

due to ability of our study tool to diagnose wide range of epileptic seizures as compared to earlier studies that focused on specific seizure types only. Similarly, our study yielded high specificity as compared to previous studies due to ability of the tool to diagnose more types of non-epileptic events like breath holding spells and syncope. A high specificity of study tool translates into high positive predictive value and low false positive rates.

We observed a lower sensitivity of study tool as compared to previous studies [10,16,17]. This can be attributed to the different type of study population as these studies enrolled children with higher risk of seizures. Parents of such children are more familiar with terminologies which can increase chances of a positive response and thus higher sensitivity with a study questionnaire [10,16,17]. In our study, we enrolled children coming to the general pediatric and neurology outpatient department with history of any abnormal body movements. Similarly, low specificity of diagnostic questionnaire in our study as compared to some previous studies can be attributed to the different type of study population as unlike these studies, our study did not include healthy children as controls [14,16,17]. Specificity of a test usually increases with healthy controls.

In subgroup analysis for age, in our study, AIIMS Modified INDT-EPI tool showed highest utility in age group of 1 month-2 years. This was in contrast to the results of the validation study [10], which showed least sensitivity (86.5%) and positive predictive value (88.4%) in age group of 1 month-2 years as compared to age >2 years, and also demonstrated that the best diagnostic accuracy was found among age group of 2-9 years. A higher sensitivity in children with comorbid NDDs could possibly be because parents of children with comorbid NDDs were more likely to understand the terminologies in the questionnaire. The original study [9] also demonstrated the increase in sensitivity (97.4%) of diagnostic questionnaire when administered to children with comorbid NDDs, as also reported later [10].

The data of children with 'indeterminate' category on the tool was removed from analysis, which may have had a modifying effect on the psychometric properties in this study. However, as the study setting was a general outpatient setting, it makes our findings more relatable to a peripheral health care setup. Thus, our findings support the usefulness of this questionnaire as a screening tool for diagnosis of abnormal body movements as possible epilepsy or otherwise.

To conclude, AIIMS modified INDT-EPI questionnaire had a high diagnostic accuracy, and can be used in the outpatient setting for a reliable diagnosis of seizure or seizure-like events in children and young adults aged 1 month to 18 years.

Ethics clearance: Institutional Ethics Committee, CMCL; No: 201812614/IECCMCL/PG Thesis-Paeds, dated Dec 14, 2018.
Contributors: PG,MS: conceptualized the study design; PG: was responsible for the data collection and analysis; MS,PV: supervised the data collection and analysis; PG: prepared the first draft of the study; MS: and PV: revised the manuscript. All authors approved the final manuscript.
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RESEARCH PAPER

Antibiotic Susceptibility, Carrier State and Predictors of Outcome of *Staphylococcus aureus* Infections in Hospitalized Children

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Objectives: To evaluate the antibiotic resistance pattern, clinical profile and predictors for adverse outcomes in children hospitalized due to staphylococcal infection; and the frequency of nasal and axillary carrier states in these children. **Methods**: This descriptive study enrolled 100 symptomatic children (aged 1 month - 12 years) in whom *S. aureus* was isolated from cultures of blood, pus or cerebrospinal fluid. All samples were processed as per the Clinical and Laboratory Standards Institute (CLSI) standards. Antimicrobial susceptibility was tested using disc diffusion method; minimum inhibitory concentration (MIC) for vancomycin was measured using E strips. Predictors for poor recovery were determined by univariate and multivariable logistic regression analysis. **Results**: Skin and soft tissue infections were the most common (47%) followed by respiratory infections (37%). Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in 62%, out of which 63% (39/62) were multi-drug resistant. Carrier state was present in 49% (93% MRSA); 80% were axillary carriers. High MIC (>1 µg/mL) for vancomycin was seen in 65% of patients, and was the only factor associated with poor recovery [aOR (95%CI) 5.3 (1.6,18.5); *P*=0.008] on multivariable logistic regression analysis. **Conclusion:** MRSA is the predominant strain in severe staphylococcal infections requiring hospitalization, and majority of them are multidrug resistant. High MIC to vancomycin among *S. aureus* is an emerging concern.

Keywords: *Antimicrobial resistance, Methicillin-resistance, Treatment failure*.

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Staphylococcus aureus is associated with significant morbidity and mortality in children, especially in low- and middle-income countries (LMICs). Community-acquired MRSA (CA-MRSA) infections have a fundamentally different epidemiology compared to hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. In India, the overall rate of MRSA in clinical specimens is reported to be high (45-60%) [2].

Less is understood about community-acquired *S. aureus* and predictors of adverse outcomes in children. There are conflicting data on whether higher vancomycin minimum inhibitory concentrations (MICs) adversely affects outcome in patients with *S. aureus* bacteremia [3]. Moreover, there is paucity of recent data related to the profile and resistance pattern of *S. aureus* infections in children. Thus, we conducted this study to describe the antibiotic resistance pattern, clinical profile and predictors for adverse outcomes in children hospitalized due to staphylococcal infection. We also aimed to study the frequency of nasal and axillary carrier states in these children.

METHODS

This observational study was conducted in the Departments of Pediatrics and Microbiology of a medical-college-affiliated public hospital, from November, 2017 to April, 2019. We included children aged 1 month to 12 years with features of clinical sepsis such as fever, chills, deep abscesses, hypotension or oliguria, and where *S. aureus* was isolated from cultures of blood, pus or cerebrospinal fluid (CSF). Culture isolate was considered a contaminant if the patient's clinical features and laboratory test did not suggest infection, follow up blood cultures were negative when the patient did not receive any antibiotic, patient recovered without any anti-staphylococcal treatment, or there was a polymicrobial growth; such patients were excluded from the study. Informed consent was obtained from parents or guardians of every participant. Assent was obtained from children 7 years of age or older. An approval from the institutional ethics committee was obtained.

A detailed history and physical examination were recorded for all participants. Complete hemogram and

blood culture were performed on all, pus and CSF cultures were collected, wherever relevant. Other investigations (ultrasonography, chest *X*-ray, echocardiography, computed tomography (CT) scan) were guided by the clinical symptoms and response to therapy.

Peripheral venous blood (1-3 mL) was drawn by aseptic method and inoculated in BACTEC 9120 bottles for culture. Samples for blood culture were collected at admission and every 48-72 hours till clearance. All the clinical samples (blood, pus, CSF, and other body fluids) were inoculated on 5% sheep blood agar and MacConkey agar plates. After overnight incubation, isolates were identified by their colony characters, morphology and staining characters. Antimicrobial susceptibility testing (AST) was done on Muller Hilton agar (MHA) by modified Kirby Bauer disc diffusion and interpreted using Clinical and Laboratory Standards (CLSI) guidelines [4]. E-test was performed to determine the susceptibility to vancomycin and linezolid. Vancomycin MIC determination was performed by agar strip method, ATCC 29213 *Staphylococcus aureus* was used as control stain and the MIC's for the control strain were found within susceptible breakpoints. To determine the nasal carrier state, one sterile cotton swab was inserted approximately 2 cm into both nostrils and rotated against the anterior nasal mucosa for 3 seconds. Similarly, axillary swabs were obtained.

All children were managed according to the National Centre for Disease Control guidelines [5]. Empirical therapy was started with amoxicillin-clavulanic acid or cloxacillin (± gentamicin). In serious infections, vancomycin was started by the treating physician at their discretion. Antibiotics were changed as per the susceptibility pattern of the organisms. For uncomplicated infections, minimum duration of treatment was two weeks. For complicated infections, liver abscess, empyema and endocarditis, treatment duration varied from 21 to 42 days from negative blood cultures depending on their clinical response [6].

The outcome was measured in terms of antibiotic resistance pattern, type of infection, clinical recovery, and nasal and axillary carriage of *S. aureus.* Isolates resistant to methicillin (cefoxitin) were labelled as MRSA [4] and those resistant to vancomycin were labelled as Vancomycin-resistant *S. aureus* (VRSA) [4]. MRSA isolates found to be resistant to three or more other antibiotics apart from beta-lactams were labelled as multidrug resistant (MDR) *S. aureus* [7]. Recovery was defined in terms of duration of fever (from enrolment to beginning of an afebrile period of 72 hours), appetite, duration of hospitalization and microbiological clearance (negative blood culture at 48-72 hour). Poor recovery was defined by fever lasting more than 7 days, poor appetite for more than 72 hours, hospitalization for more than 14 days, delayed microbiological clearance more than 72 hours, antibiotic resistance, and complications (shock, encephalopathy, ventilatory support or death).

Using the proportion of 54% MRSA amongst total staphylococcus infections in a previous study from India [7], we calculated a sample size of 96 participants with 10% absolute precision at 95% confidence level and alpha error of 0.05. We planned to enrol 100 children with confirmed *S. aureus* infection.

Statistical analysis: The data were entered into Microsoft Excel and analyzed using SPSS 20. Descriptive statistics were performed for antibiotic resistance pattern, clinical profile, nasal and axillary carrier rate, and outcome parameters. For risk factors of poor recovery, various parameters were compared between children having poor recovery against those not having poor recovery. Student *t* test was used to compare continuous variables, and chi-square test or Fischer exact test was used to compare categorical variables. Logistic regression analysis was performed for risk factors with *P* value ≤0.25 on univariate analysis to calculate adjusted odds ratio and 95% confidence interval for the outcomes of poor recovery.

RESULTS

We enrolled 100 children (56 boys) with *S. aureus* infections with one-third (*n*=31) of them aged less than 6 months and nearly half (*n*=51) were infants. Majority of the

Table I Clinical Diagnosis of Children With Staphylococcal Infections Enrolled in the Study (*N*=100)

Diagnosis	*No. (%)*
Skin and soft tissue infections	
Abscess	30 (30)
upper limb	4 (4)
lower limb	13 (13)
both upper and lower limb	2 (2)
head and neck	6 (6)
trunk and back	5 (5)
Pyoderma/cellulitis	9 (9)
Necrotizing soft tissue infection	8 (8)
Bone and joint infections	
Septic arthritis	8 (8)
Osteomyelitis	2 (2)
Osteomyelitis and septic arthritis	2 (2)
Pneumonia	29 (29)
Pneumonia with complications[a]	8 (8)
Acute meningitis	9 (9)
Sepsis without focus	14 (14)

Total percentage exceeds 100 because of the presence of more than one diagnosis in some children. [a]empyema/pneumothorax.

patients had acute complaints with mean (SD) duration of illness of 11.1 (20.3) days. Eighty-four children presented with fever and one third (*n*=28) had associated chills and rigors. Majority of participants were undernourished with mean (SD) weight for age *z*-score (WAZ), height for age *z*-score (HAZ) and weight for height *z*-score (WFHZ) as -2.9 (1.7), -2.1 (1.7) and -2.3 (1.5), respectively. Three-fourths (77%) of the participants were anemic, and 50% had leukocytosis, predominantly neutrophilic leukocytosis.

Table I depicts the sites of infection in study participants. Majority (90%) of the cases did not have any prior history (in last 30 days) of hospitalization or treatment in a healthcare facility. Skin and soft tissue infections (SSTI) were the most common presentation (47%) followed by respiratory infections (37%). Abscess was the most common manifestation of SSTI found in 64% (*n*=30). Necrotizing fasciitis, the most severe form of SSTI was present in eight cases. Eight participants had complicated pneumonia. Septic arthritis (*n*=8) was more common than osteomyelitis (*n*=2).

Table II describes the antimicrobial susceptibility pattern of all isolates. Two-thirds of the isolates (*n*=62) were MRSA. All the isolates were uniformly susceptible to netilmicin, vancomycin and linezolid. There was no significant difference in the clinical data, anthropometry and biochemical parameters between MRSA and MSSA infected children.

The MIC values for vancomycin ranged from 0.25 µg/mL to 2 µg/mL. Two-third (65%) of the patients had high (>1 µg/mL) vancomycin MIC values. The median (IQR) of vancomycin MIC of MRSA was higher as compared to MSSA [1 (1,1.5) µg/mL vs 1 (0.44,1) µg/mL, *P*<0.001).

Table II Antibiotic Susceptibility Pattern of *Staphylococcus aureus* Isolates (*N*=100)

Antibiotic	*MSSA(n=38)*	*MRSA (n=62)*
Cefoxitin,	38 (100)	0
Clindamycin[b]	33 (86.8)	36 (58.1)
Gentamicin[c]	37 (97.4)	34 (54.8)
Ampicillin[c]	30 (78.9)	1 (1.61)
Erythromycin[c]	19 (50)	3 (4.8)
Amikacin[b]	36 (94.7)	46 (74.2)
Netilmicin	38 (100)	62 (100)
Ciprofloxacin[a]	26 (68.4)	29 (46.8)
Cotrimoxazole	16 (42.1)	21 (33.9)
Vancomycin	38 (100)	62 (100)
Linezolid	38 (100)	62 (100)

Values in no. (%). MSSA-methicillin-sensitive S.aureus, MRSA-methicillin resistant S.aureus. [a]P<0.05; [b]P<0.01; [c]P<0.001.

