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1. IAP: Indian Academy of Pediatrics, HMP: Hydrophobically Modified Polymer
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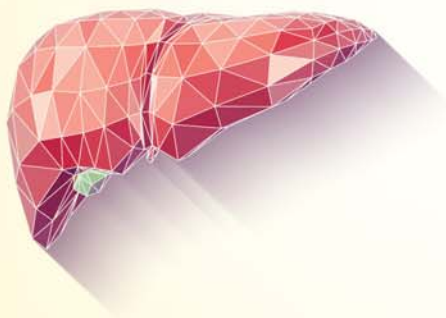
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Child Centered Care in the Post-COVID Era

REMESH KUMAR R

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More than a year has passed since the last general lockdown was imposed to prevent the spread of COVID-19. Though we often read about a possible third wave, fourth wave, and so on in the mass media, judging by the course of events that followed, these were more in the nature of false alarms. We need to continue to be cautious as ever in taking any threat to community health seriously. The novel coronavirus pandemic, which erupted first in the Chinese province of Wuhan in December 2019, has disrupted life on an unimaginable scale globally and left a trail of destruction in terms of loss of human life, disturbance to normal life and economic devastation at large. Though there were other times of alarm, such as the SARS, Zika virus, and Ebola virus epidemics in recent times, COVID-19 has been the greatest healthcare threat faced by the entire world during the last century.

Now that life seems to be finally returning to normal, it is time for us to take stock and determine our future course of action. What I wish to do is to draw a strategic perspective on the future of pediatric approaches in the aftermath of the pandemic. While this article runs the risk of appearing speculative, I wish to assert that it is well-grounded in the best research information presently available.

UNDOING TOXIC STRESS

When the pandemic first broke out, the immediate global response came in the form of harsh measures, such as total lockdown, shutting down of schools, calls for social distancing, and the avoidance of all forms of personal social interaction. Schools soon changed over to online mode and children lost out on normal life for almost two years. This forced isolation deprived children of normal social interaction and much-needed physical activity, both of which are crucial to their well-being during a very critical phase of their upbringing. A systematic review of the impact of various epidemics and social restrictions on mental and developmental health in parents and children published in the National Library of Medicine [1] observes that tools such as social restrictions, shutdowns, and school closures contribute to stress in parents and children and can become risk factors that threaten child growth and development and

may compromise the Sustainable Development Goals (SDG), which is especially significant as children's health is one of the most important issues in the SDGs. The review relates the data to adverse childhood experiences and an elevated risk of toxic stress. The more adverse experiences, the greater the risk of developmental delays and health problems in adulthood, such as cognitive impairment, substance abuse, depression, and non-communicable diseases.

“Stress that occurs continually, or is triggered by multiple sources, can take a toll on a child's health. Toxic stress that children suffer not only shapes their emotional lives as adults, but also affects their physical health and longevity,” observes an expert blog article published by Nationwide Children's Hospital [2]. The article divides stress into three types: positive stress, tolerable stress and toxic stress. While positive stress is good as it actually enhances our performance (like when we get hyperactive to meet a deadline), tolerable stress is temporary and gives us opportunities to cope (such as while being admitted to a hospital), toxic stress response can occur when a child experiences strong, frequent and/or prolonged adversity which results in changes to their baseline state. “Toxic stress has the potential to change your child's brain chemistry, brain anatomy and even gene expression. Toxic stress weakens the architecture of the developing brain, which can lead to lifelong problems in learning, behaviour, and physical and mental health,” observes the article.

Hence, it becomes clear from the above that repeated and prolonged exposure to stress stimulators with no accompanying relief measures can have a harmful long-term impact on child development. As pediatricians, in the days ahead, we need to be more alert to the child's psychosocial health and come up with the means to address such issues.

A FUTURISTIC PERSPECTIVE

A famous quote attributed to Abraham Lincoln says, “The best way to predict your future is to create it.” We are severely handicapped in predicting the long-term impact of pandemics due to the lack of availability of authentic research pertaining to it. However, one silver lining in the cloud of the COVID-19 pandemic is that it has given many

researchers a live theatre to study the long-term outcomes of large-scale health events from different perspectives. Taking an optimistic perspective, a study titled *Healthcare Transformation in the Post-Coronavirus Pandemic Era* published in *Frontiers* [3] observes: "The COVID-19 pandemic acts as a transformation catalyst, accelerating the implementation and adoption of changes in public health interventions." Thus, a new model of healthcare delivery emerges with more emphasis on preventive measures, remote care, and substantial technological dependence."

The authors point out that remote care or telehealth services, which were already being used in emergencies, crises, and routine care previously got a boost for wider utilization during the pandemic. "This system evolution is likely to serve as an adjunct for the gradual adoption of further new technologies, for example, the use of drones as delivery vehicles for critical supplies, robotics, the widespread 3D-printing of healthcare-related items, and smartphone-enabled monitoring of patient adherence to treatments," it says. It emphasizes the routine use of big data and artificial intelligence approaches to model crises and to identify and understand the weaknesses of existing systems (close to real-time) in order to strengthen existing structures.

Hence, in this scenario of rapidly changing healthcare practices across the world, it is high time for our specialty of pediatrics too to redefine itself and come up with an improved version of its being.

CHANGING FOR THE BETTER

The eminent author and social critic, Arundhati Roy, in her article *The Pandemic is a Portal*, writes: "Historically, pandemics have forced humans to break with the past and imagine their world anew. This one is no different. It is a portal, a gateway between one world and the next." Indeed, the post-pandemic scenario provides us with a new set of challenges, and we need to fine-tune our approaches to the changing reality. I personally feel that, more than anything else, we need a new conceptual framework to define the purpose and function of our profession. As indicated in the narration above, this change can mean a shift from the present clinic-based approach to the adoption of a more holistic view of child health. Rather than merely attending to clinical illness as we do at present, taking holistic care of children should become our primary objective. Focus on the psychosocial health of children, engaging in more interaction with children, outreach programmes to schools and becoming more community-oriented should help us to deliver the child-centred care we aspire for.

"Humanization of care" is the most evolved form of

thinking in health care. Here, the patient's preferences based on one's knowledge and beliefs regarding own illness are taken into account during health care, putting the patient at the centre of care [4]. In Pediatrics, this concept would translate into putting the patient and family at the centre of care usually. Child and family-Centred Care (CFCC) is thus a concept to take forward in the post-CoViD era. This had taken a back seat in many settings in CoViD times, where CoViD precautions separated families from the child or even newborn during illness. Much conclusive evidence needs to be generated in this aspect using the tested tools present already. Child-friendly, home-simulated environments in care centres if created with the backup of the Government and community will be a paradigm shift in childcare in future. The hospital stay won't be a nightmare for the children which otherwise affects their perceptions and even development in a negative way. This will involve creating child-friendly environments in care areas, where the children would love to be in, any time. Not an easy aim, the short-term goal could be to brainstorm and find out ways to achieve CFCC in our centres, leading the way in childcare, for the whole world to follow.

While the ideas discussed above are meant to serve as a starting point toward imagining a new future for pediatrics, we need organizations like IAP to take this line of thinking forward by stimulating its think tanks towards greater innovation and visionary pathfinding. As mentioned earlier, we should look upon the Sustainable Development Goal as our guidepost to the future and constantly invent or evolve creative new strategies to get closer to its objective. The only thing permanent in life is said to be change itself. Pediatrics, when compared to the original post, has evolved a lot. The transformation in recent years has been phenomenal and we are nowhere like what we were in the past. The journey from the primitive to the modern is a continuous one, and it always needs an open mind and the blossoming of fresh thoughts. I hope this article will be seen as a step forward in that direction.

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Take Home Ration Under ICDS: How Much and For Whom?

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Ensuring good nutrition for its population counts among the primary responsibilities of the government of any country. Nutrition – adequate to meet the daily needs, wholesome enough with all the macronutrients and micronutrients to meet the dietary requirements of the human body, and optimal in quantity to avoid the perils of over- or under-nutrition – is vital for human survival. The assurance of good nutrition is all the more crucial during the early childhood period (0-36 month) for meeting the needs of growth and development.

Provision of a national program for nutritional supplementation for children is an important investment for any nation, particularly for those having high burden of nutritional inadequacies among its pediatric citizens. The Integrated Child Development Services (ICDS) scheme of the Government of India is a paramount example of a national program for provision of nutritional supplementation. The program has been in existence now for over four and a half decades, and represents one of the world's largest and unique public health interventions for early childhood care and development. The provisions of nutrition supplements under the ICDS scheme are in line with the recommendations under the National Food Security Act, 2013. The Act recommends provision of 500 Kcal energy and 12-15 grams of proteins per day to the children aged 0-6 years, as Take Home Ration (THR) for the children of age 6 month to 3 year, and as morning snack and hot cooked meal for those aged 3-6 years [1].

The immense importance of Early childhood development (ECD) has been prominently highlighted recently [2], and that the 'Countdown to 2030' global distribution of 'children at risk of poor development' indicates the need for urgent action and investment in ECD. However, it has also been recognized that despite the implementation of several policies and programs including ICDS, the status of ECD in India as evident from the Composite Index, is far from optimal [2]. This calls for periodic assessment of ongoing strategies for ECD, nutrition being one of its most

vital components.

In this issue of *Indian Pediatrics*, Chevru, et al. [3] have provided an analysis of deficits in nutrient intake of ICDS beneficiaries who received THR in two districts of Karnataka. The authors have used a probability approach utilizing Estimate Average Intake (EAR) of nutrients to estimate the proportion of children at risk of inadequate nutrient intake among the ICDS beneficiaries. The authors found a significant energy deficit in children belonging to the age groups of 6-12 month and 13-36 month, despite availing ICDS benefits. They also calculated the actual risk of inadequate intake for both age groups to be between 12-47% for fat and other micronutrient (iron, calcium, zinc, folate, vitamin B12 and vitamin A), despite breastfeeding, complementary feeding and reported THR use. They further provide estimates for supplementary intake of nutrients to reduce this risk of inadequacy. These findings are of immense public health importance, especially if replicated from other diverse settings in the country.

Suboptimal childhood nutrition has always been a cause of concern in India. The National Family Health Survey 2019-21 (NFHS-5) provides updated information on the health parameters among Indian children [4]. The report documents that 36% of the under-five children are stunted, 32% are underweight (low weight-for-age) and 19% have wasting (low weight-for-height). While the parameters of childhood malnutrition have slightly improved since the last iteration of the NFHS (NFHS-4), there is still much to achieve as the stark prevalence figures show. Moreover, between 2015-16 (NFHS-4) and 2019-21 (NFHS-5), the prevalence of anemia among the children age 6-59 months has increased from 59% to 67% and continues to be higher among rural children, suggesting that focus is still required on combating the micronutrient deficiencies.

Under the ICDS program, supplementary nutrition is provided in two different forms. For children below 3 years of age, THR in the form of pre-mixes/ready-to-eat food are

provided. For the children from 3-6 years who visit the Anganwadi centers (AWCs), morning snacks followed by a hot cooked meal are provided at the center itself. In the current study, only the impact of THR has been studied as only the households with children of age 6-36 months were included. As compared to the children being fed directly at the AWC, provision of THR always has a disadvantage that it is uncertain whether the THR actually has been consumed at home by the intended beneficiary only, and to what extent. Talati, et al. [5] studied the utilization of THR, called as *balbhog*, in tribal areas of Dahod district in Gujarat. Of the eligible beneficiaries, 60% received less than the entitlement, nearly half (47%) disliked the taste, and 80% of these 'dislikers' fed the THR to their livestock. Eventually, the authors found that only 19% of the tribal children actually consumed the THR, of which more than 90% shared it with other family members. This reiterates that mere provision of additional THR cannot be the key to over-coming undernutrition. Marathe, et al. [6], in a study from Maharashtra, observed that cooked food for children below 3 years was a better strategy of providing supplementary nutrition than THR packets due to better acceptability, consumption, and adequacy of calorie and protein content (actual consumption).

Children aged 0-36 months are also a special group as breastfeeding may contribute a substantial amount of nutrient intake, leading to under-estimation of nutrient intake in this age group. Though Chevru, et al. [3] in their study mention about recording breastfeeding frequency, estimation of amount consumed during each event without test weighing is often a guesstimate as amount of milk production by mothers as well as milk intake by their infants is highly variable, especially beyond 6 months of age [7]. It would have been interesting to document the nutrient intake of children in their study excluding intakes from breastfeeding, and to check how many of them fulfilled the recommended intake of energy (200 Kcal in 6-8 month, 300 Kcal in 9-12 month, and 550 Kcal in 12-24 month) and other nutrients from complementary foods in a breastfed child [8].

While discussing the extent of childhood malnutrition in India, and the various parameters as reported in the NFHS-5, the entirety of causation cannot be attributed to lack of provision of adequate nutrition alone. It has been earlier highlighted that supplementary food should be viewed and used only as a magnet/vehicle for providing other services under the ICDS scheme [9]. Factors such as poor knowledge and implementation of infant and young child feeding practices, inadequate intake and excessive losses of nutrients due to recurrent/chronic infections, micronutrient deficiencies impairing appetite, poor dietary diversity and inadequate nutrient density of cooked food

are important reasons, especially in the age group of 0-36 months. In the study by Chevru, et al. [3], irrespective of the provision of THR, there was energy deficit among the beneficiaries considering the median value. Only a low proportion of the beneficiaries' mothers reported use of the THR in the 24-hour recall. This goes to show that there are further actions required to promote the actual utilization of the THR, including counseling and possible modifications of the THR itself to improve its quality, and provide more dietary diversity and variety.

Besides nutritional supplementation, management of undernutrition needs sustained interventions, including growth monitoring, addressing growth faltering, prevention and treatment of illnesses, prevention of infections, and with the increasing women's workforce, provision of adequate child care/daycare/crèche-based services for children under three years of age [10]. Though the ICDS scheme has been a remarkable step towards the welfare of the children of the country, there is still much ground to be covered regarding children's health in the nation as a whole. Evaluations of the lacunae regarding THR in the ongoing health related schemes in their current format, and suggestions for course corrections are a welcome step. The finding of nutritional deficits in terms of total energy intake and specific nutrients among the ICDS beneficiaries is a wakeup call to drive further research in this important field. The still hanging questions of whether to provide (as compared to hot cooked meals, or direct cash transfers), what to provide, and how much to provide as THR for the young denizens of the country need research prioritization to find the most optimum solution.

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Estimated Deficits in Nutrient Intake of ICDS Beneficiaries Who Receive Take Home Ration at Two Districts in Karnataka

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Background: The current estimates of energy and protein to bridge nutrient gap in the beneficiaries of the Integrated Child Development Services (ICDS) supplementary nutrition program use sub-optimal methodology for deficit calculation.

Objective: To estimate the nutrient deficit and the risk of inadequate nutrient intake in beneficiaries of the ICDS, aged 6-36 months, using individual 24-hour diet recalls, from districts of Chitradurga and Davanagere in Karnataka.

Study design: Cross-sectional design.

Participants: Children (aged 6 to 36 months) registered as beneficiaries of the ICDS in these districts.

Methods: Data were collected on socio-demographic factors, child feeding patterns, perception and usage of take home ration (THR), between August to October, 2019. Three non-consecutive days' 24-hour diet recall data of children were obtained from mothers, and anthropometric measurements were taken. The proportion of children at risk of inadequate nutrient intakes was

estimated using the probability approach. Assuming that 50% of a healthy population will be at risk of nutrient inadequacy such that intake and requirement distributions overlap, the proportion at actual risk of nutrient inadequacy ($\geq 50\%$) was calculated.

Results: A combined district analysis showed a median energy deficit of 109 kcal and 161 kcal in children belonging to the age groups of 6-12 month and 13-36 month, respectively. The actual risk of inadequate intake for both age groups ranged between 12-47% for fat and other micronutrient (iron, calcium, zinc, folate, vitamin B₁₂ and vitamin A), despite breastfeeding, complementary feeding and reported THR use.

Conclusion: Children who receive supplementary nutrition as part of the national program fail to meet their nutrient requirements that are essential for growth and development. The study results may help in strengthening the IYCF counselling and in modification of the existing THR, with quality and cost implications.

Keywords: Complementary feeding, IYCF, Take home ration.

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India's flagship program, the Integrated Child Development Services (ICDS) aims at tackling malnutrition in children, pregnant and lactating mothers, as one of its core objectives with a broader policy focus on child development [1]. The services that promote child growth in particular, includes Supplementary Nutrition Program (SNP), Infant and Young Child Feeding (IYCF) and Water, Sanitation and Hygiene (WASH) counseling, immunization and regular growth monitoring. Among infants, complementary feeding practices such as time of initiation, frequency, diet diversity, quantity, quality, and responsive feeding were reported to be sub-optimal, resulting in a deficit of nutrient requirements [2].

To address this nutrient gap, the SNP delivers take

home-ration (THR) to children aged between 6 to 36 months, containing measured quantities of grains and pulses in the form of a powdered multigrain mix or raw ration [3]. However, there have been complaints of poor quality, safety and usage of THR, which may fail to bridge this nutrient gap [3,4]. The prevalence for stunting,

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underweight and wasting in India is 35%, 33% and 17%, with the state of Karnataka reporting 32%, 32% and 19% respectively [5]. It appears that the SNP is far from successful, with a low decline in stunting and underweight prevalence rates of 1% and 0.7% per year and no change in wasting in under-5 children [6].

The current ICDS recommendation to bridge the nutrient gap through the THR is 500 kcal for energy and 12-15 g of protein per day per child [7]. This estimation; however, fails to apply robust and nutritionally sound principles of deficit calculation. The nutrient intake values were taken from National Nutrition Monitoring Bureau report 2004-2006 [8], and the nutrient requirements from Indian Council of Medical Research report, 1989 [9], both of which are outdated. Second, the computation of the energy and protein gaps did not consider the distribution of the intake, which entails the use of an Estimated Average Requirement (EAR), a mean value as opposed to the Recommended Daily Allowance (RDA), a safe intake value, which is EAR plus 2 SD. Third, the intake data are calculated using consumption units for children from household diet recalls, that are less than accurate [9]. Finally, there is no recommendation for dietary fats or micronutrients. Therefore, the primary objective of this study was to estimate the daily nutrient intake using individual 24-hour diet recalls, and to compute the nutrient deficit, in ICDS beneficiaries aged 6-36 months from two districts of Karnataka.

METHODS

Young children between the ages of 6 to 36 months, registered as beneficiaries of the ICDS, from Chitradurga and Davanagere districts of Karnataka, were selected for participation in the study. These districts were chosen as they differed in the type of THR distributed, socio-economic status, geographical conditions, and had proximity to each other. Eligibility for participation was based on whether the children were receiving THR from their respective anganwadi centers (AWCs), that was supplied by self-help groups at the taluk level. Children diagnosed with congenital syndromes, chronic medical or surgical conditions impairing growth, and those with severe acute malnutrition were excluded.

A total sample size of 270 (from both districts) was required to observe a 30% risk of protein inadequacy with 20% relative precision (assumed), 95% confidence interval and 20% complete response rate (for completion of diet recalls). A 30% protein inadequacy estimated from unpublished pilot data of around 40 children (from peri-urban slums) was used for the sample size calculation. Stratified random sampling was adopted for participant recruitment within a multistage sampling of AWCs. Chitradurga and Davanagere have seven and five taluks, respectively. The ICDS program divides each taluk into an average of 12 circles, with multiple villages and a minimum of 20 AWCs. Five circles within each taluk and two AWCs within each circle, were randomly sampled and those AWCs with fewer than 20 beneficiaries were not

considered. Two participants were chosen from each AWC, one from 6-12 month age group and the other aged between 13-36 month. In case the selected participant had siblings and both children matched the study criteria, the younger child was chosen (**Fig. 1**).

The study protocol was approved by the institutional ethical review board, and the Technical advisory committee of the State's Health and Family Welfare department. The study was also approved and assisted by the state's Department of Women and Child Development. Written informed consent was obtained from primary caregivers of the participants, who were also the primary respondents to assess eligibility and answer the questionnaires administered. Data were collected between August and October, 2019.

The pre-designed and piloted questionnaires were filled using the Computer Assisted Personal Interview (CAPI) tool 'Open data kit' on Android operating system tablet computers (Lenovo Tab4 10). The questionnaires captured data on socio-demographic information, respondent details, IYCF practices, form of THR received by the households, perception of quality and quantity, usage and sharing, commonly prepared recipes, and preferences of the form of THR. The socioeconomic status was categorized into groups using the Kuppaswamy classification [10].

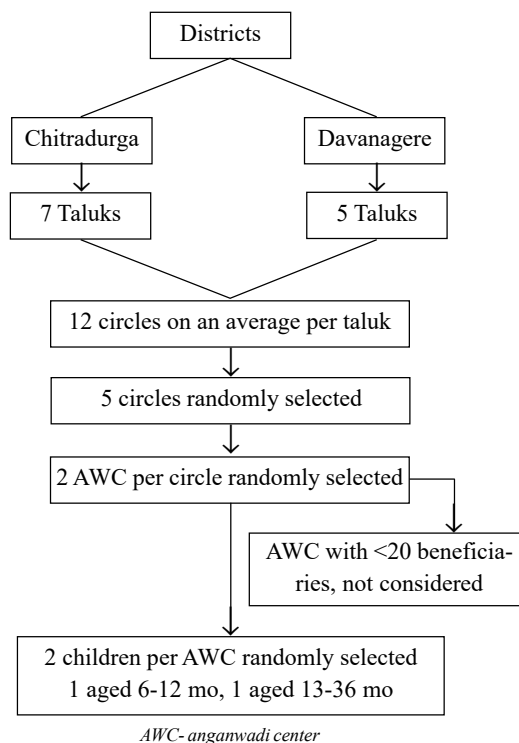


Fig. 1 Sampling strategy flow chart.

Three non-consecutive days' 24-hour diet recall data for the form of nutrients and food groups on a questionnaire were collected on two weekdays and one weekend. A 24-hour recall kit with standard portion sizes for bowl, glass, tablespoon and teaspoon was used along with models of chapatis or rotis of standard sizes, to aid in better understanding of the portion sizes used. The recalls provided information on frequency of breastfeeding, whether THR was used as part of feeding, and commercial foods consumed. Data from the recalls were entered into a validated software with standardized recipes linked to the Indian Food Composition Table that generated output on individual nutrients and food groups [11].

Anthropometric measurements included weight, length or height, mid-upper arm circumference (MUAC) and head circumference (HC). The Seca 874 digital flat scale (Seca GmbH & Co) was used to measure the weight of the infant to the nearest 10g and the Seca 417 infantometer (Seca GmbH & Co) measured recumbent length of infants less than 2 years of age to the nearest 1 mm. Stadiometer (Prestige HM 006 A) was used to measure the height of children above two years of age to the nearest 1 mm. The HC and MUAC were measured using the Seca 212 tape to the nearest 1 mm. The Seca 874 digital flat scale was calibrated every day, before use, by a standard weight of 2 kg before measuring the infants. The inter- and intra-observer variability for the four anthropometric variables was assessed, and the co-efficients of variation were noted to be <2%. In the field, minimum three consecutive measurements were taken. If the three consecutive measurements differed from the acceptable limits (weight 100 g; MUAC and HC 5 mm; length/height 7 mm) [12], readings were repeated, till there were two recurring readings, which were then used for analysis.

Statistical analysis: Analyses were performed using the R software version 3.6.3 and SPSS version 25. The usual intake of study participants was obtained from the 24-hour dietary recalls of three non-consecutive days and hence adjustments to the distribution of observed intakes were needed to partially remove the day-to-day variability in intakes (within-person variation). The statistical adjustment for within-person variability was performed using the approach proposed by the National Research Council and recommended by IOM [13]: Observed daily intake = usual intake + deviation from usual intake. Thus, usual intake =

Group mean + $\frac{\sigma_b}{\sqrt{\sigma_b^2 + \sigma_w^2}} * (\text{Individual mean} - \text{Group mean})$, where σ_b is the between individual variability, σ_w is the within individual variability. Daily intake data of certain nutrients were log-transformed for the usual intake computation and intake data were summarized by district and overall.

The population prevalence of inadequate intake was calculated for fat as detailed in **Web Appendix**. EAR was used for the deficit calculation of protein and micronutrients as per the Indian Council of Medical Research (ICMR) report [14], and few from the Institute of Medicine (IOM) report [13] when ICMR values were not available. The whole-body daily EAR was obtained for nutrient requirements that were expressed per kilogram body weight by multiplication of these values with the age- and sex-specific median weight from the WHO growth standard [12]. The details of calculation of the dietary nutrient deficit are provided in **Web Appendix**. Crude protein was corrected for its quality using the Digestible Indispensable Amino Acid Score (DIAAS) for the analysis of the dietary protein deficit. The DIAAS of rice was used in general for all cereals, while that of finger millet was used for millets, that of mung bean for all legumes, and that of egg for all animal source foods, as previously detailed [15].

The deficit in the intakes of protein, and selected micronutrients such as calcium, iron, zinc, vitamin A, vitamin B12 and folate were calculated using the probability approach [16,17] (**Web Appendix**). The EAR being the mean or average requirement will yield a proportion of 50% who are theoretically at risk of dietary nutrient inadequacy and should be the target of adequacy when evaluating population intakes. Then, the actual proportion of the population who are at risk of inadequacy is over and above 50%; for example, if the proportion at risk of inadequacy is calculated at 75%, then the proportion at actual risk of dietary inadequacy will be 25%. The required supplementary intake of protein and micronutrients was therefore computed to bring the risk of inadequacy to ≤50% while simultaneously ensuring that no intake exceeded the Tolerable Upper Limit (TUL) of intake at which point the risk of toxicity increases. The details of the 95% CI calculation for the estimated supplementary nutrients is provided in **Web Appendix**.

Reported from the questionnaire (as a yes or no response to the use of THR) versus diet recall usage (based on the documented ingredients) of THR were compared for the two districts separately, using Chi-square test. The dietary nutrient intake was compared based on THR usage within districts by generalized linear mixed models assuming log normal distribution for micronutrient and food group intake, with taluk of sampling considered as a random effect. The potential confounding of socioeconomic status was considered by including it as an additional factor in the model. Additionally, an estimate was made of the current THR's (as Nutrimix in Davanagere, which was quantifiable) contribution to the diet of beneficiaries, to bridge the energy and protein gap as per recommendation.

RESULTS

The district-wise and combined demographic, anthropometric characteristics, and habitual macro- and micro-nutrient intakes categorized by age, are provided in **Tables I and II**, respectively.

Age-wise dietary deficit and risk of inadequate intakes analyzed district-wise and combined, are provided in **Table III**. The estimated supplementary intake of nutrients to bridge the gap in dietary intake through complementary feeding, is provided in **Table IV**. If these supplementary intakes are added to the habitual intakes, <3% of children (for 13-36 month age) from Chitradurga or the combined

districts would exceed the TUL for iron, calcium and zinc.

It was also observed that 72% and 51% of the respondents reported usage of THR whereas the diet recalls revealed that only 37% and 19% included the THR in their child's diet at Chitradurga and Davanagere, respectively. All nutrients and food group intakes were comparable between THR consumers and non-consumers in both districts except folate (**Web Table I**). Vegetable intake was lower in the THR consumers ($P=0.001$) in Davanagere district. The comparisons were adjusted for the socio-economic status of the children and any intra-cluster correlation among children residing in the same taluk. THR

Table I Characteristics of Enrolled Children Receiving Take Home Ration from ICDS at Chitradurga and Davanagere Districts, Karnataka, 2019

| Characteristics | Chitradurga | | Davanagere | | Both districts | |
|-------------------------------------|-------------|------------|------------|------------|----------------|------------|
| | 6-12 mo | 13-36 mo | 6-12 mo | 13-36 mo | 6-12 mo | 13-36 mo |
| <i>N</i> | 77 | 77 | 61 | 55 | 138 | 132 |
| Boys | 43 (56) | 41 (53) | 28 (46) | 27 (49) | 71 (51) | 68 (52) |
| Family size ^a | 6 (5,8) | 6 (5, 8) | 6 (5, 9) | 6 (5, 8) | 6 (5, 8) | 6 (5, 8) |
| <i>Socioeconomic status</i> | | | | | | |
| Upper middle and above | 8 (10) | 7 (9) | 9 (15) | 9 (16) | 17 (12) | 16 (12) |
| Lower middle | 38 (50) | 46 (60) | 45 (74) | 33 (60) | 83 (60) | 79 (60) |
| Upper lower | 31 (40) | 24 (31) | 7 (11) | 13 (24) | 38 (28) | 37 (28) |
| <i>Anthropometry^b</i> | | | | | | |
| <i>N</i> | 76 | 76 | 61 | 54 | 138 | 130 |
| Height for age z-score | -0.7 (1.2) | -1.2 (1.2) | -0.7 (1.1) | -1.2 (1.0) | -0.7 (1.2) | -1.2 (1.1) |
| Weight for age z-score | -0.9 (1.2) | -1.2 (1.1) | -1.0 (1.0) | -1.3 (0.9) | -1.0 (1.1) | -1.2 (1.0) |
| Weight for height z-score | -0.7 (1.0) | -0.8 (1.1) | -0.8 (1.0) | -1.0 (0.9) | -0.7 (1.0) | -0.9 (1.0) |
| Mid-upper arm circumference z-score | -0.3 (0.9) | -0.4 (0.9) | -0.7 (0.9) | -0.7 (0.8) | -0.5 (0.9) | -0.6 (0.9) |
| Head circumference z-score | -1.0 (0.9) | -1.2 (1.0) | -1.0 (1.1) | -1.5 (0.9) | -1.0 (1.0) | -1.3 (0.9) |

Values expressed as no. (%) or as ^amedian (IQR) or ^bmean (SD).