A carrier state was found in 49 patients, out of which 32 were axillary carriers, 10 were nasal carriers and 7 were both nasal and axillary carriers, leading to 56 *S. aureus* isolates. Most (52, 93%) of these isolates were MRSA. In these 56 isolates, we compared their antibiotic susceptibility pattern to *S. aureus* isolated from site of infection in the same child. For 38 isolates, their methicillin (cefoxitin) susceptibility/resistance status was same as that of *S. aureus* isolated from site of infection. For 20 isolates, their antibiotic susceptibility pattern (for all antibiotics) was similar to the *S. aureus* isolated from infection site.

Ninety-six participants were discharged from hospital, three died and one left against medical advice. The mean (SD) duration of stay was 14.1 (5.5) days. The cause of death in three patients was sepsis, severe pneumonia and necrotizing fasciitis.

Poor recovery was present in 65 patients. On univariate analysis, severe stunting (HAZ score <-3 SD) (OR 4.54, 95%CI 1.4,14.4) and high vancomycin MIC (OR 7.0, 95%CI

Table III Factors Associated with Poor Recovery in *S. aureus* Infection (*N*=100)

Factor	*OR (95%CI)*	*aOR (95%CI)*
Age <6 mo	0.60 (0.25, 1.45)	0.39 (0.12,1.24)
Male gender	0.90 0.39, 2.05)	-
Presenting complaints		
Fever	0.57 (0.17, 1.92)	-
Chills	2.47 (0.89, 6.85)	2.38 (0.68,8.19)
Cough	0.92 (0.38,2.18)	
History		
Trauma	0.30 (0.10, 0.92)	0.39 (0.90,1.75)
Prior hospitalization	1.29 (0.31, 5.32)	-
Prior antibiotics	1.50 (0.49, 4.62)	-
Presence of abscess	0.57 (0.24,1.31)	0.65 (0.21,1.98)
BMI <-2SD	1.98 (0.85,4.60)	1.59 (0.54,4.69)
HFA *z*-score <-2SD	1.97 (0.85,4.58)	1.70 (0.61,4.73)
Hemoglobin< 10 g/dL	1.60 (0.62,4.15)	-
TLC > 15×10^9	1.46 (0.63,3.35)	-
Vancomycin MIC >1 µ/mL	7.07 (2.24,22.30)	5.34(1.56,18.5)
MRSA	1.37 (0.59,3.17)	-
Focus of infection		
Skin and soft tissue	0.66 (0.29,1.52)	-
Bone and joint	0.72 (0.21,2.48)	-
Respiratory	1.45 (0.61,3.47)	-
CNS	4.77 (0.57,39.82)	3.43 (0.33,34.4)
Sepsis without focus	1.41 (0.41,4.87)	-
Carrier state	0.51 (0.22,1.16)	0.47 (0.17,1.28)

BMI: body mass index, MRSA: methicillin resistant staphylococcal aureus, MIC: minimum inhibitory concentration, CNS: central nervous system, TLC – Total leukocyte count, HFA – Height for age.

2.2,22.3) were associated with higher odds of poor recovery, whereas history of trauma preceding the illness was associated with lesser odds of poor recovery (OR=0.3, 95%CI 0.1,0.9) (**Table III**). On logistic regression analysis, only high vancomycin MIC was a significant risk factor for poor recovery [aOR (95%CI) 5.3 (1.6,18.5); *P*=0.008].

DISCUSSION

In this study enrolling 100 children with culture positive staphylococcal infections, skin, soft tissue and respiratory tract were the most common sites of infection. MRSA was isolated in 62% isolates; 63% of MRSA were MDR *S. aureus*. Moreover, two-thirds (65%) of all *S. aureus* isolates had high MIC (>1 µg/mL) for vancomycin. Carrier state was present in almost half of the cases. High MIC for vancomycin was associated with poor recovery.

The global SENTRY surveillance program [8] conducted in 45 countries from North America, Latin America, Europe and Asia-Pacific region collected nosocomial and CA-*S. aureus* isolates from 1997-2016 and revealed that MRSA proportion of *S.aureus* had peaked till 2008, and declined since 2009. This reduction was consistent with several other regional and national surveillance programs during 2000-2010 [9]. This could be attributed to prioritizing MRSA infection prevention programs. However, in LMICs, the prevalence of MRSA seems to be increasing. In India, prevalence of MRSA was earlier reported to be 29-46% in hospital settings [10]. In the year 2013, Eshwara, et al. [7] documented MRSA in 54% of *S. aureus* bacteremia in children and adults, hospitalized in a tertiary care hospital in India. There are other recent reports of high prevalence of MRSA from developing countries [1,11]. Some of the possible reasons for high prevalence of MRSA in LMIC are irrational antibiotic prescription, socio-demographic factors like crowding and poverty resulting in circulation of resistant bacteriological strains in the community [12].

High MIC for vancomycin, a phenomenon referred to as 'MIC creep,' was first described in adults by Goldmann, et al. [13]; leading to concerns if vancomycin would be appropriate to treat invasive staphylococcal infection in presence of high vancomycin resistance and its association with poor outcome [14]. An earlier study in adults from North India documented that 50% of isolates from blood, skin and soft tissue infections had vanco-mycin MIC ≥1.5 µg/mL [15]. It has been seen that MIC creep phenomena is influenced by the type of *S. aureus* strain, type of patient population and storage of isolates [16].

We documented that high vancomycin MIC was significantly associated with poor recovery. Earlier systematic reviews [3,17] have also concluded that high MIC is associated with increased mortality and treatment failure. However, Pradhan, et al. [18], in a meta-analysis including 2955 patients from 13 reports, concluded that vancomycin MIC may not be the sole indicator of vanco-mycin treatment failure in MRSA and methodological differences, heterogenous population and differences in methods for estimation of drug susceptibility could be the other reasons.

Similar to this study, a high (42-82%) carrier state has also been reported in adults and children from other countries [19]. This may be of concern as colonized *S. aureus*, may act as reservoirs for future clinical infection and subsequent spread to the community. Lauderdale, et al. [20] observed that only nasal culture is not a sensitive marker of MRSA colonization, and if only nasal cultures are used, MRSA colonized patients are underestimated. Sending routine nasal and axillary swabs and eliminating carrier states may act as a step toward preventing community spread of MRSA.

The limitations of our study were the absence of long-term follow up to determine any recurrence of infections, lack of molecular characterization including *PVL* gene, and lack of epidemiological typing of the isolates. Another limitation in our study was that vancomycin MIC were determined by E-test which may provide 1-2 log dilutions higher MIC values than the reference broth microdilution test (BMD), which is the gold standard. However, E strip test is widely used as it is easy to perform and less cumbersome as compared to BMD. Also, E strip test when used with ATCC25923 *S. aureus* standard susceptible strain, as done in present study, maybe better correlated than BMD [4]. We, also, did not compare proportionate carriage of *S. aureus* in healthy and diseased population as we did not enrol any disease-free controls. The main strength of our study was availability of clinical data of patients till their discharge, which helped us to analyze the significance of antimicrobial susceptibility in a better way. We used E strip to detect vancomycin MIC, which is a more reliable method to determine the susceptibility of the organism to the glycopeptides.

We conclude that MRSA is the predominant staphylococcal strain in children hospitalized due to staphylococcal infections in our setting, and majority of them are multidrug resistant. Vancomycin may be used as a first line empiric antibiotic for serious staphylococcal infections and in those with documented MRSA. Vancomycin susceptibility testing can help in monitoring treatment especially in children with prolonged hospital stay or poor recovery. A higher proportion of MRSA, MDR and high vancomycin MIC in our group of patients with *S. aureus* infection is a serious concern with further risk of spread of resistant *S. aureus* infection in the community.

WHAT THIS STUDY ADDS?

- Methicillin-resistant *Staphylococcus aureus (*MRSA) was the predominant strain in children hospitalized due to staphylococcal infection acquired in the community settings.
- High MIC to vancomycin was associated with a poor outcome among *S. aureus* infected children.

Ethics clearance: Institutional Ethics Committee of Human Research, UCMS; No. IEC-HR/2017/32/99, dated Oct 17, 2017.
Contributors: KK: Conducted the study, data collection, literature review and drafted the manuscript; SK: data analysis, data interpretation, literature review, drafted and revising the manuscript. NPS: study design, provided laboratory support, supervised the study, provided critical inputs; PD: study design, supervised the study, literature review, provided critical inputs; PG: study design, supervised the study, literature review, provided critical inputs; DS: conceptualized the study, study design, literature review, data analysis, data interpretation, provided critical inputs. All authors approved the final manuscript.
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INDIAN ACADEMY OF PEDIATRICS

Kamdhenu Business Bay, 5th Floor, Plot No. 51, Sector 1,
(Near Juinagar Railway Station), Nerul, Navi Mumbai – 400706

NOTICE FOR ANNUAL GENERAL BODY MEETING OF INDIAN ACADEMY OF PEDIATRICS

Notice is hereby given that the **Annual General Body Meeting** of Indian Academy of Pediatrics for 2023 is scheduled to be held on **21st February 2023, during 60th IAP Pedicon and 30th IPA congress 2023 at Mahatma Mandir Convention and Exhibition Centre, Salt Mount Rd, Sector 13C, Sector 13, Gandhinagar, Gujarat. 382016 from 4:30 pm** onwards to consider the following agenda.

Kindly make it convenient to attend the meeting.

With kind regards,

Sd/-
DR UPENDRA KINJAWADEKAR
President, IAP 2023

Sd/-
DR VINEET K SAXENA
Hon. Secretary General, IAP 2022 & 2023

Place: Navi Mumbai **Date:** 15 January, 2023

AGENDA:

1. Confirmation of the minutes of the Annual General Body Meeting held on 21st March 2022 at Noida.
2. Business arising out of the minutes.
3. Consideration and adoption of Annual Report of the Society.
4. Consideration and adoption of the audited Statement of Accounts for the year ended 31st March 2022 and the Budget for the year 2023-2024.
5. Appointment of Auditors and fixing their remuneration for 2023-24.
6. Appointment of Honorary Legal Advisor for 2023-24.
7. Matters related to IAP Charity Activity.
8. Consideration of matters related to IAP Election for 2024.
9. Information of IAP Executive Board Members of the year 2023.
10. Matters related to 61st IAP Pedicon 2024.
11. Any other business, notice of which has been circulated with the agenda.
12. Any other business of which 30 days' notice has been given to the Secretary General in writing.
13. Any other business with the permission of the chair.

Note:

(1) If there is no quorum within half an hour of time fixed for the meeting, the meeting shall be adjourned to a later time on the same day and same place. No quorum is needed for the adjourned meeting.

(2) Kindly note that entry into the meeting hall will be permitted to only those members who give their Central IAP membership number and who bring their personal photo ID (such as Driving License with photo / PAN Card / Voter ID Card / Valid Passport / IAP Identity Card / Aadhar Card).

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REVIEW ARTICLE

Management of Hepatitis C in Children – A New Paradigm

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Introduction: With the advent of direct-acting antivirals (DAAs), the past decade has seen a paradigm shift in the management of hepatitis C (HCV) infection in children. In this review, we summarize the various treatment options for pediatric HCV infection, highlighting the recent changes in the management.

Methods: A literature search was performed using the PubMed database with the relevant keywords. Filters included were human, ages 0-18 years, and the English language.

Results: Initial phase of HCV treatment using conventional or pegylated interferon and ribavirin combination regimens yielded poor outcomes in children, especially in genotypes 1 and 4, with an overall sustained virologic response of 58%. Also, treatment with interferon and ribavirin combination was associated with significant side effects in up to 52% of those treated. Presently, various combinations of direct-acting antivirals (DAAs) have been approved in children above three years of age with documented evidence of high efficacy (SVR12 of 92% to 100%) and excellent safety, and the current standard of care.

Conclusion: With various DAA regimens now being approved for children above three years of age, the treatment of active HCV infection (HCV-RNA positive) in children has become simple. Besides the effectiveness of DAA therapy, public awareness about HCV transmission, better screening, and making the DAAs available at a subsidized price in the public sectors are necessary to eliminate HCV infection in India.

Keywords: *Direct-acting antivirals, Interferon, Outcome, Ribavirin*.

Hepatitis C virus (HCV) is a primarily hepatotropic single-stranded RNA virus belonging to the Flaviviridae family. HCV is classified into seven genotypes based on sequence variations. In India, genotype 3 is the most predominant genotype, accounting for more than 80% of the cases [1]. HCV is mainly transmitted through the parenteral route, sexual contact, and vertical transmission from mother to baby. Of all infections, 75%-85% develop chronic HCV (persistence of HCV for more than 6 months) [2]. However, the natural history of chronic HCV is relatively benign in children. It has been documented that HCV takes ten years to develop chronic hepatitis, 21 years for cirrhosis, and 29 years for hepatocellular carcinoma (HCC) [3]. Although morbidity in children is uncommon, a significant proportion of the infected children grow into adulthood with the risk of severe liver disease, including cirrhosis and hepatocellular carcinoma. A substantial shift in the treatment paradigm from interferon plus ribavirin-based therapy to all oral, safe and highly effective direct-acting antivirals (DAAs) in the current era has revolutionized the treatment of hepatitis C. Major milestones have been achieved from its initial report as a non-A, non-B virus in 1975 to the present achievement of effective virological cure. This review collates the literature on HCV treatment in children and the breakthroughs in HCV management.