Table II Macro- and Micro-nutrient Intakes of Enrolled Children Calculated From Diet Recalls in Chitradurga and Davanagere Districts, Karnataka, 2019

| Age, n | Chitradurga | | Davanagere | | Both districts | |
|-----------------------|------------------|------------------|-------------------|------------------|-------------------|-------------------|
| | 6-12 mo, 72 | 13-36 mo, 75 | 6-12 mo, 57 | 13-36 mo, 54 | 6-12 mo, 129 | 13-36 mo, 129 |
| <i>Macronutrients</i> | | | | | | |
| Energy (kcal/d) | 533 (471,650) | 845 (695,1019) | 644 (497, 782) | 729 (623,874) | 564 (485,715) | 777 (644, 974) |
| Protein (g/d) | 9 (8,13) | 21 (16,26) | 12 (8,14) | 17 (13,21) | 10 (8,14) | 19 (14,25) |
| Fat (g/d) | 23 (22,27) | 28 (22,38) | 25 (22,30) | 24 (17,30) | 24, (22,28) | 26, (21,34) |
| <i>Micronutrients</i> | | | | | | |
| Iron (mg/d) | 1.0 (0.4, 1.8) | 3.5 (2.3, 4.7) | 1.4 (0.6, 2.5) | 3.2 (2.1, 4.6) | 1.2 (0.5, 2.1) | 3.4 (2.3, 4.7) |
| Calcium (mg/d) | 240 (189, 321) | 374 (254, 617) | 273 (216, 424) | 282 (202, 393) | 261 (202, 384) | 349 (223, 518) |
| Zinc (mg/d) | 1.1 (0.8, 1.6) | 2.6 (2.2, 3.4) | 1.5 (0.9, 2.0) | 2.2 (1.8, 2.9) | 1.2 (0.8, 1.8) | 2.5 (2.0, 3.1) |
| Folate (µg/d) | 8 (3, 20) | 70 (41, 123) | 16 (7, 31) | 67 (40, 86) | 13 (4, 27) | 68 (42, 114) |
| Vitamin B12 (µg/d) | 0.13 (0.13,0.35) | 0.69 (0.32,1.15) | 0.23 (0.13, 0.49) | 0.50 (0.20,0.80) | 0.18 (0.13, 0.43) | 0.61 (0.30, 1.02) |
| Vitamin ARAE (µg/d) | 12 (3, 43) | 100 (51, 179) | 27 (9, 74) | 75 (41, 117) | 18 (6, 57) | 90 (48, 151) |

Values expressed as median (IQR). RAE-retinol activity equivalence.

Table III Risk of Inadequate Nutrient Intake in Enrolled Children in Chitradurga and Davanagere Districts, Karnataka, 2019

| Age, n | Chitradurga | | Davanagere | | Both districts | |
|-----------------------------------|---------------|----------------|---------------|---------------|----------------|---------------|
| | 6-12 mo, 72 | 13-36 mo, 75 | 6-12 mo, 57 | 13-36 mo, 54 | 6-12 mo, 129 | 13-36 mo, 129 |
| <i>Macronutrients</i> | | | | | | |
| Energy, kcal ^a | 150 (36, 205) | 121 (-27, 250) | 28 (-72, 154) | 244 (56, 416) | 109 (-23, 192) | 161 (-3, 327) |
| Protein ^b | 0 | 0 | 0 | 0 | 0 | 0 |
| Fat ^b | 22 (11, 32) | 8 (0, 19) | 8 (0, 21) | 30 (19, 40) | 16 (8, 24) | 17 (9, 25) |
| <i>Micronutrients^b</i> | | | | | | |
| Iron | 28 (28, 37) | 34 (24, 41) | 12 (0, 24) | 36 (23, 43) | 21 (13, 29) | 35 (28, 40) |
| Calcium ^c | - | 4 (0, 16) | - | 24 (10, 35) | - | 12 (3, 20) |
| Zinc | 36 (26, 43) | 0 (0, 6) | 23 (10, 34) | 9 (0, 22) | 30 (22, 36) | 0 (0, 9) |
| Folate | 47 (40, 50) | 8 (0, 20) | 48 (41, 50) | 26 (12, 37) | 47 (42, 49) | 15 (6, 23) |
| Vitamin B12 | 36 (26, 43) | 12 (1, 24) | 35 (22, 43) | 25 (12, 36) | 36 (28, 41) | 17 (8, 25) |
| Vitamin ARAE | 40 (31, 46) | 17 (5, 27) | 35 (22, 43) | 28 (14, 38) | 38 (31, 43) | 22 (14, 30) |

^aValues expressed as median (IQR). ^bValues expressed as % (95% CI). ^cEstimated average requirement not available for 6-12 mo, thus not calculated. RAE-retinol activity equivalence. For the risk of inadequate intake, the energy deficit was calculated as a difference between the Estimated Energy Requirement for standard weight based on age and sex of the participant and daily energy intake. For fat, the population prevalence of inadequate intake is the proportion of participants with intake below the fat requirement. For the rest of the nutrients, the probability approach was used as detailed in Web Appendix.

distributed in the form of Nutrimix (in Davanagere) contributed minimally to the child's diet, with energy at a median (IQR) value of 60 (45, 120) kcal/day, protein at 1.7 (1.2, 3.3) g/day and 0.4 (0.3, 0.8) g/day of fat.

DISCUSSION

This study provides details on nutrient intakes, their deficit, and the risk of nutrient inadequacy in children aged 6-36 month, who were beneficiaries of the ICDS, from two districts of Karnataka. A deficit in energy intake, and a risk of fat, iron, calcium, zinc, folate vitamin B₁₂ and vitamin A inadequacy, with breastfeeding, complementary feeding, and consumption of THR was reported. The estimated median energy deficit values, for 6-36 month (districts combined), was low by nearly one third of the current

energy recommendation of 500 kcal/day. Although the THR was distributed to the households, the usage in the child's diet was low and it failed to deliver the currently recommended energy (500 kcal/day) and protein (12-15 g/day) content. In Davanagere, children who consumed THR had a lower intake of folate, probably owing to observed lower intakes of vegetables indicating poor diet diversity.

A recent evaluation of the composition of THR by the World Food Program [18] focuses its recommendations on increasing fat content, adding micronutrients and including milk solids to improve protein quality. Evidence to support the need for improvement in THR composition was shown through an 'enhancement' of macro- and micro-nutrients along with SNP monitoring, in children aged 6-30 months, which proved to be beneficial for

Table IV Estimated Supplementary Intake of Nutrients to Reduce Risk of Inadequacy to ≤50% in Enrolled Children in Chitradurga and Davanagere Districts, Karnataka, 2019

| Nutrients | Amount of nutrient added | Risk of inadequacy after addition of extra nutrients (%) ^a | | | | | |
|-------------------|--------------------------|---|-----------------|----------------|-----------------|-----------------|------------------|
| | | Chitradurga | | Davanagere | | Both districts | |
| | | 6-12 mo (n=72) | 13-36 mo (n=75) | 6-12 mo (n=57) | 13-36 mo (n=54) | 6-12 mo (n=129) | 13-36 mo (n=129) |
| Fat (g) | 2.5 (2.3, 2.7) | 0 (0, 11) | 0 (0, 10) | 0 | 20 (7, 32) | 0 (0, 1) | 8 (0, 17) |
| Protein (g) | 2.7 (1.9, 3.4) | 0 | 0 | 0 | 0 | 0 | 0 |
| Iron (mg) | 3.5 (3.3, 3.6) | 0 | 0 | 0 | 0 | 0 | 0 |
| Calcium (mg) | 223 (202, 243) | - | 0 | - | 0 | - | 0 |
| Zinc (mg) | 1.3 (1.1, 1.5) | 0 | 0 | 0 | 0 | 0 | 0 |
| Folate (µg) | 67 (64, 70) | 0 | 0 | 0 | 0 | 0 | 0 |
| Vitamin B12 (µg) | 0.5 (0.48, 0.52) | 13 (0, 24) | 0 | 8 (0, 21) | 0 (0, 8) | 11 (0, 19) | 0 |
| Vitamin ARAE (µg) | 108 (105, 111) | 12 (1, 23) | 0 | 5 (0, 18) | 0 (0, 9) | 9 (1, 17) | 0 |

^aValues in parenthesis are 95% CI.

WHAT IS ALREADY KNOWN?

- The Supplementary Nutrition Program helps to bridge the gap in nutrient intakes of children between 6-36 months, in the form of take-home ration.

WHAT THIS STUDY ADDS?

- This study details the preferred method, and estimates risk of inadequate nutrient intake and the supplemental nutrients that are required to bridge the nutrient gap in young children, through a prospective survey.

childhood undernutrition indicators (stunting, wasting and underweight) in a rural area of Rajasthan [19]. The supplementary intake of nutrients required as estimated in this study, could guide the IYCF counselling on complementary feeding or the development of a modified (fortified) THR through the ICDS, to match the deficit in micronutrients. Inclusion of oil or ghee, green leafy vegetables and animal source foods will help bridge the deficit in macro- and micro-nutrients. Furthermore, the observation of low usage of the current THR and its failure to bridge the recommended gap, possibly owing to family sharing and poor acceptability related to quality, points to the need for improvement in the sensory quality of the THR.

This study emphasizes the need to apply appropriate statistical methods in identifying nutrient deficits at the population level, with the following merits. The SNP presently is heavily cereal-based, and efforts should be made to ensure that there is an adequate fat:energy and protein:energy ratio for the SNP, with micronutrients to fill any gaps that may exist. The observed median energy deficit, which is lower by one third of the current supplementary energy recommendation with no protein deficit, could present considerable quality and cost implications. The recommended energy content of the THR is 500 kcal per child/day and meeting this requirement with quality foods within a unit cost of Rs. 8 per child/day may be difficult. This forces the procurement of substandard commodities which coupled with poor infrastructure of self-help groups results in an inedible THR and consequently, poor acceptability and utilization [18]. If the supplementary nutrition followed the norm of filling the energy gap as calculated, the multi-grain mix production could be made cost-neutral in time, allowing for reallocation of resources for improving packaging, storage, quality control and assurance, timely delivery and tracking, thus ensuring improved THR receipt, making the system cost-effective and scalable. In addition, there is need to strengthen the counselling on the importance and necessity of THR at AWCs [20].

The strength of this study lies in its rigorous approach to identify child nutrient inadequacy through carefully

administered diet recalls. However, due to the relatively small sample size and sampling restricted to just two districts, it may lack generalizability to other districts or the State and needs further confirmation in larger number of children. It would be beneficial for the ICDS to perform periodic assessments, probably once in three years, sampling at Taluk or district level in each State, formulate recommendations to target aspirational districts and the rest of the State. Another caveat is the use median WHO body weights as the standard to calculate requirements, which may over- or under-estimate the actual requirements for those children tracking along a Z-score below or above the median, respectively.

In conclusion, the present study provides a platform for change to the existing IYCF counselling and THR nutrient recommendations, with quality and cost implications that will prove beneficial in executing the SNP through the ICDS, especially in concert with the Poshan Abhiyaan's improved and innovative efforts [21].

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

Ethics clearance: Institutional Ethical Review Board of St. John's Medical College and Hospital (No. 83/2019 dated April 12, 2019) and Technical Advisory Committee of the State Department of Health and Family Welfare Services (No. NPG/13/2019-20 dated August 1, 2019).

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Web Table I District-wise Comparison of Nutrient and Food Group Intake Between THR Consumer and Non-Consumers in Chitradurga and Davanagere Districts, Karnataka, 2019-2020

| Usage of THR | Chitradurga | | | Davanagere | | |
|---------------------------|-----------------------|----------------------|---------|----------------------|-----------------------|---------|
| | Yes | No | P value | Yes | No | P value |
| <i>n</i> | 57 | 90 | | 21 | 90 | |
| <i>Macronutrients</i> | | | | | | |
| Energy, kcal/d | 721 (536, 896) | 656 (510, 872) | 0.21 | 734 (571, 875) | 681 (504, 814) | 0.79 |
| Protein, g/d | 16 (10, 21) | 14 (9, 22) | 0.53 | 12 (9, 14) | 14 (11, 18) | 0.11 |
| Fat, g/d | 24 (21, 33) | 25 (22, 31) | 0.74 | 25 (23, 36) | 25 (21, 29) | 0.19 |
| <i>Micronutrients</i> | | | | | | |
| Iron, mg/d | 2.8 (1.1, 4.3) | 2.0 (0.8, 3.5) | 0.08 | 1.5 (0.8, 2.7) | 2.5 (1.2, 3.8) | 0.31 |
| Calcium, mg/d | 297 (200, 442) | 288 (212, 548) | 0.93 | 239 (198, 362) | 289 (215, 417) | 0.42 |
| Zinc, mg/d | 1.9 (1.1, 3.0) | 1.9 (1.0, 2.6) | 0.28 | 1.6 (0.9, 2.0) | 2.0 (1.3, 2.6) | 0.09 |
| Folate, (µg/d) | 38 (10, 112) | 30 (7, 80) | 0.38 | 25 (8, 39) | 33 (14, 75) | 0.03 |
| Vitamin B12, µg/d | 0.31 (0.13, 0.70) | 0.37 (0.13, 1.04) | 0.47 | 0.23 (0.13, 0.40) | 0.40 (0.15, 0.75) | 0.15 |
| Vitamin A RAE, µg/d | 51 (10, 112) | 46 (12, 120) | 0.79 | 40 (23, 113) | 55 (19, 98) | 0.85 |
| <i>Food Groups</i> | | | | | | |
| Cereals, g/d | 63 (27, 97) | 49 (21, 90) | 0.14 | 49 (31, 65) | 87 (31, 97) | 0.19 |
| Legumes, g/d | 1.9 (0.3, 4.7) | 0.5 (0, 4.7) | 0.07 | 8.3 (3.1, 13.7) | 3.1 (0.4, 7.3) | 0.10 |
| Vegetable, g/d | 3.21 (0.34, 11.70) | 0.88 (0, 11.06) | 0.07 | 0.11 (0, 4.51) | 6.04 (1.18, 12.89) | 0.001 |
| GLV, g/d | 0.18 (0, 0.67) | 0.04 (0, 0.53) | 0.24 | 0.01 (0, 0.65) | 0.23 (0.03, 0.64) | 0.11 |
| Nuts, g/d | 0.17 (0, 1.24) | 0 (0, 1.54) | 0.29 | 0.14 (0, 1.02) | 0.34 (0, 2.47) | 0.24 |
| Fats & Oils, g/d | 4.5 (0.9, 12.4) | 3.4 (0.8, 9.1) | 0.11 | 3.5 (2.3, 11.2) | 3.7 (1.4, 9.3) | 0.25 |
| Milk & milk products, g/d | 616 (369, 649) | 591 (477, 634) | 0.18 | 616 (552, 711) | 565 (234, 635) | 0.43 |

Values expressed as Median (IQR). Data based on dietary recalls. P value based on generalized linear mixed models adjusted for socio-economic status and intra-cluster correlation among children residing in the same taluk. THR, take home ration; RAE- retinol activity equivalence; GLV- green leafy vegetables.

WEB APPENDIX I

Details of nutrient deficit calculation

The energy deficit was calculated as a difference between the Estimated Energy Requirement and daily energy intake.

$$EER \text{ for energy } \left(\frac{kcal}{d}\right) = EER \left(\frac{kcal}{kg/d}\right) * \text{age and sex specific body weight (kg)}$$

The fat requirement was the fat in g that would contribute to 35% of the energy requirement in kcal/d for the age group 6 – 24 months and 25% for 24-36 months. The population prevalence of inadequate intake is the proportion of the age group with intake below the fat requirement.

$$\text{Fat requirement (g/d)} = \frac{EER \text{ for energy (kcal/d)} * 0.35}{9}$$

where 9 is the calories in kcal per g of fat, in the equation for 24-36 months 0.35 was replaced by 0.25 as the fat requirement for this age group is 25% of the energy.

The probability approach relates individual intakes to the distribution of requirements. A risk curve was constructed using the information on the requirement distribution of the group (median and variance) that specifies the probability that any given intake is inadequate for the individual consuming that intake and thereby gives the expected risk of inadequacy in the population. This method is robust to errors in shape specifications. Thus, if $F_R(\cdot)$ represents the cumulative density function of requirements for a nutrient in the population [17] then $F_R(a) = P(\text{requirements} \leq a)$ and will take values from 0 to 1. Then the risk curve of $\rho(a)$ is defined as

$$\rho(a) = 1 - F_R(a) = 1 - P(\text{requirements} \leq a)$$

where, P is probability, a is an individual's intake and $\rho(a)$ is the risk of an individual with an intake a .

Details of confidence interval (CI) calculation for extra nutrients added

Let the extra nutrient required by the population to meet the nutrient requirement conditions be denoted as δ . The estimate of δ is calculated as the minimum value of δ which satisfy the condition

$$P(\text{requirement} > \text{Intake} + \delta) < 0.5 \quad (1)$$

Additionally, for a uniform distribution of δ , the lower limit is that value of δ which satisfies the condition

$$P(\text{Intake} + \delta > 2.5\text{th percentile of requirement distribution}) > 0$$

$$\text{That is } \delta \text{ min} = \max(2.5\text{th percentile of requirement distribution} - \text{Intake}) \quad (2)$$

$$\delta \text{ max} \leq \text{TUL} \quad (3)$$

As the next step 1000 random values for U ($\delta_{\text{min}}, \delta_{\text{max}}$) are generated, where U is uniform distribution (4)

The estimate of δ is identified as the minimum value which satisfies condition 1 and denoted as $\hat{\delta}$.

To find the confidence interval for $\hat{\delta}$ its standard error is calculated as follows: random values of intake distribution were generated using normal or lognormal distribution. For each simulated distribution of intake, the value of δ is identified by repeating step (4) and applying condition (1). Using these values of δ standard error is calculated and obtained confidence interval using the formula $\hat{\delta} \pm 1.96 * SE(\hat{\delta})$.

Clinical Characteristics of Children With SARS-CoV-2 Infection During the Third Wave of the Pandemic: Single Center Experience

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Objective: To determine the clinical presentation and outcome of children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the third wave of the pandemic in India. **Method:** A review of hospital records was done at a tertiary care hospital, for children seen between 1 and 25 January, 2022. **Result:** Out of total 112 SARS-CoV-2 positive patients, 17 were hospitalized and 95 were treated in the outpatient department. Among non-hospitalized children, fever was the commonest feature (72, 75.7%), followed by sneezing, and loss of appetite. The median (IQR) duration of symptoms was 2.5 (1.5) days. Among hospitalized children, 10 had co-morbidities and one-third required intensive care unit admission. MIS-C was diagnosed in four patients. Out of 4 mechanically ventilated patients, two had coronavirus disease (COVID) pneumonia. The mean (SD) length of hospital stay was 7.5 (2.5) days. One child with leukemia died during management. **Conclusion:** During the third wave of the pandemic, most children had symptomatic illnesses, but recovery was fast among non-hospitalized children.

Keywords: COVID-19, Management, Multisystem inflammatory syndrome in children (MIS-C), Outcome.

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With the emergence of the Omicron variant of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), preliminary reports from other countries point towards a lower rate of severe disease in terms of the emergency visit, hospitalization, respiratory support, and intensive care admission among children [1-5].

India experienced an acute surge of infections during the third wave of pandemic from first week of January, 2022 and the majority of circulating variant was Omicron. However, data regarding clinical presentation and outcome of this new variant in children are lacking [6,7]. We present preliminary data on clinical characteristics and outcomes of children who visited the outpatient department and were hospitalized due to coronavirus disease (COVID-19).

METHODS

This review of hospital records was conducted at a tertiary care teaching hospital in Eastern India. Data collection was done after obtaining approval from the institutional ethics committee. Data of children aged between 1 month and 12 year, who visited the pediatric outpatient department or were hospitalized with evidence of SARS-CoV-2 infection in their nasopharyngeal swab real-time reverse transcription-polymerase chain reaction (RT-PCR) from 1 to

25 January, 2022, were included in the study.

As per hospital protocol, we preserved a copy of the prescription of suspected SARS-CoV-2 infected patients visiting the outpatient department (OPD). We retrieved this data for the study. The average duration of illness of positive patients who were at home care was collected from established state-run telemedicine program for all these patients. Information on demographic characteristics like age, sex, weight, and contact history, presenting signs and symptoms, and comorbidities were recorded. Multi-system inflammatory syndrome in children associated with COVID-19 (MIS-C) was defined according to WHO preliminary definition criteria [8].

For hospitalized patients, initial reports of the laboratory investigations including blood count, C-reactive protein (CRP), liver profile, renal function tests and coagulation profile were extracted. Data on other inflammatory markers such as ferritin, pro-brain natriuretic peptide, and D-dimer levels were available only for selected patients who had severe diseases requiring pediatric intensive care (PICU) admission or had features of MIS-C [9]. Bedside echocardiography was carried out for cases admitted with shock, features of MIS-C and congenital heart disease, and the results were retrieved.

Septic shock, ARDS and acute kidney injury were

defined and managed as per the Surviving Sepsis campaign international guidelines for the management of septic shock in children [10], Paediatric Acute Lung Injury Consensus Conference (PALIC) definition [11] and KDIGO guidelines [12], respectively. Fever was defined as axillary temperature above 99.5 °F according to Facility Based Integrated Management of Neonatal and Childhood Illness (F-IMNCI) [13]. Treatment received in the form of respiratory support, inotropes, intravenous immunoglobulin, steroids, aspirin, and low molecular weight heparin were noted. For admitted patients, duration of PICU and hospital stay were noted. The outcome and mortality were taken into account.

Patients, who required only home care were grouped into younger children (1-59 month) and older children (60 month-12 year) and compared for clinical characteristics and outcome.

Statistical analysis: SPSS 26.0 was used for statistical analysis. Quantitative continuous variables were compared between groups using Mann-Whitney's nonparametric tests or unpaired *t*-test. Qualitative variables were compared by the chi-square test and Fischer exact test. A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Of the 95 children in the OPD who were positive for SARS-CoV-2, none required hospitalization. Among 112 patients who required emergency hospitalization during the same period, 17 were positive for SARS-CoV-2 by RT-PCR (**Fig. 1**).

Analysis of clinical presentation of children who visited OPD revealed that fever was the most common

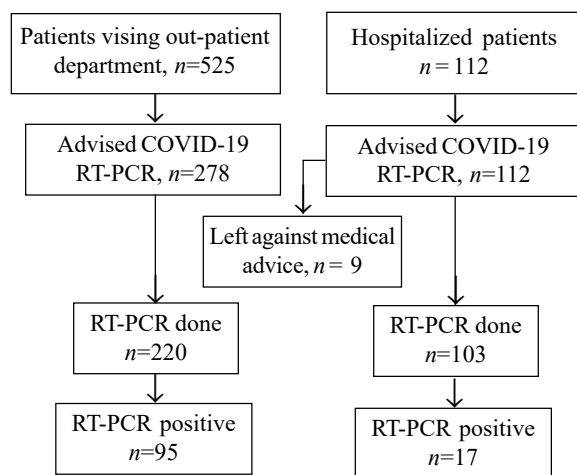


Fig. 1 Flow diagram of patients with COVID-19 attending the hospital during the study period.

clinical presentation (75.7%); fever >102° F was more common in children older than 5 years [OR (95% CI) 5.57(1.62, 17.74); *P*=0.001]. Median (IQR) duration of symptoms was comparable between the two groups [2.5 (1.5,3) vs 2.5 (2,3), *P*=0.078]. Symptoms like rigor, sore throat, and headache were more in older children, whereas under-five children had significantly higher gastrointestinal manifestations (*P*<0.05) (**Table I**).

Among the 17 hospitalized patients, the predominant clinical presentation was fever (*n*=14, 82.3%). Nine children (52.9%) had respiratory distress as the presenting symptom. Four children (23.5%) fulfilled the diagnostic criteria of MIS-C and all had severe disease. Ten children had co-morbidity (58.8%) (**Web Table I**). Echocardiography of four patients with MIS-C revealed ejection fraction (EF) less than 40%, and one had a coronary aneurysm (**Web Table I**).

Among 14 children who required respiratory support, four needed mechanical ventilation. Indications for mechanical ventilation were refractory shock, altered sensorium and pneumonia. Seven (41.1%) children received fluid boluses, and four needed inotropes (23.5%). Intravenous immunoglobulin (2 g/kg) and methylprednisolone (2 mg/kg/day) were administered to four children with MIS-C.

Table I Characteristic of Children With SARS-COV-2 Infection Treated in the Outpatient Department During the Third Wave of Pandemic, Kolkata, January, 2022 (*n*=95)

| Clinical Presentation | 1mo-5y (<i>n</i> = 54) | 5-12y (<i>n</i> = 41) | OD (95%CI) ^d |
|---------------------------------|-------------------------|------------------------|-------------------------|
| Fever ^c | 43 (79.6) | 39 (95.1) | 4.99 (0.98-48.4) |
| Temperature >102°F ^a | 6 (11.1) | 16 (41) | 5.57 (1.62-17.74) |
| Fever > 3 d | 16 (29.6) | 6 (14.6) | 2.46 (0.65-7.16) |
| Rigor ^a | 14 (25.9) | 31 (75.6) | 8.86 (3.18-25.33) |
| Sneezing ^c | 33 (61.1) | 14 (34.1) | 3.03 (1.20-7.73) |
| Stuffy nose ^c | 22 (40.7) | 20 (48.7) | 0.72 (0.29-1.77) |
| Sore throat ^c | 11 (20.3) | 17 (43.5) | 3.02 (1.07-3.86) |
| Cough | 19 (35.1) | 08 (19.5) | 2.24 (0.79-6.71) |
| Myalgia ^c | 23 (42.5) | 24 (58.4) | 0.53 (0.21-1.29) |
| Headache ^c | 04 (7.4) | 11 (26.2) | 4.44 (1.20-21.19) |
| Irritability | 12 | 0 | |
| Diarrhea ^c | 17 (31.4) | 05 (12.2) | 3.31 (1.02-12.56) |
| Loss of appetite ^b | 35 (64.8) | 14 (34.1) | 3.55 (1.40-9.14) |
| Pain abdomen | 10 (18.5) | 7 (17.7) | 1.1 (0.34-3.8) |
| Vomiting | 12 (22.2) | 4 (9.7) | 2.64 (0.79-6.55) |

Data in no. (%). ^a*P*=0.001, ^b*P*<0.005, ^c*P*<0.05. ^dReciprocal odds ratio; ^esubjective symptoms, that were documented for children above 3 years of age.

WHAT THIS STUDY ADDS?

- Clinical characteristics and outcomes of SARS-CoV-2 infected children during the third wave of pandemic in India are presented.

Another four children with pneumonia or ARDS were treated with dexamethasone (0.15 mg/kg/day). ICU care was required in 6 (35.2%) patients. The mean (SD) length of hospital stay was 7.5 (2.5) days. One patient died due to complications related to comorbid acute myeloid leukemia.

DISCUSSION

In this review of hospital records, we present preliminary data on clinical characteristics of pediatric patients with confirmed SARS-CoV-2 infection during the third wave of the pandemic. Among the 95 patients who required home care predominant clinical features were fever, coryza, and anorexia. Gastrointestinal manifestations were more common in younger children. High-grade fever was noted more frequently in older children. Among hospitalized patients, two-thirds had comorbidity, one-third required ICU and four required mechanical ventilation.

Pediatric data from South Africa during Omicron surge revealed that young children (0-4 years) were the most affected (62%) [14]. Mean hospital stay was longer in our study cohort than South African children (6.5 vs 3.2 days). It may be because half of the children had comorbidity and four patients had MIS-C. The prevalence of MIS-C during the Omicron surge has not been described in literature yet. The ICU admission rate was also more frequent in our study (35% vs 8%) [14]; though, the requirement for oxygen therapy and need of mechanical ventilation were similar. Like our findings, all deaths were related to complex underlying comorbidity.

Among under-5 children in USA, the Omicron cohort had significantly lower emergency visits, hospitalizations, ICU admissions, and mechanical ventilation than those in the Delta cohort [3]. Similar trends were observed for other pediatric age groups (5-11 and 12-17 years) [3]. Being a hospital-based study, we were unable to delineate true incidence of hospitalization, and need for ICU care and mechanical ventilation.

During the initial phase of pandemic, irrespective of age, headache and fatigue were the two commonest presentations [15]. Contrary to the previous waves, fever and upper respiratory tract symptoms were more common and none of our children complained about anosmia during the third wave. The median illness duration was longer and 4.4% of children had illness duration of at least 28 days [15]. Duration of illness among children who required home

care was 2.5 days during the third wave of the pandemic. It indicates that although a higher number of children are symptomatic, they recover fast compared to previous waves. But we could not ascertain whether the Omicron variant leads to long-term sequelae.