HCV Prevalence - INDIAN SCENARIO

There is a scarcity of data on the prevalence of HCV infection in Indian children. A hospital-based study from North India [4] documented HCV as the cause in 5% (3/60) of Indian children presenting with cirrhosis. Schmelzer, et al. [5], in a modeling study, showed the global estimate for HCV viremic prevalence in children between 0–18 years of age was 0.13%, corresponding to over 3 million children with HCV in 2018. The same study showed a 0.04% (0.03-0.08) HCV prevalence in Indian children; however, the results were by extrapolation using regression analysis based on biological and epidemiological plausibility rather than by real epidemiological studies. Nevertheless, for various reasons, these reports likely underestimate the true prevalence. Most children with HCV infection are asymptomatic and, thus, are unaware of their status. Also, a recent change in epidemiological patterns has been reported, with an increased surge in the adolescent age group because of intravenous drug abuse and the opioid epidemic. A high HCV disease burden in young adults is a primary driver of an increased infection rate in pregnant women and as a consequence, more children are born to HCV-infected mothers (vertical transmission). In an adult

study, Puri, et al. [6] estimated that the prevalence of HCV infection in India is between 0.5% and 1.5%. Similar results were documented by Goel, et al. [7] in a systematic review with a prevalence of 0.49% in the low-risk adult population. The only community-based study from India, Chowdhury, et al. [1] have shown the prevalence of HCV among children (<10 years) is 0.31%, and 0.83% among adolescents (10-19 years) [1]. Multi-transfused children are at a higher risk of having HCV infection (13-65%) [8]. Though HCV screening has become mandatory since 2002, the serological tests used for screening cannot pick up cases in the window period. In developed countries, with the use of NAT-based (nucleic acid technology) screening in blood banks, the risk of transfusion-transmitted infection has been reduced significantly. In India, individual donation (ID) NAT testing is not yet compulsory and as a result of which HCV is still rampant among multi-transfused children [9].

MANAGEMENT OF HCV IN CHILDREN

The current era of DAA therapy has made a paradigm shift in the management of HCV infection in children, with recently published guidelines suggesting that the regimen of pegylated-interferon (PEG-IFN) and ribavirin (RBV) should not be utilized [10]. A review of historical antiviral therapeutic strategies, including PEG-IFN plus ribavirin, is warranted to appreciate the degree of superiority of DAA therapy over previous older HCV regimens.

Initial Phase of HCV Treatment

The initial phase of HCV treatment was based on interferon (IFN) monotherapy starting from the early 1990s before advanced treatment in the form of long-acting pegylated interferon plus ribavirin was approved in the late 2000s. The achievement and persistence of undetec-table HCV-RNA off treatment, defined as the sustained virologic response (SVR) at 6 month of stopping therapy is a satisfactory endpoint for a virological cure. Jacobson, et al. [11] reviewed 19 trials using IFN-alpha monotherapy for children with HCV infection, documenting an overall SVR of 36%. Most of the adverse events were mild and did not result in any treatment discontinuation. As none of the studies systematically recorded these adverse events, only a qualitative description of these events is available. The common adverse effects reported were influenza-like symptoms, fever, weight loss (reportedly regained after the treatment), neutropenia, alopecia, allergic reactions, pruritus, thrombocytopenia, and febrile convulsions [11].

Druyts, et al. [12], in a metanalysis of eight randomized control trials (RCTs) evaluating the efficacy of PEG-IFN (alfa-2a or alfa-2b) and ribavirin combination therapy in children, reported an SVR of 58%, with a higher SVR for genotypes 2 and 3 (87% and 89%) than for genotypes 1 and 4 (61% and 52%). The most common side effects seen were leukopenia (52%), neutropenia (32%), injection site erythema (27%), alopecia (13%), anemia (11%), pruritus (10%) and thrombocytopenia (5%) leading to a discontinuation rate of 4% [12]. Therapy has also been shown to negatively affect body weight, linear growth, and body composition, putting children at risk for developmental blunting [13]. Neuropsychiatric disturbances such as mood alteration, irritability, agitation, and aggressive behavior were reported in up to 30% of children [13]. Ribavirin is also a known teratogenic agent (category X) in women of childbearing age.

Further complicating the use of this combination regimen was the prolonged duration of treatment (with a total of 48 weeks for genotypes 1 or 4 and 24 weeks for genotypes 2 or 3), child-unfriendly formulation (subcutaneous injection), the need for intensive monitoring, and the known serious side effects profile. Ultimately, the treatment with PEG-IFN and ribavirin regimens, with their well-proven drawbacks, left pediatric gastroenterologists searching for alternatives. This often resulted in the deferral of treatment in expectation of improved therapeutic options in the near future.

Present Status of HCV Treatment

The origin of the newer agents for HCV treatment in the form of DAAs is based on the advanced understanding of HCV virology. HCV genome encodes for a 3011 amino acid residue polyprotein which undergoes proteolysis to yield ten individual proteins. Among them are three structural proteins (two envelope glycoproteins E1 and E2 and core protein) and seven non-structural (NS) proteins, which are p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (RNA polymerase activity), which participate in post-translational proteolytic processing and replication of HCV genetic material. These drugs target specific non-structural proteins of the virus and disrupt viral replication and infection.

Direct-acting Antivirals- A Boon for HCV Cure

DAAs are categorized into four classes based on their mechanism of action and therapeutic target. The four classes are non-structural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors (**Fig.1)**. Monotherapy with DAA should be avoided. Regimens should contain a combination of two different classes of

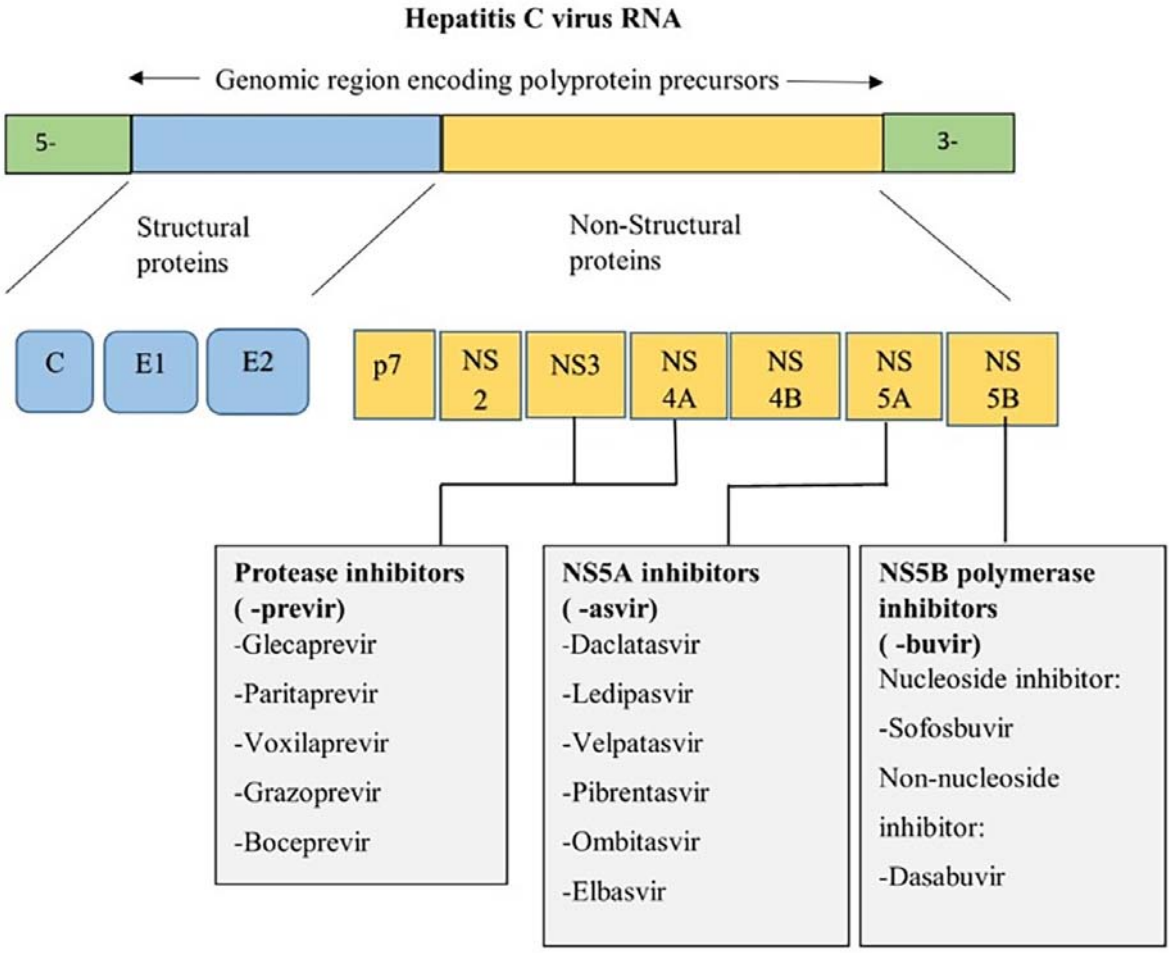

Fig. 1 HCV genome with its encoded proteins as targets for direct-acting antiviral agents.

DAAs, as drugs from the same class share cross-resistance. Various combinations of DAA-regimens (with a high genetic barrier to resistance) have been approved for children with HCV infection, showing high effectiveness and excellent safety with an adverse event profile comparable with placebo (**Table I**).

Ledipasvir-sofosbuvir: The first pediatric study assessing the IFN-free treatment with DAAs was a phase 2, multicentric, open-label study which evaluated the efficacy and safety of ledipasvir plus sofosbuvir in 100 children between the age of 12 to 17 years with chronic HCV genotype 1 infection [14]. Overall, 98% of patients reached SVR12 (at 12 weeks after stopping therapy), and no patient had a virologic failure. Two children who did not achieve SVR12 were lost to follow up either during or after treatment [14]. The approval of ledipasvir plus sofosbuvir in the pediatric population aged 3 through 11 years was supported by two clinical trials, which demonstrated high SVR12 rates of 99% and 97%, comparable to those seen in adults [15,16]. Across the three studies, there were no serious adverse events with the most common side effects reported being headache (18% to 27%), fever (17% to 21%), vomiting (24%), abdominal pain (15%), diarrhea (14%), and fatigue (13%) [14,17,18]. Ledipasvir plus sofosbuvir was approved by the Food and Drug Administration (FDA) in 2017, initially for children 12 to 17 years of age, with an extension to those over three years of age in 2019. Ledipasvir plus sofosbuvir is currently recommended for children aged ≥3 years with genotypes 1, 4, 5, or 6 [10].

Sofosbuvir-Velpatasvir: Jonas, et al. [19], in an open-label study, evaluated the efficacy of sofosbuvir plus velpatasvir for 12 weeks in children more than six years of age without cirrhosis or with compensated cirrhosis having genotypes 1, 2, 3, 4 or 6 HCV infection. Most of the study participants (147/173; 85%) were treatment-naive, and the rest (26/173; 15%) were treatment-experienced. Overall, SVR12 was ≥92%, with no treatment-related

Table I Studies on the Efficacy and Safety of DAA Regimens in the Treatment of HCV Infection in Children

DAA regimen	*Author, year, age group, number of study participants*	*Genotype*	*SVR12(%)*	*Common adverse events*
Ledipasvir and sofosbuvir combination	Balisteri, et al. [14], 2017; 12-17 y, *n*=100	1	98	Headache (18 -27%), fever (17-21%), vomiting (24%). No serious adverse events.
	Murray, et al. [17], 2018; 6-11 y, *n*=90	1	98	No reported drug discontinuation due to serious adverse events
	El Khayat, et al. [15], 2018; 12-17 y, *n*=144	1,4-6	99	
	Schwarz, et al. [16], 2019; 3-6 y, *n*=34	1 or 4	97	
Sofosbuvir and velpatasvir combination	Sokal, et al. [18], 2020; 3-17 y, *n*=216	1-4,6	92	Headache (20%), fatigue (17%), vomiting (15%), cough (12%), nausea (10%)
	Jonas, et al. [19], 2019; 6-17 y, *n*=173	1-4,6	>92	A severe adverse effect reported was auditory hallucination (0.5%)
Glecaprevir and pibrentasvir	Jonas et al. [20], 2020; 12-17 y, *n*=47	1-4	100	Nasopharyngitis (26%), upper respiratory tract infection (19%), headache (14-17%) etc.
	Jonas, et al. [21], 2021; 3-12 y, *n*=81	1-4,6	98	

DAA – direct-acting antivirals; SVR 12 – sustained virologic response 12.

severe adverse events or discontinuation [19]. Sofosbuvir plus velpatasvir use in pediatric patients aged 3-17 years has been assessed by the phase-2 registration trial (*n*=216), demonstrating high efficacy (SVR12 in 92% cases, virological failure in <1%) [16]. Overall tolerability of the drug was good, with the common side effects reported in the study were headache (20%), fatigue (17%), vomiting (15%), cough (12%), nausea (10%), etc. and serious adverse effects in the form of auditory hallucinations in one patient (0.5%) and treatment discontinuation due to side effects in 1.3% [18]. Based on reports of experience in adults, coadministration with amiodarone is not recommended due to the risk for symptomatic bradycardia. Sofosbuvir plus velpatasvir was approved by FDA in 2020 as a pan-genotypic regimen initially for children above six years of age, followed by an extension to three years and more in 2021 [10].