Single center retrospective nature of this study could introduce case selection biases, over representation of symptomatic patients, and reporting and follow-up issues. Many children in the age group of 1 month to 5 year could not express subjective symptoms. We did not carry out genome sequencing to confirm the presence of Omicron variant in the patients.

Our analysis showed that during the third wave, COVID-19 infections in children were associated with symptomatic illness, but fast recovery among non-hospitalized children. There is an early indication of substantial need for ICU care and organ support among hospitalized children. The study findings might be helpful for primary care physicians, pediatricians, and parents for early identification, isolation, and appropriate management of children.

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

Ethics clearance: IEC; No. MC/KOL/IEC/NON-SPON/1363/1/33 dated Jan 24, 2022.

Contributors: MS: conceptualization, design of the study, drafting, analysis of data, preparing manuscript, final approval; AG: design of the study, analysis and interpretation of data, review and editing of manuscript; MCK,OR: conceptualization, acquisition of data, drafting of manuscript, analysis of data; MKM: design of the study, analysis and interpretation of data, administrative work and statistical analysis; MN: conceptualization, design of the study, statistical analysis, review and editing, administrative work, final approval. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Web Table I Clinical characteristics of Children Hospitalized With COVID-19 During Third Wave of the Pandemic, Kolkata, January, 2022 (n=17)

| <i>Age group</i> | <i>No. (%)</i> |
|---------------------------------------|----------------|
| 1 month – 59 months | 11 (64.7) |
| Male sex | 9 (52.9) |
| <i>BMI</i> | |
| Underweight | 7 (41.1) |
| Normal | 8 (47.0) |
| Contact history | 12 (70.5) |
| <i>Signs and Symptoms^a</i> | |
| Fever and URI | 14 (82.3) |
| Respiratory distress | 9 (52.9) |
| Shock | 8 (47.0) |
| Convulsion | 6 (35.2) |
| Skin and mucosal changes | 2 (11.7) |
| MIS-C | 4 (23.5) |
| ARDS | 2 (11.7) |
| Comorbidities ^b | 10 (58.8) |
| Congenital heart disease | 4 (23.5) |
| Type-1 diabetes | 2 (11.7) |
| Cerebral palsy | 2 (11.7) |
| Intestinal obstruction | 2 (11.7) |
| <i>Outcome</i> | |
| ICU Requirement | 6 (35.2) |
| PICU stay (d) ^c | 7 (2) |
| Hospital stay (d) ^c | 7.5 (2.5) |

Values in no. (%) BMI – Body Mass Index Cut-off value - 1month to 5 yrs - WHO z-scores ; 5 – 12 years underweight <18.5 kg/m² and overweight >25 kg/m². URI ^a four each had Altered sensorium, Diarrhoea, vomiting, pain abdomen, Oliguria; ^bone child had acute myeloid leukemia or ^cmean (SD).

Anthropometric and Pubertal Outcomes in Girls With Classical Congenital Adrenal Hyperplasia

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Objective: To evaluate the anthropometric and pubertal outcomes, over a spectrum of treatment regimens and compliance. **Methods:** We reviewed records of the patients with classical CAH seen at the endocrinology clinic of a tertiary care center between 1995 and 2016. **Results:** 25 females were included in the study, the majority (80%) with simple virilizing variant. All patients had genital ambiguity since birth, yet 40% (10/25) presented much later with menstrual complaints. All patients received hydrocortisone, but some switched to dexamethasone ($n=7$) or prednisolone ($n=4$). 7/9 (77.9%) girls who achieved target height, were on hydrocortisone. Menarche occurred with corticosteroid treatment in 60% (15/25) patients at a median (IQR) age of 16 (12-22) years. **Conclusion:** Hydrocortisone seems to have a beneficial effect on linear growth. Once target height is achieved, dexamethasone may be considered as an alternative.

Keywords: Dexamethasone, Hydrocortisone, Prednisolone, 21 α -hydroxylase deficiency, Puberty.

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Glucocorticoid and mineralocorticoid replacement therapies are the mainstay of therapy in salt-wasting (SWCAH) and simple virilizing (SVCAH) variants of classical congenital adrenal hyperplasia (CAH). As an increasing number of these patients are reaching adulthood, it is important to understand the long term anthropometric and pubertal outcomes in these patients, along with challenges related to compliance to a lifelong therapy. We undertook this study to evaluate the anthropometric and pubertal outcomes, over a spectrum of treatment regimens and compliance.

METHODS

The records of patients of 46 XX, classical CAH (21-alpha hydroxylase deficiency), who had registered in the endocrinology clinic of a tertiary center between 1995 and 2016, were reviewed for the purpose of the study. The study was approved by the institutional ethics committee.

A patient was recorded as a case of classical CAH if unstimulated and/or stimulated 17-hydroxyprogesterone (17OHP) levels were >100 ng/mL after 250 μ g ACTH bolus in a patient with suggestive clinical features [1,2]. Degree of hirsutism, virilization of genitalia and body mass index (BMI) were recorded. Ultrasound and magnetic resonance imaging (MRI) were done for internal genitalia, supplemented by laparoscopy/laparotomy as needed.

Karyotype was done by the conventional G banding method. Gender identity, role and behavior were assessed with the help of a clinical psychologist and by using Utrecht Gender Dysphoria Scale-Gender Spectrum (UGDS-GS). Gender assignment was done considering the gender identity, sex of rearing, and after discussing the fertility prospects with the parents and the patients. Luteinizing hormone, follicle stimulating hormone and testosterone were measured with radioimmunoassay till 2006, and electro-chemiluminescence immunoassay (ECLIA) from 2007 onward. 17-OHP was estimated by radioimmunoassay.

Treatment was monitored by auxologic, clinical and biochemical profile. Hormonal control in adult female patients with CAH was defined as 17-OHP and testosterone levels of 4-12 ng/mL and less than 0.6 nmol/L, respectively [3]. Reference used for calculation of the target height SDS, was the 50th centile for adult Indian girls as per Indian Academy of Pediatrics chart [4].

Statistical analysis: Descriptive variables are presented as mean (SD) or median (IQR), when skewed. Categorical variables are presented as proportions.

RESULTS

Total number of patients of classical CAH registered was 55. Eventually, 25 patients with 46,XX classical CAH were included in the study (14 were 46 XY; 16 were 46 XX but

with missing data). Median (range) duration of follow up of all 25 patients was 12 (4-25) years. Majority (15/20, 75%) of patients with simple virilizing CAH were noticed to have ambiguous genitalia at birth, yet nine patients presented in the peripubertal period with chief complaint of primary amenorrhea, while one patient presented with oligomenorrhea (**Table I**).

All girls were initially started on hydrocortisone. Cost and availability, together with frequency of dosing necessitated switchover in some cases (**Table I**). Five patients received reverse circadian glucocorticoids. One patient developed Cushingoid features on dexamethasone and required switching back to hydrocortisone. Twenty one patients of CAH continued mineralocorticoid supplementation with fludrocortisone (100-150 ug), while four patients with simple virilizing CAH stopped it, due to hypertension and hyperkalemia.

Mean (SD) height achieved in the 25 patients was 148 (6.8) cm (range 137 to 167 cm), which is 10 cm shorter than the 50th centile of an adult Indian girl (height SDS -1.53).

Final height achieved was more than target height in 36% (9/25) patients. Out of these, seven were on hydrocortisone. Rest 64% (16/25) were an average 7 cm shorter than their genetically determined target height (height SDS -1.15). Eight out of these 16 were non-compliant, with persistent elevation of testosterone [median (range) 6.33 (1.5-18.8) nmol/L] and 17OHP levels [median (range) 27 (19-70.4) ng/mL] during follow-up.

Median (range) BMI of patients on hydrocortisone therapy ($n=13$) was 20.9 (12.9-24) kg/m², on prednisolone therapy ($n=4$) was 22.1 (20.6-28.3) kg/m² and on dexamethasone (ever received, either alone or in combination with hydrocortisone) ($n=8$) was 27.3 (18-34.2) kg/m².

Out of 25 patients, 15 (60%) patients had presented in pre-pubertal period and witnessed spontaneous menarche while on corticosteroid replacement, at a median (range) age of 16 (12-22) year. Median (range) age of thelarche was 12 (10-13.8) year in these patients. Nine patients who presented with primary amenorrhea, had menarche after corticosteroid replacement [median (range) age 16 (13-19)

Table I Clinical and Hormonal Profile, Corticosteroid Treatment and Outcomes of Women With Classical Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

| Characteristics | Simple virilizing type ($n=20$) | Salt wasting type ($n=5$) |
|---|--|--|
| Presenting manifestation | Ambiguous genitalia (15) Oligo-/amenorrhea (10) Hirsutism (5) Undue gain in height (2) Deepening of voice (4) | Salt-losing crisis (4) Ambiguous genitalia (2) Failure to thrive (1) |
| Age at presentation (mo) ^a | 144 (1, 240) | At birth |
| Baseline 17 (OH)P levels, ng/mL ^a | 111 (37, 51.5) | 128 (121-236) |
| Baseline testosterone levels, nmol/L ^a | 1.1 (1.1, 2.5) | 1.8 (1.03-1.9) |
| ACTH, pg/mL ^a | 190 (84.7, 203.7) | - |
| <i>Genetic analysis</i> | | |
| Both gene deletion ^b | 2 | - |
| Single gene deletion | 6 | - |
| <i>Mutations</i> | | |
| R356W- Heterozygous | 11 | |
| Other known (μ 2g / P30L / V28IL / Q318X) | 8 | |
| Unknown (R216K / P357P / M365N / S268T / L307 frameshift) | 3 | 1 (P267L) |
| Data not available | 5 | 4 |
| <i>Treatment</i> | | |
| Hydrocortisone | 11 | 2 |
| Prednisolone | 4 | 0 |
| Dexamethasone | 5 | 2 |
| Hydrocortisone + dexamethasone | 0 | 1 |
| <i>Outcomes</i> | | |
| Hormonal control ^c | 6 (30) | 3 (60) |
| Final height \geq target height | 5 (25) | 4 (80) |

Value in no. (%) or ^amedian (IQR). ^bCYP21 A2 gene;. ^c17-hydroxyprogesterone levels <12 ng/mL and serum testosterone levels <0.6 nmol/L.

year]. During follow-up, 64% (16/25) had irregular cycles and 36 % (9/25) had regular cycles, including one patient who achieved menopause. Amongst the eumenorrheic patients, five were on dexamethasone replacement.

Hirsutism was noted in 9 patients, with a median (range) Ferriman- Gallwey score of 18 (13-21). According to Rotterdam Criteria, 32% (8/25) patients had developed secondary polycystic ovarian syndrome.

Most patients (18/25, 72%) had undergone genital reconstruction surgery. Out of these, isolated clitoral surgery was performed in 12 patients and combination of clitoral and vaginal surgery in six patients. Five of them underwent surgery during adulthood, the rest had it in childhood.

Two patients got married and sought pregnancy. For the first patient, genetic analysis was done by chorionic villus sampling, for the mutations in the mother (R356W and μ 2g) prior to conception and reported negative. She conceived spontaneously on dexamethasone 0.5 mg and was switched to hydrocortisone once pregnancy was detected. She delivered a healthy baby by cesarean section (due to cephalopelvic disproportion). Stimulated 17OHP levels of the baby were within normal range. The second patient has been trying for conception for last two years. She has uncontrolled disease with 17 OHP levels of 215 ng/mL, and has been started on prednisolone instead of hydrocortisone.

DISCUSSION

Majority of the patients in our study did not achieve the final height as per their genetic potential (64%), had irregular menstrual cycles (64%), and only one patient in our series conceived spontaneously and delivered a healthy baby, possibly attributable to non-compliance. Similarly, in a study of 86 patients with CAH from eastern India, majority of patients (64%) were lost to follow-up [5].

Various postulated predictors of height include the clinical form of CAH, age at diagnosis, degree of hormonal control, and dosage of steroids. Six out of 16 patients in the study could not get the benefit of linear growth possibly due to delayed diagnosis and late initiation of treatment. In a meta-analysis of 35 studies [6], mean final height of patients with CAH was found to be 1.38 SD score lower than the population mean, and was also lower than genetically determined target height [6]. Khadilkar, et al. [7] have shown that use of hydrocortisone is associated with optimal height outcome as compared to prednisolone. Out of nine patients who were able to achieve target height in our series, seven were on hydrocortisone. Mineralocorticoid replacement and salt supplementation in infants are also important to attain optimum height [8].

In spite of genital ambiguity since birth, many patients sought medical advice only in the peripubertal period due to menstrual abnormalities. The delay may be attributable to lack of awareness and social stigma. In another study conducted at our center [9], three out of 328 patients presenting with primary amenorrhea were diagnosed with CAH. Breast development and menarche have been reported to be delayed in girls with CAH [10], which was also seen in our study as menarche occurred at a median age of 16 years. At the time of final follow-up, 64% (16/25) patients had irregular menstrual cycles due to poor hormonal control. Five out of the remaining nine patients having regular menstrual cycles were on dexamethasone, suggesting the possibility of better compliance and consequently hormonal control, due to once daily dosing. The downside to dexamethasone treatment is the weight gain, as seen by the high average BMI of patients on dexamethasone therapy. Although multiple mechanisms have been put forth to explain obesity in CAH patients, the type of corticosteroid may have a significant role [11].

There is scarcity of data available on the fertility rate in classical CAH [12]. Traditionally low pregnancy rates have been reported in CAH [13]. Factors contributing to impaired fertility in CAH are adrenal overproduction of androgens and progesterone, ovarian hyperandrogenism, anovulation, genital surgery, delayed psychosexual development and reduced sexual activity [14].

Strength of the study was the ability to assess several pertinent issues related to linear growth and pubertal outcomes, in a reasonable number of subjects. Limitations of our study are involvement of young individuals, precluding detailed evaluation of fertility outcomes, and non-assessment of cardiometabolic risk and bone health.

Our study underscores the need to raise awareness among primary care physicians regarding the evaluation of children with ambiguous genitalia and/or recurrent vomiting and failure to thrive, as well as individualized treatment protocols for better compliance.

Linear growth and gynecological outcome in girls with 46, XX classical CAH due to 21-hydroxylase deficiency in our series is highly unsatisfactory, mainly owing to delayed diagnosis or non-adherence to treatment. Early referral and diagnosis, individualized treatment protocols and ensuring compliance to therapy could potentially lead to better long term outcomes in these patients.

Ethics clearance: Institute Ethics Committee, PGIMER, Chandigarh; No. INT/IEC/2019/000498 dated March 16, 2019. *Contributors:* MS, RW, JK: made substantial contributions to the conception or design of the work; JK, RW, MS: substantial contribution to the acquisition, analysis, or interpretation of data for the work; JK, RW, AB, SB: drafting the work or revising it

WHAT THIS STUDY ADDS?

- Long term anthropometric and pubertal outcomes of 46 girls with classical congenital adrenal hyperplasia are presented.

critically for important intellectual content. All authors approved the final version of manuscript, and agree to be accountable for all aspects related to the study.

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Validation of Hindi Translation of Survey of Well-Being of Young Children Tool in Indian Children

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Objective: To validate the Hindi translation of Survey of well-being of young children (SWYC), a screening questionnaire to detect developmental delay and emotional-behavior problems by primary caregivers in Indian children. **Methods:** This cross-sectional observational study was done at the child development clinic of our private-sector tertiary care hospital. 180 children of either sex, 60 each in age group of 9, 18 and 24 months were enrolled in the study (30 high-risk and 30 low-risk in each group). Hindi translated version of SWYC age-specific questionnaire was administered to the parents, followed by a standardized development assessment by using the Bayley Scale of Infant and Toddler Development (BSID III). **Results:** SWYC Milestone score and Emotional/behavior scores showed a statistically significant correlation with BSID III ($P < 0.001$). Milestone score's overall sensitivity in detecting developmental delay was 94.4% and specificity was 93.4%. The sensitivity was best for the 24-month (100%) and specificity was best for 18-month questionnaire (96.7%). Behavioral score's overall sensitivity was 68.4% and specificity 92.3%. The best sensitivity was for 18-month questionnaire (72%), and specificity for 24-month questionnaire (100%). SWYC had better sensitivity for detecting developmental delay in high-risk group (95.4%), and higher specificity in low risk group (95.5%). **Conclusion:** SWYC has strong test characteristics for detecting milestone delay and emotional/behavior problems in Indian children.

Keywords: Developmental delay, Emotional-behavior problems, Screening tool.

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Most of the available screening tools in India do not assess emotional/behavioral problems in children [1]. Pediatricians frequently fail to identify children with developmental-behavioral problems if they use only clinical impressions rather than formal screening [2]. It is mainly in the first few years of life that the development of sensory-motor, social-emotional and cognitive skills occurs, which is essential for success in the next stages of life [1,2], and interventions at this stage help in improving outcomes [3]. The American Academy of Pediatrics (AAP) committee on childhood disability [3] recommends screening all children using standardized developmental screening tools at 9, 18, and 30 (or 24) months of age.

The Survey of well-being of young children (SWYC) is a comprehensive, first-level developmental-behavioral screening tool for children under 5.5 year of age [4]. The psychometric properties of the original SWYC has been shown to be adequate (sensitivity 0.7-0.89, specificity 0.54-0.9) [2-6]. It is designed to be completed by parents or other caregivers in the context of pediatric primary care visits, but can also be used in other settings [6]. The entire

instrument takes most parents 10 minutes to complete. There are 12 SWYC forms as per age, and these are available in various languages. However, no study is available on its use in Indian children. We planned this study to evaluate the ability of SWYC to detect developmental delay and emotional/behavior problems in Indian children.

METHODS

The study was conducted at the Child development clinic, of our hospital, from October, 2020 to September, 2021 after institutional ethics committee clearance. Consecutive children in three age groups; 9 month (9 month, 0 day to 11 month, 31 day), 18 month (18 month, 0 days to 22 month, 31 day), and 24 month (23 month, 0 day to 28 month, 31 day), attending the pediatric outpatient department of the hospital were enrolled in the study, after informed parental consent. Risk stratification was done and the included children were stratified into high-risk group (children with any of the following risk factors: history of hospitalization in the first four days of life, birthweight <2 kg, gestation age <37 weeks, history of central nervous systems infections, known dysmorphic syndrome or chromosomal anomalies,

evolving cerebral palsy or developmental delay, and or history of two or more episodes of afebrile seizures) and low-risk groups (children with none of the above mentioned risk factors). Children with non-availability of birth records, and without accompanying primary caregiver at the time of evaluation were excluded from the study.

The SWYC is a structured interview with 40 questions that assesses multiple domains of a child's well-being: cognitive, language, and motor development; behavioral and emotional adjustment; autism risk; and family stress [8,9]. To assess these domains, each SWYC form includes four components: *i*) SWYC Milestones, which is a questionnaire with 10 questions for each age group to evaluate developmental milestones (cognitive, motor, social, and language skills); *ii*) Baby Pediatric Symptom Checklist (BPSC) for age below 18 month or Preschool Pediatric Symptom Checklist (PPSC) for children aged 18 to 65 months [10,11], *iii*) Family Questions domain contains 9 items, child behavior and learning/development; and, *iv*) Parent's Observation of Social Interaction (POSI) to assess risk for autism spectrum disorder (ASD) for children between 16 and 36 month of age [11]. We evaluated only the SWYC Milestone scores and Emotional /Behavior domain. Although, designed as a comprehensive screening tool, it is acceptable to use individual parts of SWYC separately to meet particular needs [6].

For the present study, only 9-month, 18-month, and 24-month questionnaires were used. The SWYC questionnaire was translated into Hindi language and back translated to English language and this procedure was repeated until the back translation matched the English version. The translation was done independently by language experts.

Sample size calculation was done based on a previous study [7] to assess the SWYC— the minimum required sample size at 5% level of significance was taken. Total 180 children of either sex, 60 in each of the three specified age strata (9 months, 18 months, and 24 months) were enrolled in the study. In each age group, 30 'low-risk' and 30 'high-risk' children were enrolled. A detailed history and physical examination were done for all the children at the time of enrolment, followed by the administration of the Hindi version of the SWYC screening tool by a pediatric resident, who was trained by a developmental pediatrician, to any of the available parents, mostly mothers.

On the same day, developmental assessment of the child was also done by a single clinical psychologist using the Bayley Scale of Infant and Toddler Development (BSID III). Clinical psychologist was blinded to the scores on SWYC. Developmental quotient (DQ) <85 was taken as the cut-off score on BSID III [12] for labelling developmental

delay. We compared the mean DQ (sum of cognitive, language and motor DQ) <85 with SWYC Milestone score, and DQ in social-emotional domain <85 with SWYC emotional/behavioral score.

A child failed on SWYC screening, when the scores were not as per the screening threshold. Children who failed on developmental screening were subjected to early intervention including parent counseling and training.

Statistical analysis: The Statistical Package for Social Sciences (SPSS) was used for all analyses. The psychometric properties of SWYC were calculated using BSID III as gold standard. Wilcoxon-Mann-Whitney U test was used to make group comparisons. The Chi-square test was used to observe the association between SWYC and BSID III scores. Spearman correlation coefficient was used for correlation between the SWYC and BSID III scores.

Table I Demographic Characteristics of the Study Sample

| Characteristics | No. (%) |
|--|------------|
| Male gender | 111 (61.7) |
| <i>Mother's age (y)</i> | |
| <20 | 2 (1.1) |
| 20-29 | 120 (66.7) |
| 30-35 | 50 (27.8) |
| >35 | 8 (4.4) |
| <i>Antenatal problems^a</i> | |
| Anemia | 10 (5.6) |
| Pregnancy-induced hypertension | 15 (8.3) |
| Antepartum hemorrhage | 6 (3.3) |
| Gestational diabetes mellitus | 5 (2.8) |
| Cesarean delivery | 118 (65.6) |
| <i>Mother's education^b</i> | |
| Primary | 6 (3.3) |
| Secondary | 12 (6.7) |
| Graduate | 66 (36.7) |
| Postgraduate | 92 (51.1) |
| <i>Father's education^b</i> | |
| Primary | 5 (2.8) |
| Secondary | 8 (4.4) |
| Graduate | 79 (43.9) |
| Postgraduate | 86 (47.8) |
| <i>Risk factors in the high risk group^c</i> | |
| Prematurity | 13 (14.4) |
| Low birth weight | 9 (10) |
| Hospitalization in first 4 d | 33 (36.7) |
| Evolving cerebral palsy/developmental delay | 23 (25.6) |
| Known dysmorphic syndrome/chromosomal abnormalities | 11 (12.2) |
| Epilepsy | 5 (5.6) |

^a2 mothers had fever with rash in the antenatal period; ^b4 mothers and 2 fathers were illiterate; ^chistory of a neuro-infection was present in 2 children.

Table II Screening Test Characteristics of Survey of Well-Being of Young Children (SWYC) Milestone Score and SWYC Emotional/Behavior Score for Predicting Bayley Scale of Infant and Toddler Development Social Emotional score <85

| Age group | SWYC components | Sensitivity | Specificity | PPV | NPV | Diagnostic accuracy |
|-----------|--------------------------|-------------|-------------|-------|-------|---------------------|
| 9 month | Milestone score | 89.7% | 93.5% | 92.9% | 90.6% | 91.7% |
| | Emotional/behavior score | 61.9% | 89.7% | 76.5% | 81.4% | 80% |
| 18 month | Milestone score | 93.3% | 96.7% | 96.6% | 93.5% | 95% |
| | Emotional/behavior score | 72% | 88.6% | 81.8% | 81.6% | 81.7% |
| 24 month | Milestone score | 100% | 90% | 90.9% | 100% | 95% |
| | Emotional/behavior score | 70.0% | 100% | 100% | 76.9% | 85% |
| Overall | Milestone score | 94.4% | 93.4% | 93.3% | 94.4% | 93.9% |
| | Emotional/behavior score | 68.4% | 92.3% | 86.7% | 80% | 82.2% |

PPV: positive predictive value, NPV: negative predictive value.

Statistical tests with a 5% level of significance were considered significant.

RESULTS

Out of the total of 180 children enrolled in the study, 61.7% were boys. Most of the mothers were aged 20-29 year at the time of conception. Antenatal problems were detected in 21.1% of the mothers. **Table I** shows the baseline characteristics of the enrolled children, and the presence of risk factors.

The overall sensitivity of SWYC in detecting developmental delay was 94.4% and specificity was 93.4%. The sensitivity was found to be good for detecting developmental delay in all the three age groups (9, 18, and 24 months). The sensitivity was much higher in the high-risk group (95.4%) as compared to the low-risk group (50%).

The overall sensitivity of SWYC in detecting behavior problems was 68.4% and specificity was 92.3%. The sensitivity was best for the 18 months questionnaire (72%) and the specificity was best for the 24 month questionnaire (100%) (**Table II**). The sensitivity for emotional / behavioral questionnaire was found to be good for 18 and 24 month and was low for 9 month questionnaire. This may be related to the fact that parental assessment of detecting behavior problems in infancy is less objective. The sensitivity for detecting behavior problems in high-risk group was 68% and 100% in low-risk group.

DISCUSSION

In this study to evaluate the SWYC as a screening tool for developmental and behavior problems in the Indian children, we found that the tool had good psychometric properties for screening of developmental delay. The sensitivity of SWYC for detecting developmental delay was good for children of all three age groups tested, the specificity was best for the 24 month questionnaire. The overall sensitivity and specificity of SWYC in detecting behavior problems was also statistically significant. While

sensitivity for emotional/behavior questionnaire of SWYC was low for 9 month age group. This may be related to the fact that parental assessment of emotional/ behavior/ domain in infancy is less objective. The test characteristics of the SWYC were studied both in low-risk and high-risk children also. The limitation of our study is the small sample size, as well as the hospital-based setting.

The validity and reliability of the original SWYC version is similar to those of other screening instruments quoted in the literature. Psychometric properties of original SWYC were found to be adequate. Other studies have used SWYC to screen for developmental delay only using SWYC milestones without taking into account the emotional/behavioral aspects. SWYC is a useful screening tool to detect emotional/behavior problems in Indian children, especially at 18 and 24 months of age. Though further large scale studies are needed to evaluate SWYC in the Indian population at all age groups.

Ethics clearance: IEC, Sir Ganga Ram Hospital; No. EC/01/21/1824 dated Feb 26, 2021.

Contributors: PS: involved in study designing, recruitment of the patients, literature review and final revision of manuscript; IN,RT: assessment of the patients and literature review. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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WHAT THIS STUDY ADDS?

- The Survey of well-being of young children (SWYC) showed good sensitivity and specificity to detect developmental delay as well as emotional/behavioral problems in children.
- The sensitivity of SWYC for detecting developmental delay was higher in the high-risk group whereas specificity was higher in the low-risk group.

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RECOMMENDATIONS

Indian Academy of Pediatrics Consensus Guidelines for Probiotic Use in Childhood Diarrhea

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Justification: Several probiotic species and strains, single or combined, have been evaluated in childhood diarrheal disorders, and recommendations have ever been changing as newer trials are published. Therefore, there is a need to develop a guideline for Indian children describing the current role of probiotics in clinical practice.

Objectives: To develop a guideline for the use of probiotics in children with diarrhea.

Process: A national consultative group (NCG) was constituted by the Indian Academy of Pediatrics (IAP), consisting of subject experts. Sub-topics were allotted to various experts as paired groups for detailed review. Members reviewed the international and Indian literature for existing guidelines, systematic reviews, meta-analyses and trials. Thereafter, two virtual structured meetings of the group were held on 2nd and 22nd August, 2020. The management guidelines were formulated by the group and circulated to the participants for comments. The final guidelines were approved by all experts, and adopted by the IAP executive board.

Recommendations: The NCG suggests *Lactobacillus GG* as a

conditional recommendation with low-to-moderate level evidence or *Saccharomyces boulardii* as a conditional recommendation with very low-to-low level evidence as adjuvant therapy in acute diarrhea. The NCG also recommends the use of combination probiotics in neonatal necrotizing enterocolitis (NEC), as these reduce the risk of NEC stage II and above, late-onset sepsis, mortality and also time to achieve full feeds. The NCG does not recommend the use of any kind of probiotics in the therapy of acute dysentery, persistent diarrhea, *Clostridium difficile* diarrhea and chronic diarrheal conditions such as celiac disease, diarrhea-predominant irritable bowel syndrome and inflammatory bowel disease in children. Risk of antibiotic-associated diarrhea (AAD) is high with some antibiotics and most of these cases present as mild diarrhea. The NCG recommends probiotics only in special situations of AAD. *L. rhamnoses GG* or *S. boulardii* may be used for the prevention of AAD. VSL#3, a combination probiotic, may be used as an adjuvant in active pouchitis, and for prevention of recurrences and maintenance of remission in pouchitis.

Keywords: Antibiotics-associated diarrhea, Celiac disease, Irritable bowel syndrome, Neonate, Necrotizing enterocolitis.