Glecaprevir-Pibrentasvir: Jonas, et al. [20] in part 1 of the DORA study among 47 adolescents with chronic HCV infection (genotype 1, 2, 3, 4, or 6) reported a high efficacy (SVR12 100%) with just eight weeks of treatment duration and no serious adverse events or treatment-related discontinuation. Part 2 of the DORA study supported the approval of glecaprevir plus pibrentasvir in the pediatric population aged 3 to 11 years, achieving high SVR12 rates of 96% (77/80) with no serious adverse events [21]. One child (1.2%) discontinued the drug due to a non-serious erythematous rash [20]. Both the studies (DORA part 1 and DORA part 2) reported only mild to moderate side effects commonly as nasopharyngitis (26%), upper respiratory tract infection (20%), headache (14% to 17%), vomiting (14%), fatigue (11%), fever (11%), diarrhea (10%) etc. [20,21]. An added advantage of this combination is its availability in the granule form (packaged as sachets) rather than as tablets aiding easier administration, especially in younger children without the need to score the tablets. However, it is not yet available in the Indian market, unlike ledipasvir-sofosbuvir and sofosbuvir-velpatasvir combinations. Glecaprevir plus pibrentasvir was approved by FDA in 2019 as a pan-genotypic regimen initially for children above 12 years of age, followed by an extension to three years or more in 2021 [10].

Sofosbuvir-Daclatasvir: Abdel Ghaffar, et al. [22], in an open-label, prospective study evaluating the efficacy and safety of sofosbuvir-daclatasvir in 40 children (above eight years of age or >17kg) with genotype 4 HCV infection showed high efficacy with SVR12 of 97.5% and no treatment-related serious adverse events or drug discontinuation. The most commonly reported side effects were cough (8%), fever (5%), and fatigue (5%). Similar results were reported by El-Shabrawi, et al. [23] in a study of 10 children with HCV infection (pan-genotypic), documenting an SVR12 of 100% and no serious adverse

events. The data to support the use of this combination in younger children (above three years of age) was based on modelled pharmacokinetic data in adolescents [24]. Based on this evidence, WHO has recommended using sofosbuvir plus daclatasvir in children above three years of age regardless of the genotype [25]. However, due to lack of well-powered studies and no direct study in children less than 8 years of age, the combination is not yet approved by the FDA and is not currently recommended by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in the treatment of pediatric HCV infection [10].

Indolfi, et al. [26], in a systematic review and metanalysis of 39 pediatric studies (1796 subjects) using various combinations of DAA regimens in children and adolescents, showed a pooled proportion among those receiving all doses of treatment and reaching SVR12 of 100%. Reported side effects were mild, the most common being headache (19.9%) and fatigue (13.9%), while serious adverse events were uncommon, highlighting the efficacy and safety of the various DAA regimens [26].

Implications of DAAs for HCV in Children

Although no direct studies are comparing DAAs with the older regimens (PEG-IFN and ribavirin), reported evidence suggests a high efficacy (92% to 100% vs 58%), mild or no serious side effects (discontinuation rate due to adverse effects <1.5% vs 4%) and very low risk of relapses (<1% vs 7%) for DAA based regimens over Peg-IFN plus ribavirin [10,12,27], no need to do a liver biopsy to document significant fibrosis in genotype 1. On the

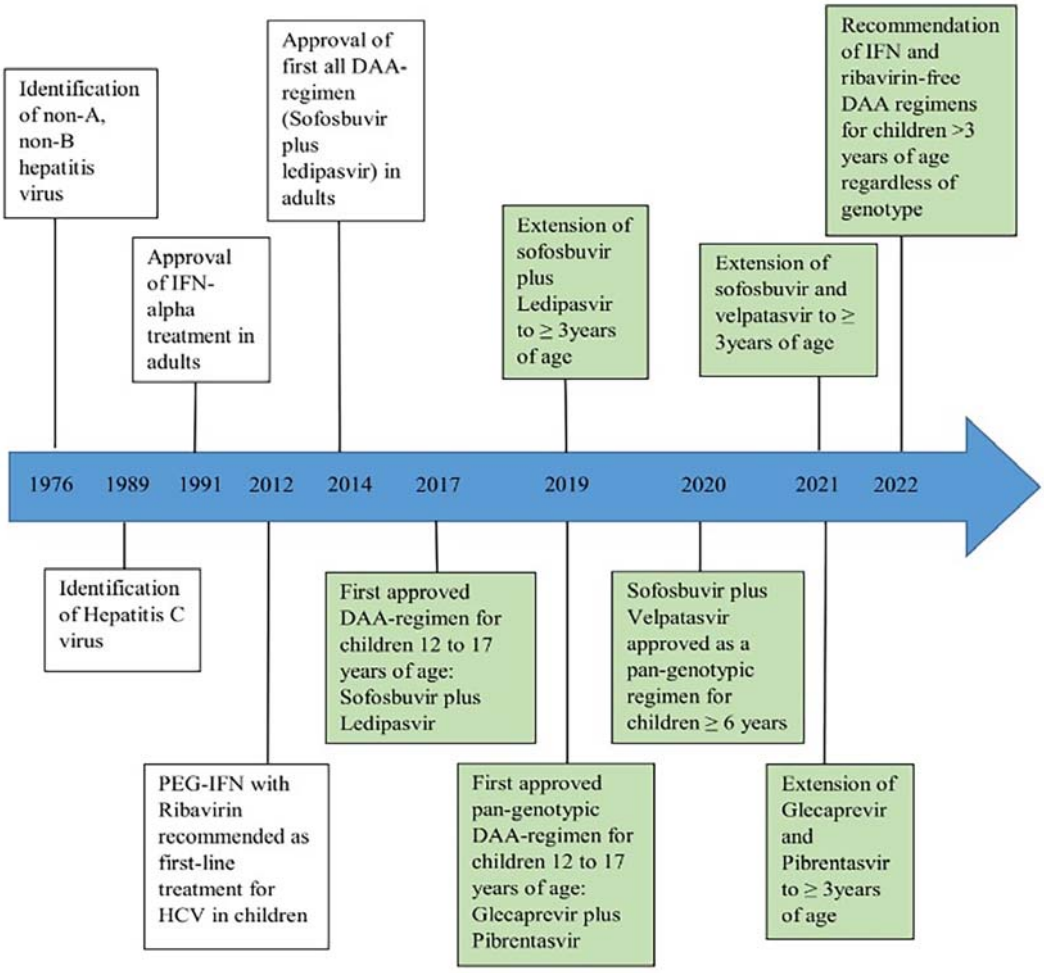

Fig. 2 Timeline of advancements in HCV discovery and treatment. Colored boxes signify milestones related to the approval of DAA therapy for children and adolescents.

basis of this well-documented evidence, updated recommendations paved the way for a completely IFN and ribavirin-free DAA-based treatment in children above three years of age irrespective of the genotype **(Fig. 2)** [10,25]. Also, therapy with DAAs is indicated for all children (>3 years) with active/current HCV infection (HCV-RNA positive) even if they are asymptomatic or have normal liver function tests; and liver biopsy is not necessary for starting treatment [10,28]. The rationale for this recommendation comes from well-documented evidence of the high efficacy and safety of DAA combination regimens in curing HCV infection thus preventing the risk of later development of complications like cirrhosis [10,28]. Additionally, curative DAA therapy during childhood or adolescence supports HCV treat-ment by preventing viral transmission, which is a major pillar in global/national preventive health strategies [10,28]. This has led to a significant shift from the historical approach of treatment deferment to a more aggressive strategy of initiating DAA therapy for all children (older than three years of age) with HCV infection, irrespective of liver function tests, genotype, or degree of liver injury [10,28].

CURRENT RECOMMENDATIONS

Whom and When to Treat

All children diagnosed with active HCV infection (HCV-RNA positive) who are above three years of age should be treated with a DAA-approved regimen regardless of disease severity, alanine aminotransferase (ALT) levels, genotype, history of treatment experience, and whether the infection is acute or chronic [10]. A liver biopsy is not necessary to initiate treatment in children with HCV. Testing for HCV genotype should be considered for those in whom it may alter treatment recommendations based on the age and availability of pan-genotypic regimens. Screening for HBV infection (i.e., HBsAg, anti-HBc, and anti-HBs) is recommended before initiating HCV DAA therapy due to the risk for HBV reactivation during or after treatment.

Treatment Regimens

Simplified treatment regimens are recommended for treatment-naive or interferon (± ribavirin) experienced children without cirrhosis and with compensated cirrhosis. Approved genotype-based and pan-genotypic DAA regimens and the drug doses are summarized in **Table II**. Decompensated liver disease and recurrent HCV after liver transplantation is rare in children. DAA-experienced pediatric HCV patients are rarely encountered in clinical practice (**Table III**).

Treatment in Special Situations

Recommendations for treatment of co-infection with HIV, co-infection with Hepatitis B, decompensated cirrhosis, and allograft recipients from HCV viremic donors are given in **Box I**.

CONCLUSION

There is a paradigm shift in the management of HCV infection in children with the approval of highly effective and safe DAA therapy. Current guidelines recommend only DAA-based combination regimens for treating HCV infection in children above three years, regardless of liver function test values, duration of infection (acute or chronic), and the genotype. Besides the effectiveness of

Table II Recommended DAA Regimens for Treatment-naive or Interferon-experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommendation	*Duration of treatment*	*Dose (weight based)*
Combination of ledipasvir plus sofosbuvir for children aged ≥3 y with genotype 1, 4, 5, or 6	12 wk	Once daily dose of ledipasvir/sofosbuvir < 17 kg= 33.75 mg/150 mg 17 to <35 kg = 45 mg/200 mg ≥35 kg=90 mg/400 mg
Combination of sofosbuvir plus velpatasvir for children ≥3 y of age with any genotype	12 wk	Once daily dose of sofosbuvir/velpatasvir < 17 kg= 150 mg/37.5 mg 17-<30 kg= 200 mg/50 mg ≥30 kg=400 mg/100 mg
Combination of glecaprevir plus pibrentasvir for children aged ≥3 y with any genotype	8 wk	Once daily dose of glecaprevir/pibrentasvir < 20 kg= 150 mg/60 mg ≥20 kg to <30 kg= 200 mg/80 mg ≥30 kg to <45 kg= 250 mg/100 mg ≥45 kg or ≥12 y=300 mg/120 mg

A longer duration of therapy (16 wk) may be needed for genotype 3 interferon-experienced patients.
Source: Reproduced from reference 10, with permission.

Table III Recommended Treatment Regimens for DAA-experienced Children Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommendation	*Duration*
Genotype 1: Ledipasvir plus sofosbuvir for children aged ≥3 years with prior exposure to interferon (± ribavirin) plus an HCV protease inhibitor regimen	12 wk (without cirrhosis) 24 wk (with compensated cirrhosis)
Genotype 4, 5, or 6: Ledipasvir plus sofosbuvir for children aged ≥3 years without cirrhosis or with compensated cirrhosis, having prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen	12 wk
Genotype 1, 2, 4, 5, or 6: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg having prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors	8 wk (without cirrhosis) 12 wk (with compensated cirrhosis)
Genotype 3: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors	16 wk
Genotype 1: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to NS3/4A protease inhibitors but no NS5A inhibitor exposure	12 wk
Genotype 1: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure	16 wk

Source: *Reproduced from referemce 10, with permission. DAA-direct-acting antivirals; HCV-hepatitis C virus.*

Box I Recommendations for the Management of Hepatitis C in Special Situations

Co-infection with HIV

- All HIV-positive children with HCV co-infection should be started on antiretroviral therapy (ART) irrespective of CD4 cell count.
- HCV treatment with DAA should be initiated in the presence of HCV viremia.
- ART and DAA regimens should be selected with particular consideration for potential drug-drug interactions.

Co-infection with HBV

- HCV treatment is indicated for children with HCV viremia.
- Treatment of HCV with DAAs may cause reactivation of HBV. Children fulfilling the standard criteria for HBV treatment should receive antiviral treatment.
- HBsAg-positive patients undergoing DAA therapy should be monitored for HBV DNA every 4 to 8 weeks during treatment and for three months post-treatment for those who do not meet treatment criteria for HBV.
- Although HCV-positive children with occult HBV infection have a very low risk of HBV reactivation during DAA therapy, they require close monitoring. Monitoring should be done with ALT levels at baseline, at the end of treatment, and on follow-up, with HBV-DNA and HBsAg tested in whom ALT levels increase or fail to normalize during or post-treatment.

Decompensated cirrhosis (Rare in children)

- Regimens with extended duration (24 weeks) or the addition of low-dose ribavirin are used in these patients.
- Any protease inhibitor-containing (e.g., glecaprevir, grazoprevir, and voxilaprevir) or interferon-based regimens are contraindicated.

Allograft recipients (*HCV negative recipients from HCVviremic donors*)

- Informed consent and formulation of treatment and follow-up strategies are necessary.
- Prophylactic (before HCV RNA results, immediately pre-transplant or day 0 post-transplant) or preemptive (day 0 to within one-week post-transplant as clinically possible) DAA therapy with a pan-genotypic regimen is recommended.
- For recipients of liver grafts, early treatment within the first two weeks is recommended after a liver transplant.

Source: *Reproduced from reference 10, with permission.*

DAA therapy, increasing awareness about the mode of HCV spread, better screening (use of ID-NAT-based tests in blood banks), and making the DAAs available at a subsidized rate in the public sectors are necessary to eliminate HCV infection from India without a preventive vaccine.

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Management of Hyperbilirubinemia in Newborn Infants 35 or More Weeks of Gestation: American Academy of Pediatrics, 2022

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Guidelines for management of hyperbilirubinemia in newborn babies 35 week or more have recently been updated by the American Academy of Pediatrics (AAP). This article compares the two guidelines (previous guidelines in 2004 and new guidelines) and lists the changes in diagnosis and management of hyperbilirubinemia proposed in the new guidelines along with implications for our setting.

Neonatal hyperbilirubinemia is a common problem faced by the pediatricians managing newborns. It is the seventh most common of cause of neonatal mortality in first 7 days of life worldwide and can lead to devastating long term sequelae including kernicterus spectrum disorder (KSD) [1]. American Academy of Pediatrics (AAP) recently revised their previous guidelines on management of hyperbilirubinemia in newborns born at or above 35 weeks of gestation [2,3]. These guidelines have been designed primarily for developed countries where disease profile is different and proper facilities for follow-up care are available. Infants in developing countries have different risk factors (prematurity, sepsis etc.), and facilities for prompt detection and treatment are sparse. Even so, AAP guidelines have been widely used and have been referred to in our national guidelines, primarily for defining treatment thresholds [4]. Given their routine use, it is important for pediatricians caring for neonates to be aware of the updated changes in these guidelines (**Table I**).

ASSESSMENT, MONITORING AND PREVENTION OF HYPERBILIRUBINEMIA

The new AAP guidelines 2022 re-emphasize the need for visual assessment of jaundice every 12 hours after birth and need to measure either transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) if jaundice is present in the first 24 hours of life. It is now recommended to measure bilirubin (TcB or TSB) in all babies between 24 to 48 hours of life as visual inspection is deemed far too inaccurate to assess the level of jaundice. Although TSB should be used as the definitive test to guide the need for phototherapy or exchange transfusion, TcB values are valid for screening the need for TSB estimation and decreasing need for sampling. TSB should be done if TcB value is within 3mg/dL of phototherapy threshold or ≥15 mg/dL. New guidelines also advise to consider the rate of rise of bilirubin if multiple values of TcB or TSB are available, terming rise of ≥0.3 mg/dL/h in first 24 hours and ≥0.2 mg/dL/h thereafter as exceptional, indicating hemolysis and need for direct antiglobulin test (DAT). The increased focus on objective measurement by either TSB or TcB makes it difficult to follow the guidelines strictly in LMICs. This is due to limited availability of TcB and even serum bilirubin estimation machines at primary and secondary health care settings where infants are first assessed for jaundice and where the visual inspection (guided by Kramer's chart) is relied upon for defining the need for testing [5].

Among the risk factors for neurotoxicity, asphyxia, lethargy, temperature instability and acidosis in the 2004 guidelines have been replaced by the term 'significant clinical instability' in the preceding 24 hours, thereby broadening the scope, depending on the clinical judgement. This along with sepsis, hypoalbuminemia (≤3 g/dL), hemolytic disease (including isoimmune, G6PD deficiency or other hemolytic conditions) and low gestation age (<38 weeks) are the hyperbilirubinemia neurotoxicity risk factors, thereby lowering the threshold for treatment.

New guidelines have reinforced the importance of providing support for breastfeeding and advice that oral supplementation with water or dextrose should not be given to prevent jaundice.

Blood group and DAT is recommended in all the babies born to Rh-negative mother whose antibody status is unknown; if positive, TSB is recommended 4

Table I Important Changes in 2022 Revision of American Academy of Pediatrics Guidelines on Hyperbilirubinemia

2004 Guidelines [2]	*2022 Guidelines [3]*
Antenatal maternal antibody screening	
Maternal screening recommended. No specific or detailed recommendations for interpretation of DAT following anti-Rh prophylaxis use in the mother.	Maternal screening for anti-erythrocyte antibodies in Rh-negative mothers, and if positive to test infant for blood group and DAT. A positive DAT may be ignored in cases when DAT is positive only for anti-Rh, and mother turned positive only following anti-Rh prophylaxis.
Screening for jaundice	
Universal screening by visual assessment every 8-12 h. TSB or TcB measurement, if jaundice appears in first 24 h or seems excessive.	Universal TSB or TcB screening is recommended between 24-48 h or prior to discharge if it occurs earlier.
Risk factors for significant hyperbilirubinemia	
–	Include lower gestational age, jaundice in the first 24 h, TSB/TcB nearing PT threshold or use of PT before discharge, hemolytic conditions, exclusive breastfed infant with suboptimal intake, scalp hematoma, and history of PT in parents or siblings. Additions: Down Syndrome Omissions: Maternal age, male gender and East Asian race.
Hyperbilirubinemia neurotoxicity risk factors	
Albumin <3g/dL, sepsis, isoimmune hemolytic disease, G6PD deficiency, acidosis, asphyxia, and significant lethargy.	Gestational age <38 wk, albumin <3 g/dL, sepsis, hemolytic conditions and significant clinical instability in previous 24 h.
Breastfeeding jaundice	
Formula or EBM supplementation recommended for breast fed infants receiving phototherapy, in case of excessive weight loss or dehydration.	Better described as Suboptimal intake hyperbilirubinemia. In infants with TSB nearing the PT threshold, with history suggestive of suboptimal feeding and excess weight loss, supplementation with formula can be considered.
Home-based PT for discharged newborns	
Home-based PT may be used for newborns with TSB 2-3 mg/dL below the PT threshold, and not to be used in any infant with risk factors.	Home-based PT recommended to be used for discharged newborns who meet the following criterion: Gestation ≥38 wk, age >48 h, adequately feeding, no risk factors for neurotoxicity, no previous phototherapy, TSB concentration no more than 1 mg/dL above the phototherapy treatment threshold, an LED-based phototherapy device available, TSB measured daily.
Discontinuation of PT	
No standard for discontinuation. PT may be discontinued when TSB falls below 13-14 mg/dL.	PT can be discontinued when TSB falls 2 mg/dL below the cut-off at which PT was initiated. Longer duration recommended for those with risk factors for rebound hyperbilirubinemia.
Rebound hyperbilirubinemia	
Risk factors: No particular risk factors listed.	Gestational age below 38 wk, PT initiation below 48 h, and hemolytic disease.
Timing of measurement: Within 24 h after discharge, if initiated early, discontinued before 3-4 d of life, and in a newborn with hemolytic disease.	On the day after PT is stopped (at least 12 h, preferably 24 h). Earlier measurement (at 6-12 h) for those with aforementioned risk factors.
Method: Not mentioned.	TcB can be used if at least 24 h have elapsed since stopping PT.
Escalation of care threshold	
Definition: No such threshold defined.	2 mg/dL below exchange threshold defined as "escalation of care" threshold.
IVIG recommended in isoimmune hemolytic disease TSB within 2-3 mg/dL of exchange threshold.	*Treatment/monitoring*: NICU admission, intravenous hydration and intensive PT.

contd....

Table I *continued*

2004 Guidelines [2]	*2022 Guidelines [3]*
	Consider IVIG in isoimmune hemolytic disease. 2-hourly TSB monitoring to be done till it falls below the threshold.
	Workup: Measure total and direct bilirubin, albumin, blood chemistry, blood group, send for cross match to arrange blood for ET, CBC, and G6PD levels in all these infants.
Exchange transfusion (ET)	
For readmitted infants, ET considered only if TSB remained above exchange threshold after 6 h of intensive PT (except for those infants who presented with features of ABE).	Recommended for ABE or TSB at exchange cut-offs. Recommendations no longer vary for during birth hospitalization and readmissions in this regard.
Hematocrit of blood: Not specified	Recommend use of blood with 40% hematocrit for ET for the benefit of increasing bilirubin clearance with additional albumin.
Risk assessment before discharge and subsequent follow up	
Schedule based on Bhutani nomograms for risk stratification, based on pre-discharge bilirubin (TcB or TSB).	Schedule based on difference between pre-discharge TcB/TSB (measured at least 12 h after birth) and phototherapy cut-off.

ABE-acute bilirubin encephalopathy, CBC-complete blood count, DAT-direct antiglobulin test, EBM-expressed breast milk, ET-exchange transfusion, G6PD-glucose-6-phospphate dehydrogenase, IVIG-Intravenous Immunoglobulin, PT-phototherapy, TcB-transcutaneous bilirubin, TSB-total serum bilirubin.

hourly twice followed by 12 hourly, along with early initiation of phototherapy.

In case of prolonged jaundice persisting beyond 3-4 weeks in breastfed and 2 weeks in formula-fed babies, measurement of TSB with direct bilirubin is recommended, along with evaluation for hypothyroidism.

TREATMENT OF HYPERBILIRUBINEMIA

New guidelines have raised the threshold for initiation of phototherapy and exchange transfusion at all gestations, recognizing that bilirubin neurotoxicity occurs well beyond the threshold of 2004 guidelines [6]. While raising these thresholds, it is emphasized that these guidelines are applicable only to developed nations as they require strict monitoring and follow-up post discharge and thus may not be applicable if follow-up is uncertain, as is often the case in resource-limited settings. To mitigate the issue of uncertain follow-up in LMICs, some experts advocate a lower threshold for initiation of treatment in secondary care settings, while maintaining the same cut-offs in tertiary care settings given that the follow up is certain and regular [5].

In the new guidelines, hour-specific phototherapy and exchange transfusion thresholds have been provided for each week of gestation age from 35 to 40 weeks in the low-risk group and 35 to ≥38 weeks for babies with hyperbilirubinemia neurotoxicity risk factor group. New thresholds also consider the postmenstrual age of the neonate and suggest that TSB should be measured within 12 hours after starting phototherapy.

Discontinuation of phototherapy, which was earlier advised at TSB <13-14mg/dL, is now advised when TSB falls 2mg/dL below the threshold at which it was started. Further fall in TSB may be targeted if there is a substantial risk of rebound hyperbilirubinemia (as suggested by age <48 hours at start, gestational age <38 weeks or in setting of hemolytic disease) [7]. In these cases, it is also advised to measure TSB 6-12 hours after stopping phototherapy. In others, TSB is to be repeated the day after stopping phototherapy. TcB can replace TSB if used at least 24 hours after stopping phototherapy [8].

Major additions to these guidelines are statements about "escalation of care" when TSB approaches exchange transfusion (ET) threshold (defined as 2 mg/dL below ET threshold). Escalating care, described as a medical emergency, includes immediate admission to NICU with facility of ET, intensive phototherapy, intravenous hydration, blood tests for albumin, TSB, direct bilirubin, and arranging blood for ET. It is followed by TSB measurement at two-hourly intervals till TSB falls below escalation value.

Guidelines maintain previous stand of optional treatment with intravenous immunoglobulin (IVIG; 0.5-1g/kg)over 2 hours in patients with isoimmune hemolytic disease which can be repeated after 12 hours if they require escalation of care [9].

Any infants showing signs of advanced bilirubin encephalopathy (hypertonia, retrocollis, and apnea)

should receive ET irrespective of TSB. Blood with hematocrit of 40% is preferred for ET, with the rationale that it would provide additional albumin augmenting binding of bilirubin.

Post-discharge follow up is now based on the difference between TcB/TSB value at discharge and phototherapy threshold. Use of risk nomogram by Bhutani, et al. [10] for this purpose is no longer advised as they do not consider gestational age and risk factors.

IMPLICATIONS FOR PRACTICE

The actual impact of new thresholds on number of babies receiving phototherapy and exchange, and by extension, on the healthcare system, will become clear in future. Considering that the treatment threshold has been increased for all gestations, there is a probable potential to decrease the treatment requirement and the duration of hospital stay. However, there is an invigorated emphasis on monitoring and follow up, and a recommendation for rapid and timely escalation of care. This is aided by TcB machine facilitating rapid serial evaluation, which is still not readily available in our setting. Availability of TcB machines at delivery centers or alternative like smart phone applications or newer point of care serum bilirubin machines along with structured follow-up schedule is imperative for successful adoption of these guidelines. Individual centers will need to devise an effective machinery to provide optimal follow up services bearing in mind that increased treatment threshold carries a potential of devastating consequence of chronic bilirubin encephalopathy if follow up is inadequate. This can be done by making the follow up for jaundice an essential part of neonatal care and making the discharging unit responsible for follow up. Additionally, the risk factors including infection are also different in LMICs. The contribution of infections to severe jaundice or kernicterus has been reported to vary from 14% in Africa to 31% in Asia, compared with 2% in major HICs [11]. Delays in delivering effective treatments, routinely available in developed countries, continue to account for the high burden of neonatal hyperbilirubinemia in LMICs.

Besides evaluation, it is evident that treatment guidelines cannot be implemented in their entirety in our settings. Home phototherapy would not be feasible in most cases. Additionally, the recommendation to stop phototherapy only after TSB is 2 mg/dL below the initial phototherapy threshold is impractical to be applied in case of isoimmune hemolytic anemia, where the phototherapy may be initiated in the first few hours of life. Another example is the recommendation to use blood with hematocrit of 40% for ET. It will be interesting to see if there is an increase in the requirement of subsequent packed RBC transfusion in these babies. So, it is prudent that the experience and practical issues faced with the new guidelines are reported and recommendations more suitable to our setting can be formulated.