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Diarrhea, accounts for approximately 11% of childhood deaths worldwide [1-3]. The role of probiotics in different subtypes of diarrhea has been discussed in the literature and in various practice guidelines. Eubiosis refers to the harmony and balance of pathogenic bacteria and healthy bacteria in our gut. Dysbiosis is an imbalance of microbes that may result after an acute or chronic insult to the gut leading to perpetuation of the illness. However, the perpetuation may not necessarily be attributable to the pathogenic organisms. Unlike adults with a stable gut flora in a healthy

state, the gut colonization is different in children, more so in infants and preterm neonates. The type of delivery, gestational age, neonatal risk factors, antibiotic use and breast milk exposure are some of the factors determining the quality and quantity of gut microbiota in children. The optimal microbiota balance in various stages of childhood is unknown [4]. Probiotics, when administered in adequate amounts, confer beneficial effects by replacing the pathogenic bacteria with favorable ones, interfering with pathogen attachment, inactivating toxins, having antisecretory effects, reducing the loss of water and

electrolytes from the gut, strengthening gut barrier integrity, releasing gut protective metabolites, and having loco-systemic immuno-modulatory effects [5]. Despite the promising role, the question as to whether a certain probiotic is the one-stop primary answer or an adjuvant in the therapy of diarrheal diseases and the long-term effects of probiotics in permanent modification of gut microbiota and sustained immunomodulation are unanswered [6].

OBJECTIVE

To develop a guideline for the use of probiotics in children with diarrhea.

PROCESS

A group of national experts, designated by the Indian Academy of Pediatrics (IAP), reviewed the current evidence related to the role of probiotics in childhood diarrhea and formulated practice guidelines. The initial meetings were held on August 2, 2020, and August 23, 2020, on a virtual platform. The key questions addressed included *i*) Do probiotics improve the overall outcome of the diarrheal state? *ii*) Which is/are the probiotic(s) recommended? *iii*) What dose and duration of the probiotic(s) should be administered? *iv*) Any serious adverse effects of probiotic(s)? *v*) Any deviation from international guidelines? *vi*) Any special recommendations in the Indian context?

Pediatric literature of last 15 years till August, 2020 (Medline indexed publications) were deliberated upon, with controversies, if any, being debated upon by the experts. Discontinued probiotic strains were excluded from the discussion. The GRADE approach was used to assess the certainty (i.e., quality) of evidence (CoE) [7], and the strength of recommendations was graded as strong or conditional [8] (**Table I**) A consensus was agreed upon for each of the diarrhea subtypes. A writing group was designated for the manuscript. The draft was sent by email to all experts and their suggestions were incorporated in the final guidelines.

GUIDELINES

Acute Gastroenteritis

Before 2017, recommendations and practice guidelines came from North American and European societies, whereas, heavy caseload with more severity and high mortality were being handled in centers in Asia, Africa and Latin America (**Box I**) [9-15]. Efficacy of probiotics in acute diarrhea is usually measured in terms of duration of diarrhea, stool volume and duration of hospitalization for caregivers and physicians. Modified Vesikari score (MVS) is used for research purposes to assess response [16]. Two recent double-blind randomized controlled trials

Table I Quality of Evidence and Strength of Recommendations Used for These Guidelines [1,2]

| Category | Inference |
|-----------------------------------|---|
| <i>Quality of evidence</i> | |
| High quality | Further research is unlikely to change our confidence in the estimate of effect |
| Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low quality | Any estimate of effect is uncertain |
| <i>Strength of recommendation</i> | |
| Strong | Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences |
| Conditional | Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision. |

(RCT) from North America changed the perception of probiotics in acute diarrhea [17,18]

Lactobacillus rhamanosus GG: The PECARN probiotic study [17] from United States of America, randomized 943 preschool children to *L. rhamanosus GG (LGG)* and placebo groups. The trial used a statistical enrichment design to compensate and represent for those who were likely to benefit (such as longer duration of symptoms) in their cohort. The study failed to show any superiority of the probiotic over placebo in overall MVS or secondary individual components (stool consistency, stool frequency, vomiting frequency, time to vomiting abatement, intra-venous fluid requirement, rate of hospital admission, follow-up visits, missed daycare, missed employment hours of caregivers, and household transmission) [17]. A systematic review and meta-analysis on LGG also showed no significant reduction in stool volume (18 RCT, $n=4208$), reduction in diarrhea duration by -0.85 days (95%CI: -1.15 to -0.56) (15 RCT, $n=3820$), daily dose $>10^{10}$ CFU fared better than $<10^{10}$ CFU (15 RCT, $n=2007$), better results in Europe than non-Europe (15 RCT, $n=2007$) and reduction in hospitalization stay by -1.22 days (95%CI: -2.33 to -0.1) (5 RCT, $n=990$) [9]. Another meta-analysis (with a different

Box 1 Reasons for Heterogeneity of Various Probiotic Studies [9-15]*Patient factors*

Setting: Low income vs high income countries (Human Development Index)

Severity of diarrhea

Immunization status

Nutrition status

Viral vs bacterial vs unidentified etiology

Intervention factors

Day of intervention in acute diarrhea

Single vs combination probiotic

Strain and dose of bacteria

Duration of therapy

Type of trial (randomized vs. open label)

Methodology issues

study inclusion) concluded that LGG had a reduction in diarrhea duration by 24 hours, higher dose $>10^{10}$ CFU fared better than $<10^{10}$ CFU, showed similar performance in Asians and Europeans, was most effective if introduced <72 hours of diarrhea, and had better results in rotaviral diarrhea subset [13]. Based on this information, routine testing for rotaviral diarrhea may not be required as probiotics would have already been instituted before the rotavirus test results are available.

L. rhamnosus R0011 and L. helveticus R0052: The PERC-PROGUT trial randomized 886 preschool children from Canada, with mild diarrhea, to receive *L. rhamnosus* R0011 and *L. helveticus* R0052 combination or placebo. The results were similar to the PECARN study. Probiotic was not superior in terms of MVS or secondary outcomes as compared to placebo. Development of moderate-severe gastroenteritis was 26% in probiotic group vs 25% in placebo [OR 1.06; 95% CI 0.77 to 1.46; $P=0.72$] within 14 days. The two trials (PERC-PROGUT and PECARN) were criticized for inclusion of children with mild severity, those already immunized for rotavirus, stool testing for viral etiology, concurrent antibiotic exposure, questionable viability of probiotics in liquid form, and timing of probiotic administration (after 48 hour of diarrhea onset) [19-22]. The PERC-PROGUT study also did not find any significant differences between probiotic vs placebo in viral shedding response for adenovirus, norovirus and rotavirus. No differences were seen in the bacterial and parasitic diarrheal subgroups [23].

Saccharomyces boulardii: Studies with *S. boulardii* had major limitations due to poor designs and limited data outcomes. The analysis was inconclusive regarding stool volume. Reductions were seen in diarrhea duration by

mean -1.06 (95% CI -1.32 to -0.79) days (23 RCT, $n=3450$), hospitalization by mean difference -0.85 (95% CI -1.35 to -0.34 days (8 RCT, $n=999$), and reduced diarrhea episodes in the following days (day 2-7) of implementation [10].

L. reuteri DSM 17938: Two systematic reviews were available on *L. reuteri* DSM 17938. The first review in 2016 could not make any logical interpretations due to the extreme heterogeneity in studies [24]. The second analysis in 2019 included only four studies with 347 patients. The reduction in stool volume was inconclusive. The mean difference in reduction in diarrhea duration was by -0.87 (95% CI -1.43 to -0.31) days and in hospitalization by -0.54 (95% CI -1.09 to 0.0) days [25]. Another RCT also concluded the lack of efficacy of the above probiotics in acute gastroenteritis [26].

L. acidophilus: Chau, et al. [27] randomized *L. acidophilus* vs placebo in 150 school children in Vietnam. The probability of still having diarrhea till 216 hours after implementation was similar in both groups [27].

Bacillus clausii: There is a paucity of well-designed studies regarding *B. clausii* in children. A meta-analysis failed to provide any practical conclusions [28].

Current International recommendations

The European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) made updated recommendations in 2020 [11,12]. They provide weak recommendation for the use of LGG, *S. boulardii* and *L. reuteri* with low-quality of evidence. Use of *B. clausii*, *L. helveticus*, or a combination of probiotics is not recommended in acute diarrhea [11,12]. Based on the moderate quality of evidence, the American Gastroenterology Association (AGA) guidelines (2020) [8,15] do not recommend any probiotic use in children with acute diarrhea (conditional recommendation with moderate quality of evidence).

Indian experience

Unlike their first RCT [29], Basu, et al. [30], in their second RCT, demonstrated a significant reduction in duration of diarrhea, hospital stay and consistency of third-day stools with LGG $>10^{10}$ CFU/day [30]. Another RCT [31] in infantile diarrhea did not demonstrate any benefit of LGG. An RCT [32] in children aged 0.5-5 years showed reduction in diarrhea duration and improvement in consistency by 1 score in the LGG group as compared to controls, with both rotavirus positive and negative groups. In a double-blind RCT by Das, et al. [33], *S. boulardii* had a marginally lesser duration of diarrhea and hospitalization as compared to controls, among children below 5 years. Another double-blind RCT in the same age group showed marginal

benefit in the amount of oral rehydration solution (ORS) consumed, faster rehydration and earlier semi-formed stools with *S. boulardii* than placebo [34]. There is a paucity of well-designed studies from India. The summary of NCG recommendations for acute diarrhea is shown in **Table II**.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is primarily a disease of premature infants, but may also be seen rarely in 10% of term and near-term babies. The etiology of NEC is multifactorial and there are increasing concerns of abnormal gut microbiota playing a key role in its pathogenesis. The role of probiotics has been evaluated for the prevention and progression to stages 2-3 NEC, late onset sepsis, mortality, and time required until full enteral feeding [35]. The statistical benchmarks required to assess impact of any probiotic are: *i*) reduction of mortality prevalence from 7.5% to 5% (number required for analysis 1465); *ii*) reduction of NEC ≥ 2 prevalence from 10% to 5% (number required for analysis 431); and *iii*) reduction of prevalence of late-onset sepsis from 25% to 15% (number required for analysis 247). Prerequisites before administration of probiotics in preterm babies include *i*) certificate of analysis: purity, viability, antibiotic susceptibility; *ii*) available microbiological laboratory to detect fungemia; *iii*) inability of any of the probiotics to produce D-lactate; *iv*) absence of antibiotic resistance capability; and *v*) informed consent from parents [35].

International experience

Under standard safety guidelines, ESPGHAN conditionally recommends [35]. *L. rhamnosus GG ATCC 53013* or a combination probiotic (*B. infantis Bb-02*, *Bifidobacterium lactis Bb-12*, and *Streptococcus thermophiles TH-4*) for prevention of NEC stage ≥ 2 . No recommendations were made by ESPGHAN regarding probiotics for the reduction in mortality or prevention of late-onset sepsis or on the duration of therapy. In some studies, probiotics were administered for two weeks. However, the majority of the studies administered probiotics for 4-6 weeks or until discharge. No recommendations were made for *L. reuteri* DSM 17938 and *L. acidophilus* NCDO 1748 (ATCC 4356, LA37, or NCIMB 30316) containing regimen as they are partially D-lactate-producing strains, for which there was insufficient safety data available in preterm infants. *S. boulardii* has the potential to cause fungemia in those neonates with central venous catheters, who are critically ill, or in immunocompromised patients [35].

A strain-specific systematic review and network analysis found that the time to enteral feeding was significantly reduced with three different probiotic

interventions: *L. reuteri ATCC 55730* or *DSM 17938* (3 studies, $n=626$ infants) by 3.3 (range 0.62-6.4) days; for the combination of *B. bifidum*, *B. infantis*, *B. longum* and *L. acidophilus* (2 studies, $n=247$ infants) by 4.7 (range 0.70-8.6) days, and for the combination of *B. longum BB536* and *L. rhamnosus GG* (based on 1 study with 94 infants) by 10 (3.6-16) days [36]. A meta-analysis by Bi, et al. [37] (34 studies, $n=9161$) showed an overall advantage of probiotics in preventing the incidence of necrotizing enterocolitis, gut-associated sepsis, and decrease mortality in preterm infants. AGA guidelines conditionally recommend (moderate-high quality of evidence) the use of a combination of *Lactobacillus* spp. and *Bifidobacterium* spp. (*L. rhamnosus ATCC 53103* and *B. longum subsp infantis*; or *L. casei* and *B. breve*; or *L. rhamnosus*, *L. acidophilus*, *L. casei*, *B. longum subsp infantis*, *B. bifidum*, and *B. longum subsp longum*; or *L. acidophilus* and *B. longum subsp infantis*; or *L. acidophilus* and *B. biūdum*; or *L. rhamnosus ATCC 53103* and *B. longum Reuter ATCC BAA-999*; or *L. acidophilus*, *B. bifidum*, *B. animalis subsp lactis*, and *B. longum subsp longum*), or *B. animalis subsp lactis* (including DSM 15954), or *L. reuteri* (DSM 17938 or ATCC 55730), or *L. rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35) over no and other probiotics in low birthweight preterm babies. Best outcomes have been observed in babies <32 weeks of gestation and weighing <1500 g [38].

Indian experience

Most of the studies have used multi-strain probiotics [39-41] and a few used single-strain probiotics [42]. Probiotic supplementation was continued till discharge, till reaching full feeds, or for a pre-specified duration between 7 and 21 days. Most studies focused on preterm infants <34 weeks while some studies also included infants between 34 and 37 weeks of gestation [39-42]. The meta-analysis by Balasubramaniam, et al. [43] showed reduced risk of NEC \geq stage II [RR (95%CI) 0.36 (0.20,0.66); $P<0.001$; 9 RCTs], late-onset sepsis [RR (95% CI) 0.56 (0.45, 0.71); $P<0.001$; 7 RCT] and mortality [RR (95% CI) 0.62 (0.41,0.95); $P=0.03$; 8 RCTs] in the probiotic group. Probiotics also reduced the time to full feeds [mean difference (MD) -4.09 d (95% CI -4.52, -3.65); $P<0.001$; 5 RCTs] and duration of hospital stay [fixed effects model (FEM): MD -2.00 day (95% CI -2.46,-1.53); $P<0.001$; 6 RCTs].