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Lead Toxicity: The Unbeaten Menace

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Despite it being known for centuries that lead is toxic to man, the uncontrolled hazard continues to affect millions of human lives till date. As per Global burden of disease dataset 2019, nearly 800 million children in world have unsafe levels of lead in body, more than 50% of whom belong to South East Asia [1]. Talking about India alone, we have almost a whopping 275 million kids with elevated lead levels, highest among all countries [1]. Further, India accounts for 26% of global deaths due to lead poisoning, 2,30,000 premature deaths recorded in the year 2017 alone [2]. An increase of 53% and 30% in rates of deaths and disability due to lead poisoning has been reported since 1996-2000 [2]. Over the last five decades, the sources of lead in human life have changed, diagnosis has evolved, and the management has refined but the menace continues unabated.

THE PAST

The study by Sinclair, et al. [3] 50 years back, was conducted to measure blood lead levels in symptomatic children and results compared with the control group. A lead level of 60 µg/100 mL of blood was considered as abnormally high. The study divided the children into three groups, group 1 of 50 children with history of pica with anemia or/and abdominal pain or/and neurological abnormalities; group 2 of 25 children with acute encephalopathy and group 3 of 30 children with diseases not associated to lead poisoning. The authors also checked urinary coproporphyrin and *X*-ray of long bones in children with high blood lead levels. The study results suggested a high mean blood lead level in children with pica (68.1 µg/100 mL) and encephalopathy (79.4 µg/100 mL) when compared to controls (28.7µg/100 mL). Of the total children in each group, 46% and 36% children in pica and encephalopathy group, respectively, showed raised lead levels as against 3.3% children in control group. Abdominal pain in association with pica or encephalopathy was a significant factor. Urinary coproporphyrin levels showed no significant correlation with blood lead levels. The most common sources of lead cited were *surma, sindoor, holi* colors and morning sample of drinking water from tap (lead pipes were used then). Flaking paint as pica was more prevalent in the West, as against mud or white washed walls in India during those times. Other sources quoted in various studies at that time included lead bottles, lead containing medications (especially skin and herbal), adulterated spices, lead foils and glazed pottery. Industrialization was an upcoming cause as an environmental lead contaminant.

THE PRESENT

Fifty years down the lane, a lot has changed but the menace of lead toxicity continues. No lead levels are considered safe but as one of the major revisions made by World Health Organization (WHO) and Centre for Disease Control (CDC), blood levels >5 µg/dL has been labelled as unsafe [3]. In 2021, the Lead Exposure and Prevention Advisory Committee (LEPAC) further recommended CDC to use a blood reference value of 3.5 µg/dL to identify children with high blood lead levels [4].

As per the United Nations Children Fund (UNICEF) and non-profit Pure Earth 2020, a third of the world's children, nearly 800 million, are affected by lead poisoning, of which India accounts for 275.5 million [1]. A loss of up to 5 IQ points has been noted with lead poisoning [5]. Other associated features include reduced attention span, leaning disabilities, behavioral disorders, abdominal pain, anemia and encephalopathies.

Multiple studies have since been done across India, including Delhi-NCR (National Capital Region) regions to assess blood lead levels and its sources in children. In a study conducted in India by George foundation under 'Project Lead Free' in late nineties, 22,000 children were screened for high lead levels (>10 ìg/100 mL), 51% of which were found to be positive [6]. In spite of phasing out of leaded gasoline, considered as one of the major causes of lead toxicity in nineties, children affected with lead toxicity continued to increase [2,7]. In a meta-analysis published in 2018, 31 studies assessing blood lead levels in Indian population were included. The study showed mean BLL of 6.86 µg/dL (95% CI: 4.38-9.35) in children, which is above the safe levels [8].

In a major study conducted in Delhi by the Energy and Resources Institute (TERI) and UNICEF in 2012 [9], 23% of children living along the Yamuna river had lead levels more than 10 µg/dL. The most probable explanation given is contamination of water by dumping of industrial wastes. The food grown in the nearby soil, especially green vegetables like spinach have high metal content. Through this contaminated food and water, lead enters the human body causing various health effects. In another study done in Delhi school children aged 4-6 years [10], it was found that nearly 18% children had elevated lead levels (>10 µg/dL) [10]. The same author conducted a similar study 10 years later in another subset of Delhi school students aged 6-10 years [11], and found 12% of children to have elevated lead levels (>10µg/dL), giving a ray of hope, though the fall could be attributed to many other reasons such as area of study, surrounding industry and less incidence of pica in this age group.

With the phasing out of leaded gasoline, a fall in percentage of children with elevated blood lead levels was expected but the same did not happen, due to rapidly expanding industrialization. In the present scenario, industrialization and its effluents have become the major source of lead contamination of environment. In 2009, a study from Delhi measured the lead loading in household dusts [12]. The geometric mean of dust lead loading for floor and interior window sill samples was found to be 19.7 µg/ft^2 and 75.5 µg/ft^2, respectively. This was much more than the geometric means of same samples checked in US in 2000 and recorded as 1.1 µg/ft^2 and 9.4 µg/ft^2 in floor and windowsill samples, respectively [12].

Among other causes of lead exposure, recent studies have shown a very high level of lead found in paints (especially yellow paint), and artificial jewelry (maximum in pink color), crossing the permissible limits by almost 1000 times. Besides industrial waste (especially lead-based industrial products like batteries), paints and artificial jewelry, other sources of lead exposure include glazed pottery, fossil fuel burning and some healthcare products including herbal medicines [13-15].

THE FUTURE

Pediatricians and health care workers should routinely assess the environmental exposure to lead in their OPD practices. All children with symptoms suggestive of lead levels or with history suggestive of high environmental exposure should be screened for blood lead levels. Those found to have high levels should immediately be removed from the source of contamination. Others should be counselled on the sources of lead exposure and their prevention. Those with iron deficiency should be treated with iron supplementation as lead absorption increases in the presence of iron deficiency. Specific treatment in terms of chelation therapy should only be initiated in high lead exposure (>44 µg/dL), after consultation with an expert and knowing the risks and benefits of the therapy [16].

An urgent need of a government action plan is needed at state and national level to tackle the rising risk of lead poisoning. Joint efforts by policy makers and the people of country can help us to curb this silent killer [17].

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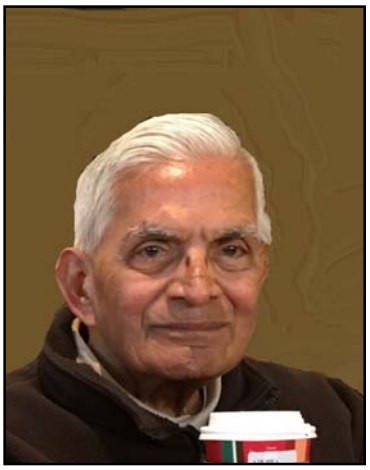
OBITUARY

Dr. Natesan Janakiraman



(1 August, 1930 – 30 November, 2022)

Dr. Natesan Janakiraman passed away peacefully in Chicago on 30th November, 2022, after a brief illness, at the age of 92.

Dr. Janakiraman was born on August 1, 1930 in Rangoon, Burma. His family fled to Madras by land to escape the Japanese invasion of Burma during World War II. He completed his medical education in Madras and then worked in small villages before migrating to the USA, where he joined Cook County Hospital in Chicago as an Intern. He spent his entire professional career here. He set up the first PICU at Cook County Hospital. He also became the Dean of the Chicago Medical School. In these capacities, he mentored an entire generation of medical students and pediatric residents. Dr. Jay, as he was fondly called, was known for his clinical acumen and humane approach to medicine.

In the early 1990s, Dr. Jay brought the Pediatric Advanced Life Support (PALS) course of the American Heart Association to India and conducted India's first PALS program in Madras. Subsequently, he conducted several additional PALS courses all over India and was instrumental in setting up the PALS training program in India. He was a known for his no nonsense approach and would not allow delegates to enter even if they were a few minutes late. He did not hesitate to fail senior professors if they were not up to the mark.

Dr. Jay attended various Pediatric Intensive Care Conferences in India whenever he visited. He was known for his humility and gentle powers of persuasion.

The entire Pediatric Intensive Community in India owes a huge debt of gratitude to Dr. Jay. He is survived by his wife, Vatsala, two daughters and several grandchildren.

Multisystem Inflammatory Syndrome in Children (MIS-C): Comparison of the First and the Second Waves

This study comparing the different parameters of children suffering from multisystem inflammatory syndrome in children (MIS-C) in Kolkata, India, during the two waves (July, 2020-January, 2021 and April-July, 2021) showed that the second wave had a higher propensity of Kawasaki disease (KD)-like presentation, cardiac affection and pediatric intensive care unit admission, and increased incidence of use of steroids for treatment.

Keywords: *Delta variant, Kawasaki disease, Steroids*.

Multisystem inflammatory syndrome in children (MIS-C) is a well described hyperinflammatory syndrome occurring 2-8 weeks after symptomatic/asymptomatic severe acute respiratory syndrome 2 (SARS-CoV-2) infection [1,2]. The first MIS-C wave hit eastern India around July, 2020 and lasted till January, 2021. The second wave of MIS-C started in April, 2021 and went on till July, 2021. The second coronavirus disease 2019 (COVID-19) wave in India was mainly of the Delta variant, and resulted in higher number of hospital admissions in adults and increased mortality [3]. The second wave of MIS-C that occurred in the aftermath of this COVID wave was shorter lasting, but like the adult Delta wave, was more intense, affecting a higher number of children younger than 5 years.

This is a single-center study of MIS-C patients diagnosed by the World Health Organization (WHO) criteria admitted at Institute of Child Health, Kolkata, a tertiary care pediatric hospital in eastern India. Hospital records of the clinical presentations, laboratory data, echocardiographic features, treatment protocols and outcomes of these patients were retrieved from hospital records and analyzed.

The comparative data between the two waves of MIS-C are summarized in **Table I**. There was an appreciable change in the clinical picture with increased incidence of patients presenting with only fever without organ involve- ment, and Kawasaki disease (KD)-like presentations. Majority of children during the first wave had abdominal symptoms and rashes, the numbers were much less during the second wave; but there was a higher propensity of cardiac affection and need for pediatric intensive care unit (PICU) admission. Statistical analysis of the results by the assumptions of the two sample *z*-proportion hypothesis test showed that history of SARS-CoV-2 positivity was statistically significant during the second wave, presence of rashes and abdominal symptoms were significant during the first wave.

Table I Characteristics of Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) Following the First and the Second Wave of Coronavirus Disease 2019 (COVID-19), Kolkata

Clinical presentations	*First wave (n=75)*	*Second wave (n=48)*
Age (y)[a]	5.66 (3,8)	4.62 (1.7,7)
History of SARS-CoV-2 positivity	32 (42.5)	33 (68.75)
Rash	64 (86)	19 (39.5)
Abdominal symptoms	53 (70.6)	20 (41.6)
Only febrile phenotype	3 (4)	13 (27.1)
Myocarditis	21 (28)	19 (39.5)
Coronary artery dilatations	22 (29.3)	23 (47.9)
PICU admission	34 (45.3)	28 (58.3)
Death	0	3 (6.3)
Treatment		
Intravenous immunoglobulin (IVIG)	29 (38.7)	0
IVIG + steroids	43 (57.3)	32 (66.6)
Only steroids	4 (5.3)	14 (29.1)
Biologics (infliximab)	0	3 (6.3)

Data presented as no. (%) or [a]median (IQR). SARS-CoV-2-severe acute respiratory syndrome coronavirus 2; PICU-pediatric intensive care unit.

The second wave also saw a paradigm shift in management, with an increased early use of steroids. During the first wave, especially in the earlier months, there was a predominance of intravenous immuno-globulin (IVIG) use. However, with passage of time and experience, use of methylprednisolone increased with the result that none of the patients were treated by only IVIG during the second wave. On the contrary, many patients without myocarditis responded only to methylpre-dnisolone and did not require IVIG. Use of early steroids increased, and only patients with myocarditis and KD-like presentation received IVIG. Infliximab was used by us in three IVIG and steroid resistant KD-like patients, who also had coronary artery dilatations.

We had previously done a retrospective analysis on the use of steroids in treating MIS-C [5]. We found that more severe cases of myocarditis with reduced ejection fraction required steroids in addition to IVIG for treatment. During the second wave, we initiated treatment with methylprednisolone in all and IVIG was added in patients with severe myocarditis presenting with shock. Patients presenting with features of myocarditis and shock were

started on pulse methylprednisolone (10 to 30 mg/kg/day), sicker children received higher doses, usually resulting in clinical improvement by the next 2 to 3 days.

There was no mortality during the first wave, whereas there were three deaths during the second wave; one due to refractory macrophage activation syndrome (MAS) and two with late referral, who succumbed to severe myocarditis and refractory hypotension.

The antigenic shift of the virus led to differences in severity and outcome between the two COVID waves. This difference was also evident amongst the MIS-C patients with change in clinical presentations, the Delta variant leading to a disease of increased severity and poorer outcome.

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Neonatologist-Performed Ultrasound-Guided Internal Jugular Vein Cannulation

We retrieved data of ultrasound-guided neonatal internal jugular vein (IJV) cannulations done between November, 2020 and March, 2021. Of the 33 ultrasound-guided IJV cannulation in neonates, 32 were successful with overall success rate of 97%. Median (IQR) number of attempts per insertion was 2 (1,3.5). There were no major complications observed during the insertion of the catheter. In one instance, inadvertent carotid artery puncture was encountered, without significant bleeding.

Key words: *Central line, Percutaneous, Simulation, Training*.

Trial registration: CTRI/2021/07/034944

Traditionally, cannulation of internal jugular vein (IJV) is performed by a 'blind' technique based on anatomical landmarks [1]. This technique; however, has a high failure rate and may be associated with several complications such as inadvertent carotid artery puncture, pneumothorax or hemothorax, and formation of hematoma, particularly in young infants [1,2]. Ultrasound (USG)-guided IJV cannulation is a standard technique in pediatric population and is reported to have reduced risk of cannulation failure as compared to conventional approach [3]. Literature on neonatal USG-guided IJV cannulation is limited, and has been mainly described by anesthesiologists or pediatric surgeons [2,4-6].

We describe the success rate and complications of neonatologist-performed USG-guided IJV cannulation

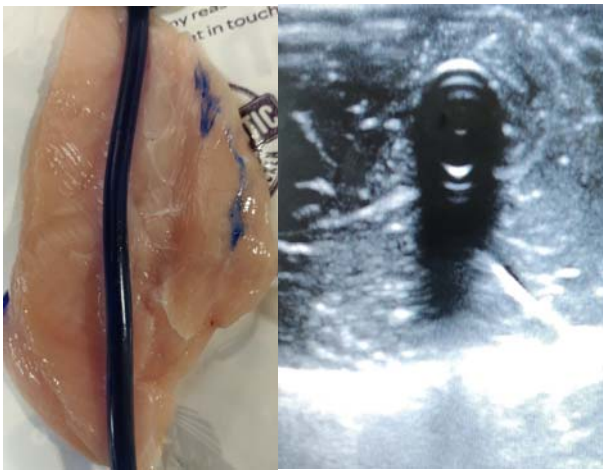

Fig. 1 Chicken breast simulator and its ultrasound image. Left side shows one chicken breast with dye filled tube. It is covered with another breast on top and wrapped with a plastic cover. Right side shows ultrasound image of model casting an acoustic shadow resembling a large vein.

from a tertiary care unit. The unit is a 32-bedded level 3B accredited neonatal intensive care unit. The unit has more than 1200 admissions per year, of which approximately 60% are extramural neonates; most being referred in critical condition such as hypoxic respiratory failure or shock, without any reliable venous access. In this retrospective study, demographic and clinical details of neonates who underwent IJV cannulation between November, 2020 and March, 2021 were retrieved. Outcome measures were success of cannulation, number of attempts per cannulation, catheter dwell time, and complications such as carotid artery puncture, pneumothorax, hematoma formation, cardiac tamponade, arrhythmia and central line-associated blood stream infection. The study was approved by institutional ethics committee and registered with the Clinical Trial Registry of India. The neonatologists acquired necessary training and expertise by first observing the cannulation performed by interventional radiologists, and then practicing puncturing at artificial targets in phantom models. This was followed by training on a simulation model, prepared by placing a rubber tubing filled with fluid, tunnelled in between chicken breast pieces, tightly wrapped in a plastic cover (**Fig. 1**) [7].

All IJV cannulations were performed by one of the two neonatologists, using Sonosite M Turbo machine with 13-6 MHz linear probe. Informed consent was obtained from the parents before the procedure. Neonates were positioned in the Trendelenburg position by placing a shoulder roll and head was tilted to the opposite side. We used short-axis, out-of-plane method, in which, USG probe was kept in a perpendicular manner, approximately at the base of Sedilot triangle to visualize IJV and surrounding structures in cross section. Internal jugular vein was differentiated from carotid artery based on its ellipsoid shape, larger size, presence of compressibility and absence of pulsatility. Venepuncture was performed under real time USG visualization with a 22-gauge cannula, introduced just behind the mid-point of the probe, at an angle 45-60% and directing it towards the ipsilateral nipple. Non-dominant hand was used to hold the probe and dominant hand was used for needle puncture. Successful puncture was ascertained by free flow of blood through the cannula, following which a guide-wire of calibre 0.46 mm was introduced through it. Subsequently, cannula was removed, while keeping guide wire in place and a catheter of 22-gauge, 4 cm length (leaderflex, Vygon) was threaded over the guide wire using Seldinger technique. Following this, guide-wire was removed and line was secured, after ensuring free flow of blood. Radiograph was done to confirm tip position and to evaluate for complications such as pneumothorax or hemothorax. Number of attempts and complications were routinely recorded on the patient's case record. Maximum five attempts were made, following which the procedure was abandoned. Cardiac tamponade was identified by sudden onset hypotension, muffled heart sounds and enlarged cardiac silhouette on radiograph. Cardiac arrhythmia was defined as any change in the normal sequence of heart rhythms during or after catheterization and confirmed on electrocardiogram. Central line-associated blood stream infection was defined as positive blood culture not related to an infection at another site, when the jugular line was in place at the time of or within 48 hours before the onset of infection.

During the study period, a total of 33 IJV cannulations were performed on 29 neonates. Of these, 32 (97%) were successful. Median (IQR) number of attempts per insertion was 2 (1, 3.5). All IJV cannulation were performed on extra-mural neonates, who had no access for umbilical or peripherally inserted central venous catheters. Majority (68.2%) of cannulations were performed on right IJV. The mean (SD) birth weight and gestation of neonates were 2405 (860) g and 35.17 (4.2) weeks, respectively. Nineteen neonates were mechanically ventilated at the time of line insertion. Cumulative success rate with first, second and third attempt was 39%, 51.5% and 75.8%, respec-tively. Median (IQR) catheter dwell time was 13.5 (7.0, 17.5) days. There were no major complications observed during insertion of catheter. In one neonate, who was extremely preterm, inadvertent carotid artery puncture occurred without significant bleeding. Attempt to cannulate was unsuccessful in another neonate, who was born at term gestation. In this patient, cannulation was attempted without use of sedation, as there was no IV access available prior to procedure. Central line associated blood stream infection was reported in three cases. All except three catheters were removed once not required. One catheter was removed on day 8 of insertion due to local extravasation, while two were removed on day 15 and day 22 due to catheter occlusion.

Literature regarding feasibility and success rate of neonatologist-performed USG-guided IJV insertion is limited. Goldstein, et al. [5] reported feasibility of USG-guided IJV cannulations in 20 neonates, which were performed by pediatric surgeons or anesthesiologists [5]. Cannulations were performed successfully in all neonates without any complication related to the procedure. Similarly, Tapia, et al. [2], in a case series of USG-guided IJV cannulation performed on neonates by pediatric surgeons, observed a high success rate (94%) with median (IQR) number of attempts 2 (1,8). Authors reported procedure related complications in none of the

neonates [2]. Oh C, et al. [4] reported serious complication in one out of 12 IJV cannulations performed by pediatric surgeons, in the form of hemoericardium [4].

USG-guided cannulation of peripheral veins in neonates is technically challenging as these vessels have a narrow lumen and small diameter. We performed IJV cannulation in extramural neonates, in whom the umbilical and peripheral veins were exhausted. Internal jugular vein was preferred over femoral veins as it is a larger and more easily accessible vein with a diameter that exceeds femoral vein by at least 50% [8]. We used single tube, chicken breast simulation model for training. Further improvement of this model can be done by inserting another fluid-filled tube to simulate carotid artery and therefore enhancing skills to avoid carotid artery puncture.

To the best of our knowledge, this is the first feasibility report of neonatologist-performed USG-guided IJV cannulation. Our findings suggest that neonatologist-performed USG-guided IJV cannulation is feasible, with success and complication rates comparable to those reported with other interventional operators [2,4-6]. Before contemplating the procedure on neonates, intensivists should acquire adequate skills by undergoing systematic training on simulation models.

Ethics clearance: EIC, Sir Ganga Ram Hospital, No. EC/04/21/1875, dated June 08, 2021.
Contributors: AT, MM: conceptualized the project; AT: wrote the protocol and had primary responsibility of patient screening, enrolment and data collection; AT: performed the statistical analysis and wrote the first draft of the manuscript; MM: helped in statistical analysis and manuscript writing; NK,PG: supervised during enrolment, outcome assessment and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Effect of Favoritism on Junior and Mid-Level Faculty

Favoritism is defined as "showing of special favor or partiality and the state or fact of being a favorite" [1]. While it is human to connect better or feel more comfortable with one individual compared to the others but obvious display and/or conduct of favoritism by those in administrative position has been shown to hamper team work and organizational growth. At an individual level, it appears to breed dissatisfaction in those who are not the so called chosen ones and negatively impact their overall performance [2,3]. As in other fields, medicine is also not untouched by favoritism. There is limited data on its impact on professional performance and satisfaction in the medical fraternity. Therefore, we created an online survey to ascertain the perceived prevalence of favoritism.

A survey was created on the SurveyMonkey-platform, and shared with assistant professors to professors or junior and senior consultants in government and private teaching hospitals, who had at least one senior person supervising them directly (head of department, or unit head).

The survey was shared with 100 medical professionals among the author's contacts, and 93 responded Of these, 62 (66.7%) were women, and 58 (62.4%) were from government teaching hospitals. Nearly three-fourth (72.3%) participants were junior-to-middle level medical professionals (**Table I**).

Table I Baseline Characteristics of the Respondents (*N*=93)

Characterstics	*Value*
Age (y)	41 (4.83)
Qualification	
MBBS (graduation)	11 (11.8)
MBBS and MD/DNB (post graduation)	48 (51.6)
MBBS, MD/DNB and Super specialty training	34 (36.6)
Specialty	
Pediatrics	31 (33.3)
Medicine	18 (19.3)
Surgery	13 (14)
Orthopedics	11 (11.8)
Other clinical specialities	9 (9.7)
Paraclinical specialities	11 (11.8)
Professional level	
Junior consultant	9 (9.6)
Consultant	17 (18.2)
Senior consultant	8 (8.6)
Assistant professor	21 (22.6)
Associate professor	24 (25.8)
Professor	14 (15.0)

Values in no. (%) or [a]mean (SD).

Among the respondents, 82 (88.5%) believed that they had been at the receiving at the end of favoritism sometime or the other. Thirty four (36.6%) participants reported that favoritism had impacted their professional satisfaction, 66 (71.2%) felt the impact of favoritism on their performance and that it influenced/ impacted their career. The results are summarized in **Web Table I**.

Favoritism by leaders at any level creates an environment of partiality and inequality, which is detrimental to the performance outcomes and working of any organization as a whole [2,3]. However, very little has been said about favoritism in medical institutes, especially among faculty, and its impact on their career progression, future choices and professional satisfaction [4,5]. This may possibly be a result of organizational silence or even cultural censorship. Such a work environment is sure to promote cynicism adding to personal stress in an already stressful environment. It may also result in loss of quality and productivity as reported in our survey, and also in previous studies [6].

An obvious limitation of our study is that the survey participants answered queries regarding favoritism by their senior colleagues as perceived by them, and the seniors' viewpoint was not studied. The views of many others being considered to be favorites may be different, and not solicited. Another limitation may be the relatively small number of survey participants, and the highly selective nature of the sample, which may lead to some skewing of results.

We feel that this small study raises important issues, and further studies with larger number of faculty may give a clearer picture.

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

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Iron Overload in an Infant With Rh-Isoimmunization

A late preterm (gestational age-36 wk) baby girl weighing 2.1 kg was born to a 30-year-old, G4A2L1 mother delivered through cesarean section. Mother had Rh-ve blood group, had a living child with Rh+ve blood group in G1 pregnancy; and G2 and G3 were aborted in first trimester. She did not receive anti-D prophylaxis during initial three pregnancies. In the current pregnancy (G4), fetal hydrops fetalis was detected in 24-week antenatal scan, indirect coombs test (ICT) was 1:256 titre positive. She was managed with five intra uterine transfusions (IUT) between 25-34 weeks of pregnancy. Baby had received phototherapy and exchange transfusion for severe hyper-bilirubinemia during first postnatal week.

At one-month of age, baby presented with moderate anemia (hemoglobin - 8.3 gm/dL), without icterus and organomegaly. She was afebrile, active, and with appropriate weight gain. Her blood group was O positive (due to multiple IUTs). Her reticulocyte count was 3.5%, mean corpuscular volume MCV- 74 fL, negative direct Coombs test (DCT) and microcytic normo-chromic red blood cells (absence of hemolysis) found in peripheral smear. She had hyperferritinemia (755, 655 ng/mL) with raised serum iron (138,129 g/dL) and transferrin saturation (76.7%, 56.6%) with low TIBC (180,228 mcg/dL) on day 29 and 63 of age, respectively. On follow up at age of 3 month and 6 month, she had only raised hyperferritinemia (322, 225 ng/mL), with normal hemoglobin (12 g/dL) at 6 month. Baby was managed conservatively with routine supplementation of vitamin D, without any iron chelation therapy.

This neonate presented with asymptomatic anemia and was found to have iron overload. The presence of hyperferritinemia in our case was similar to previous case studies following multiple IUTs [1-3]. The possible differential diagnosis could be common causes of anemia or either existing hemolysis due to Rh-isoimmunization, or suppression of erythropoiesis due to iron overload, or excessive nadir of physiological anemia of infancy [2].

The burden of Rh-isoimmunization is more prevalent in developing countries like India. It causes hydrops fetalis and increases neonatal morbidity [4]. IUT is the management option for severe fetal anemia, guided by antenatal middle cerebral artery Doppler. Currently, the facility for IUT is available only in few referral tertiary care centers of India, and the infants are subsequently followed by pediatricians. We suggest that pedia-tricians should be cautious in prescribing iron supplementation to such infant, who have received multiple intrauterine transfusions.

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Web Table I Survey Findings on Impact of Favoritism (*N*=93)

Your position in your hospital/institute	Junior consultant Consultant Senior consultant Assistant professor Associate professor Professor	9.6% 18.2% 8.60% 22.58% 25.81% 15.05%
Are you involved in teaching and research apart from your clinical work	Yes No	83.70% 16.30%
Have you ever felt that your senior in the department or organization is playing favorites	Always Usually Sometimes Rarely Never	21.51% 37.63% 30.11% 3.23% 7.53%
Have you been able to understand or figure out the reason why your senior has been favoring someone	Always Usually Sometimes Rarely Never	13.98% 36.56% 33.33% 8.60% 7.53%
Has the reason for favoritism something that you feel you could influence/change or generally in your hands	Always Usually Sometimes Rarely Never	.60% 7.53% 16.13% 49.46% 18.28%
Do you think that the favoritism has impacted your performance at work	Always Usually Sometimes Rarely Never	10.87% 10 19.57% 18 42.39% 39 14.13% 13 11.96% 11 1.09%
Has the favoritism influenced/impacted your career in terms of promotions/getting grants/better position in your organization	Yes No	68.82% 31.18%
How much would you say that favoritism has impacted your professional satisfaction	A great deal A lot A moderate amount A little None at all	13.98% 22.58% 24.73% 27.96% 10.75%

NEWS IN BRIEF

Urban Green Space Cover and Mental Health

With the growing urbanization, more and more green areas have been replaced by massive human settlements and factories, causing many health problems in populations living in these areas. Green cover not only reduces the air pollution but it also attenuates the noise and heat levels in the cities. Acknowledging the role of trees in mitigating the climate crisis, governments, local organizations as well as corporates are now focusing on increasing the green cover in and around the cities to improve the ecosystems. Green spaces do not only include urban forests or parks, but also the trees in the streets, gardens or roof tops. Studies have shown that people living near urban green spaces have fewer mental health problems, better cognitive function, mood, have healthier babies and longer life expectancy compared to those living in areas without it.

Availability of green spaces vary significantly between different cities as well as even within cities. How much green space is good for health? This question has been bothering urban planners for long time. In order to find the answer to this question, a team of researchers from Spain studied a population-based sample of 3145 individuals aged 15–97 years in a cross-sectional study. Authors evaluated the relationship between 3-30-300 green space rule (every citizen should be able to see at least three trees (of a decent size) from their home, have 30 percent tree canopy cover in their neighbourhood and not live further than 300 m away from the nearest park or green space) and mental health status of the participants. Mental health was assessed using 12-item General Health Questionnaire (GHQ-12) and medical history (use of tranquilizer/ sedatives or antidepressants and psy-chiatrist or psychologist visits). After analyzing their findings, author concluded that participants meeting the 3-30-300 green space rule had better mental health compared to the others, thus generating an evidence to guide the planning of green cover in the urban areas.
(Environmental Research 05 December, 2022)

mRNA Vaccines to Combat Malaria

During October, 2021, World Health Organization recommen-ded widespread use of first anti-malarial vaccine - RTS, S/AS01 (RTS, S) malaria vaccine among children in areas with moderate to high *P. falciparum* malaria transmission, resulting in the significant reduction in the severe malaria cases. Despite the extensive preventive efforts, globally there were ~247 million cases of malaria and 6,19,000 malaria deaths in 2021.

A research team from George Washington University has developed two newer mRNA vaccines to curb malaria infection and its transmission. The team evaluated the efficacy of experimental vaccine candidates targeting - Pfs25 and PfCSP (*Plasmodium falciparum* circum-sporozoite protein) – interrupting the disease process of the parasite and its transmission. These vaccines were delivered as mRNA-Lipid Nano Particle (mRNA-LNP) in mice. Researchers found that these vaccines induced a powerful immune response regardless of whether they were given individually or in combination. They also suggest that to achieve malaria elimination goals, a combination of vaccines targeting both the infection stage and sexual/midgut stages is expected to provide effective ways to interrupt malaria transmission. With the advent of these vaccines, one of the oldest and most severe disease may be eliminated in the near future.
(*npj vaccines 01 December, 2022*)

Vitamin B12 Supplementation for Plant-Based Diets

Due to the efforts of the animal welfare organizations or change in the dietary choices, globally more and more people are turning towards the plant-based diets. Also, due to their anti-oxidant, anti-inflammatory, lipid-lowering, immunomodulatory effects, these diets are getting more attention. But every change comes with a cost, thus consuming plant-based diet only, increases the risk of deficiency of micronutrients like iron, calcium and vitamin B12 etc. Vitamin B12 is essential for DNA synthesis, red blood cell production and nervous system. As plants cannot synthesize vitamin B12, consumption of plant-based diets only increases the risk of development of cognitive deficits, depression, dyspnea, postural hypotension, muscle weakness, as well as mental and physical fatigue. In a recently published paper, authors suggest that vitamin B12 deficiency can manifest with subtle neurological symptoms like fatigue, depression, memory impairment even in the absence of hematological manifestations. They recommend daily supplementation of vitamin B12 for individuals taking strict plant based diets, especially in the high risk groups like, pregnancy, young infants of the mothers taking plant based diets and age > 60 years. They also advocated the estimation of B12 levels, if no supplements were taken during the last 6 months.
(*European Journal of Nutrition 05 December, 2022*)

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CLIPPINGS

Neurodevelopmental outcomes at 1 year in infants of mothers who tested positive for SARS-CoV-2 during pregnancy (*JAMA Netw Open. 2022;5:e2215787*)

The likely association of COVID-19 infection of mother with children neurodevelopment outcome is not yet established. SARS-CoV-2 might enter the central nervous system from the nasal mucosa, lamina cribrosa, and olfactory bulb or through retrograde axonal transport.The virus has neurovirulence, activating cytokine storms, affecting brain vasculature and blood–brain barrier . Studies have revealed that SARS-CoV-2 infection in pregnancy has adverse neurodevelopmental out-comes in progeny, like autism spectrum disorders, schizophrenia, cerebral palsy, cognitive dysfunction, bipolar disorder, and anxiety and depression. In this prospective cohort study, the neurodevelopmental status of 298 infants born to SARS-CoV-2 infection positive mothers, was assessed at 10-12 months post-discharge using the Ages and Stages Questionnaire, 3rd edition (ASQ-3). 90% infants had favorable outcomes and only 10% exhibited developmental delays. Maximum women had SARS-CoV-2 infection in their third trimester. The majority of developmental delays among infants was in those whose mothers had SARS-CoV-2 infections during the first (P=0.039) and second trimesters (P=0.001) than in those whose mothers had SARS-CoV-2 infections during the third trimester. Although the neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections appeared favorable, more studies with larger sample sizes and prolonged follow-up periods are essential.

Associations of secretory activation breast milk biomarkers with breastfeeding outcome measures (J Pediatr. 2022:S0022-3476(22)00877-0)

The foremost cause for early discontinuation of breastfeeding is mother's perception of inadequate milk supply. In the initial phase of postpartum, the transition of mammary gland from secretory differentiation to activation is depicted by bio-markers, along with the initiation of copious milk production. In secretory activation, milk composition changes occurs sequentially, which occurs within 72 hours for healthy mothers. There occurs a decrease in protein and sodium concentrations, and sodium-potassium ratio. Later milk synthesis occurs by upregulation of the trans cellular pathways), resulting in increase in lactose and citrate concentration and closure of paracellular pathways leading to decrease in sodium, protein, and sodium-potassium ratio, and an increase in potassium and lactose. This prospective, longitudinal descriptive study collected ante partum, D10, and day 60 postpartum (D60) questionnaire data, and D10 milk samples. Protein, lactose, and citrate were analyzed with enzymatic spectrophotometric assays. Sodium and potassium were analyzed with inductively coupled plasma optical emission spectrophotometry. 92 mothers provided a D10 breastmilk sample and completed D10 questionnaires, and D60 questionnaires were completed by 83. Mothers with impaired secretory activation sodium (>23.0 mM) on day 10, seemingly to report D10 insufficient milk supply perception; and less D10 feeding/pumping frequency per day. They also had partial breastfeeding at D60. Mothers with D10 impaired secretory activation sodium to potassium ratio >0.8, were more presumable to partially breastfeed at D60. As, elevated milk sodium and sodium to potassium ratios are biomarkers related to low milk supply, so instantaneous milk testing can be useful in recognizing lactation compromise and can help in improving lactation duration.

Quality improvement initiative to improve infant safe sleep practices in the newborn nursery (BMJ Open Qual. 2022;11:e001834)

American Academy of Pediatrics (AAP) safe sleep recommen-dations in 1992 and the initiation of the 'Back to Sleep' campaign had led to a reduction in sudden infant death syndrome (SIDS). Still a significant number of deaths are attributed to SIDS. The practicing of safe sleep practices (SSP) within a hospital has shown to improve SSP at home. A prospective study was done with the use of quality improve-ment (QI) methodology, to increase adherence to infant safe sleep practices, with a goal to improve the proportion of infants having 'perfect sleep' to 70% within a 1-year period. Multiple Plan-Do-Study-Act cycles (7 cycles) were performed. Initial cycles targeted nurse and parental education, while later cycles focused on providing sleep sacks/wearable blankets for the infants. The percentage of infants with 'perfect sleep' increased from a baseline of 41.9% to 67.3%.And even the progresses were sustained over 12 months later.

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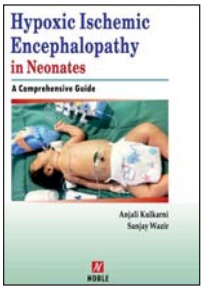
BOOK REVIEW



Hypoxic Ischemic Encephalopathy

ANJALI KULKARNI, SANJAY WAZIR
Noble Vision (Medical Book Publishers), Delhi.
Pages: 282; Price: Rs. 895/-

The authors have edited an excellent book on hypoxic ischemic encephalopathy (HIE), which will be useful for neonatology trainees and practicing neonatologists alike. Some of our general comments on the book are as follows:

The color plates provided by the editors at the start of the book give a good overall visual impression of the recent modalities used in field of HIE. They have covered difficult topics like HIE in preterm neonates, and MRI in HIE in a very lucid and clear manner, which makes it easy to understand. The highlights of this book are recent advances like NIRS in HIE, seizure detection and management in the context of HIE, and a lucid explanation of the ILAE 2021 position statement. The individual authors have also taken great efforts to include the latest evidence from clinical trials, and position papers for all chapters.

Our comments regarding specific chapters are as follows: Chapter 1 and Chapter 3 emphasize all recent amend-ments in NRP like delayed cord clamping, initial FiO2 requirement, optimum use of pulse oximeter and ECG. The relatively more recent concept of intact cord resuscitation has been introduced to readers in a comprehensive way. Chapter 2 summarizes all the modalities of antenatal fetal surveillance and provides useful recommendations on controversial topics like the choice of tests and the timing of delivery based on these tests. Chapter 7 summarizes all the biomarkers of asphyxia. The well-constructed tables make it easily digestible for readers.

There are a few minor points that the editors and the respective chapter authors can consider revising in the next reprint. In Chapter 1, a line stating that when the two-thumb technique is used, the provider must stand at the head-end to allow space for the other person securing umbilical lines (potentially the next step in resuscitation) – as has been included in latest NRP guidelines. In the same chapter, the initial dose of IV epinephrine (0.02 mg/kg) and endotracheal epinephrine (0.1 mg/kg) can be incorporated. In Chapter 8, continuous low voltage has been inadvertently described as both upper and lower margins <5. It should be changed to upper margin <10 and lower margin <5. The editors can add the concept of 'Expanded Apgar score' as it has been advocated by both AAP and ACOG since 2015. In Chapter 15, the editors can mention that the dose of leviteracetam is loading dose of 40 mg/kg and maintenance with 40-60 mg/kg. This is according to the standard treatment workflow for neonatal seizure given by ICMR. In Chapter 16, the cut-off value of FENa for pre-renal AKI can be modified to 2.5. Many workers have suggested using 2.5 as FENa cut off because FENa is inversely proportional to gestational age, and a few preterms may lose more urinary sodium in initial few days.

We suggest that Chapter 22 could include a few extra paragraphs on "Early stimulation" and "Principles of physiotherapy". Chapter 23 summarizes all the metabolic disorders which can masquerade as perinatal asphyxia. However, well-constructed algorithms may give a more practical approach for the readers.

Notwithstanding the minor changes suggested above, the book was a delightful read and a much needed addition to the bookshelves of all those who practice neonatal care, especially those who are practicing in India and developing countries.

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