Since there is low to moderate level of certainty about the effects of probiotic supplements on the risk of NEC and associated morbidity and mortality (**Table II**), large, high-quality studies are needed. Studies comprising one probiotic with another, single strain versus combination, route of administration (powder/liquid), optimal dose, time of initiation, duration of therapy and quality of enteral

Table II Summary of National Consultative Group (NCG) Recommendations in Various Disease Conditions of Diarrhea

| Condition/Recommendations | Strength of recommendation | Quality of evidence |
|---|----------------------------|---|
| <i>Acute diarrhea</i> | | |
| <i>Lactobacillus rhamnosus</i> GG $\geq 10^{10}$ CFU/d, typically 5-7 d or | Conditional | Low to moderate level |
| <i>Saccharomyces boulardii</i> 250 to 750 mg/d, for 5-7 d | Conditional | Very low- to-low level |
| Above probiotics can be used as adjuvant therapy in acute diarrhea. The marginal cost-benefit advantage must be carefully considered before prescribing them in impoverished conditions in India. No recommendations can be made for <i>Lactobacillus reuteri</i> DSM 17938, <i>Lactobacillus acidophilus</i> and <i>Bacillus clausii</i> . No recommendations can be made for combination probiotics. | | |
| <i>Prevention of NEC</i> | | |
| Combination of <i>Lactobacillus</i> spp. 1×10^9 to 6×10^9 CFU and <i>Bifidobacterium</i> spp. 3.0 to 3.5×10^8 CFU for 4 to 6 wk or up until discharge | Conditional | Moderate-high In preterm (less than 37 wk gestational age) and low birth weight babies |
| <i>L. rhamnosus</i> GG ATCC 53013 1×10^9 to 6×10^9 CFU for 4 to 6 wk or up until discharge | Conditional | Moderate-high Low for prevention of NEC stage ≥ 2 |
| Probiotics seem to be useful in reducing risk of NEC \geq stage II, with reduction of late onset sepsis, mortality and also reduce the time to full feeds (Indian data). There is moderate- high quality of evidence in preterm (less than 37 weeks gestational age), low- birth weight using probiotic combination of <i>Lactobacillus</i> spp. and <i>Bifidobacterium</i> spp. Conditionally recommends <i>L. rhamnosus</i> GG ATCC 53013 as a single probiotic in situations of non- availability of suitable combination of <i>Lactobacillus</i> spp. and <i>Bifidobacterium</i> spp. Probiotics are more effective in human milk fed babies. | | |
| <i>Antibiotic associated diarrhea (AAD)</i> | | |
| NCG does not recommend routine use of probiotics for the prevention of AAD in immunocompetent children being treated with antibiotics. However probiotics may be prescribed for prevention of AAD in certain special situations where the risk of AAD is very high or if AAD has the propensity to result in prolonged morbidity or mortality. | | |
| Whenever used, the probiotic should be prescribed for the entire duration of antibiotic therapy. | | |
| <i>C. difficile</i> diarrhea is not common in Indian children (personal experience of NCG), and does not recommend probiotics for the specific purpose of preventing CDAD. | | |
| In children with prior history of AAD (two or more separate episodes), either <i>Lactobacillus rhamnosus</i> GG or <i>S. boulardii</i> may be used. | Conditional | Low to moderate |
| In children where there is an expected high risk of morbidity/mortality due to AAD (e.g., hospitalized sick children, underlying chronic diseases), <i>Lactobacillus rhamnosus</i> GG only should be used. | Conditional | Low to moderate |
| <i>Pouchitis</i> | | |
| In active pouchitis probiotics may be used as an adjuvant therapy | Conditional | Low quality |
| Probiotics seem to be beneficial for prevention of recurrences and also for maintenance of remission in pouchitis | Conditional | Moderate |
| Probiotic used may be either VSL#3 or a mix of strains as suggested by ACG guideline. Doses in children are given in the text. | | |

AGA: American Gastroenterological Association. No recommendations for acute dysentery, persistent diarrhea, celiac disease, diarrhea predominant irritable bowel syndrome, and inflammatory bowel disease, as there is a lack of published evidence.

feeding (mother/donor/formula milk) are required. Subgroup analyses on <28 weeks gestational age babies, <1000g birthweight babies and term safety issues (immunity, endocrine, metabolic, behavioral) are needed. Demography-based issues (geography, gender, ethnicity, peripartum culture practices) are also a concern.

Acute Dysentery

Dysentery has a 100-fold higher incidence in Asians as compared to developed countries, mostly among children

aged 1-4 years living in low and middle-income countries. The Global Enteric Multicenter Study (GEMS) [32], upon analysis of samples with quantitative PCR, found Shigella to be the major pathogen in dysentery (attributable fraction 63.8%), and the second most common pathogen in watery diarrhea (attributable fraction 12.9%) [33]. There is a poor rationale and limited data for the use of probiotics in dysentery in children. Hence the group recommends against the use of any kind of probiotic in acute dysentery (non-*Clostridiodes difficile* causes) (Table II).

Antibiotic-associated Diarrhea

Antibiotic-associated diarrhea (AAD) is defined as diarrhea that occurs on exposure to prolonged antibiotics, provided other etiologies have been excluded. The risk of AAD is higher with antibiotics like aminopenicillins without/with clavulanate, cephalosporins, clindamycin, and anti-anaerobic agents, whether given orally or through intravenous route. Most AAD presents as mild diarrhea. Rarely they may cause fulminant pseudomembranous colitis where usually, no pathogen is identified. *C. difficile* is the most common incriminating agent in those with underlying diseases such as inflammatory bowel diseases, cystic fibrosis, and neoplasms.

International experience

The ESPGHAN 2016 [46] assessed report 21 RCTs ($n=3255$ children), and the pooled results showed that probiotics as compared to placebo or no intervention reduced the risk of AAD by 52% (21.2% vs 9.1%, respectively; RR 0.48, 95% CI 0.37–0.61). Only two probiotics (*LGG* and *S. boulardii*) could be assessed with certainty. Compared with placebo, the administration of these probiotics also reduced the risk of *C. difficile*-associated diarrhea (4 RCTs, $n=938$, RR 0.34, 95% CI 0.15–0.76).

The Cochrane systematic review (33 studies; $n=6352$) studied *Bacillus* spp., *Bifidobacterium* spp., *Clostridium butyricum*, *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp., alone or in combination, and concluded that probiotics reduce the incidence of AAD (NNTB 9, 95% CI 7 to 13) with high doses (≥ 5 billion CFUs/day) being preferable. Thus, they recommended *LGG* or *S. boulardii*; however, with a need for a large well designed multi-centred randomized trial. They could not conclude the efficacy and safety of the other probiotic agents [47].

In children on antibiotic treatment, AGA guidelines suggest the use of *S. boulardii*; or the two-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R; or the three-strain combination of *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, and *B. bifidum*; or the four-strain combination of *above three* with *S. salivarius* subsp *thermophilus* for prevention of *C. difficile* infection (conditional recommendation, low quality of evidence). AGA also recommends that probiotics can be reasonably avoided in patients having severe illnesses, where the cost-benefit ratio is poor and also in those with a very small risk of *C. difficile* development (particularly in the outpatient settings) [8,15].

C. difficile-associated diarrhea

The Cochrane review (31 trials, $n=8672$ adults and children) suggested that probiotics reduce the risk of CDAD by

60%. Trials with a baseline CDAD risk of 0–2% and 3.5% did not show any difference in risk but trials enrolling participants with a baseline risk of $>5\%$ for developing CDAD demonstrated a large (70%) risk reduction. Regarding the detection of *C. difficile* in the stools, pooled complete case results from 15 trials (1214 participants) did not show a reduction in infection rates. No major adverse events were reported. The review concluded that probiotics are effective for preventing CDAD (NNTB=42 patients, 95% CI 32 to 58), especially in those with CDAD baseline risk $>5\%$ (NNTB=12; moderate certainty evidence). Of all the probiotic agents, *S. boulardii* CNCM 1745 >5 billion CFU/day was found useful [48]. AGA does not recommend the use of probiotics in CDAD due to a considerable knowledge gap [8,15].

Indian scenario

There is a paucity of data in India regarding AAD in children. A study from Bhopal [49], showed that 64% under-5 children with a diagnosis of acute gastroenteritis from outpatient services received antimicrobials [49]. Another study [50] from a tertiary referral hospital in Eastern India showed that 80% of 265 children received 535 antimicrobial agents, of which 85% were based on empirical decisions. Of these 2.2% developed loose stools as adverse events [50]. The cost vs benefit of preventive use of probiotics in AAD cannot be entirely gauged. *C. difficile* is present in stool culture of 15% of pediatric acute diarrhea, of which only 2.9% are toxigenic [50]. It is toxigenic *C. difficile* that assumes importance in pathogenesis of AAD.

Persistent Diarrhea

There is limited data on the use of probiotics for persistent diarrhea in children [4,8]. There is a suggestion that *S. boulardii* and LGG decrease the duration and frequency of loose stools along with reduction of hospital stay in children with persistent diarrhea [51,52]. In a Cochrane meta-analysis (4 trials; $n=464$) [53], it was found that probiotics reduced the duration of persistent diarrhea [MD (95% CI) 4.02 (4.61 to 3.43 days); 2 trials, $n=324$]. Stool frequency was reduced with probiotics in two trials. One trial reported a shorter hospital stay [53]. In clinical practice, it is noted that most children with acute diarrhea may have already received probiotics before they enter the persistent phase. NCG does not recommend the use of probiotics in the management of persistent diarrhea (Table II).

Chronic diarrhea with underlying gastrointestinal conditions

The role of probiotics in children with such conditions is mostly extrapolated from adult studies.

International experience

AGA does not recommend any probiotic in irritable bowel syndrome-diarrhea (IBS-D), induction or remission of Crohn's disease, induction or remission of ulcerative colitis (UC), due to lack of adequately powered studies [8,15]. ECCO-ESPGHAN guidelines [54] do not recommend the use of probiotics in the management of Crohn's disease. Probiotic agents (e.g., VSL#3, *E. coli* Nissle 917) can be considered in mild UC as adjuvant therapy or in those intolerant to mesalamine [54,55]. In celiac disease, multiple attempts have been made to use probiotics as an alternative management strategy but none have been able to significantly alter the epithelial recovery, intestinal permeability and microbial signature. Lifelong gluten-free diet still continues to be the only proven therapy in celiac disease [56,57]. NCG does not recommend the use of probiotics in chronic diarrhea with underlying gastrointestinal conditions (**Table II**).

Pouchitis

Pouchitis is a problem in those who have undergone colectomy with an ileal pouch-anal anastomosis (IPAA), in various disease conditions such as ulcerative colitis, IBD-undifferentiated or polyposis coli. Probiotics may be considered in active pouchitis, primary prevention of pouchitis or recurrence of pouchitis. There is some evidence regarding the efficacy of VSL#3 [a mixture of eight probiotic strains: *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* (subsp. *bulgaricus*)] in preventing the initial episode and further relapses of pouchitis. The Asia-Pacific [58] guideline states that in pouchitis, VSL#3 may be considered based on the evaluation of individual cases. Due to the lack of literature in children, doses of VSL#3 as per a previous pediatric study in IBD [59] may be adopted for its use in this disease state also. Doses of 450 billion bacteria/day in 4-6 years of age (weighing 17-23 kg), 900 billion in 7-11 years of age (weighing 24-33 kg), 1350 billion in 11-14 years of age (weighing 34-53 kg) and 1800 billion in 15-17 years of age (weighing 54-66 kg) [59]. In adults and children with pouchitis, AGA recommends a 8-strain combination of [*L. paracasei* DSM 24733, *L. plantarum* DSM 24733, *L. acidophilus* DSM 24733, *L. delbrueckii* subsp. *bulgaricus* DSM 24733, *B. longum* DSM 24733, *B. breve*, DSM 24733, *B. longum* subsp. *infantis* DSM 24733, and *S. salivarius* subsp. *thermophilus* DSM 24731] over no or other probiotics (conditional recommendation, low quality of evidence) [8,15]. Cochrane meta-analysis concluded that it was uncertain if probiotics had an advantage over placebo in all the above three settings [60]. NCG recommendations for pouchitis are given in

Table II. In these guidelines, the VSL #3 pre-paration refers to the original De Simonie formulation.

Probiotics Currently Available in India

A recent publication [61] has comprehensively summarized the composition and laboratory correlation of the commercially available probiotics in India till recently. Significant differences were noted in some of the brand preparations and the next-generation sequencing results with regard to the probiotic organism. In some of the probiotics, new strains were found on cultures that were not a part of the original label [61]. They also highlighted the differences in the label concentrations and the in vitro viable cell count on culture indirectly signifying the actual bioavailability [61]. In combination probiotics such as VSL#3, there are other issues regarding the recommended concentration and marketed concentration. Hence the prescription of the probiotic should be carefully written keeping in mind the rationale, actual species and strain, marketed concentration, mode of delivery (sachet, capsule, syrup or vial), projected bioavailability and shelf life. Among the recommended single-strain probiotics in this guideline, LGG and *S. boulardii* are marketed in India. With regards to NEC in preterms, an exclusive combination of *Lactobacillus* spp. and *Bifidobacterium* spp. in the recommended concentrations are not available yet in India. It is cautioned that some of the marketed combination probiotics contain *S. boulardii*. At present, the marketed VSL#3 is available in India at lower concentrations than the international standards. In view of the above lacunae, pharmaceutical manufacturers in India should take appropriate steps in accordance with the scientific guidelines.

CONCLUSIONS

Probiotics in India should be used judiciously, after obtaining complete information regarding the strains present, CFU, shelf life and storage requirements. The decision to use a probiotic should be in line with scientific evidence keeping in mind the cost-benefit ratio.

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**NOTIFICATION FOR FELLOWSHIP COURSE IN PEDIATRIC INTENSIVE CARE,
PEDIATRIC EMERGENCY MEDICINE AND PEDIATRIC PULMONOLOGY
2022-2023 SESSION**

The Institute of Child Health and Hospital for Children, Egmore, Chennai is conducting one year post doctoral fellowship courses in **Pediatric Intensive Care, Pediatric Emergency Medicine and Pediatric Pulmonology** under The Tamilnadu Dr MGR Medical University. These courses will impart specialised knowledge in all aspects of pediatric intensive care, emergency medicine and pulmonology. The pediatric intensive care and pediatric emergency medicine training will empower the candidates to independently manage critically ill children and help establish pediatric intensive care and pediatric emergency medicine departments at other medical colleges and in district hospitals. The Pediatric Pulmonology training will empower the candidates to manage Pediatric pulmonology cases and Bronchoscopy.

The eligibility for the course is M.D. (Pediatrics)/Diploma in National Board (Pediatrics)

| Name of course (Post doctoral fellowship) | No of seats | course duration |
|---|-------------|-----------------|
| 1. Pediatric Intensive Care | 2 | 1 year |
| 2. Pediatric Emergency Medicine | 2 | 1 year |
| 3. Pediatric Pulmonology | 2 | 1 year |

Out of the two seats one will be allotted to service candidate and one will be allotted to private candidate in each course. If seat is not filled up in one category the seat will be allotted to eligible candidate from other category.

The course fee is Rs 50,000 [Rupees Fifty Thousand Only] for all candidates. This should be paid at the time of admission, as demand draft favouring "The Director and Superintendent", Institute of Child Health and Hospital for Children, Egmore, Chennai. 600008.

Selected service candidates will be deputed for the course and they will be eligible for pay and allowances as per GO. MS. No.156 dt 22.6.2011.

The application form can be downloaded from the Tamilnadu Dr MGR medical university website www.tnmgrmu.ac.in. The rules and regulations of the fellowship course and eligibility criteria are clearly given in above mentioned website.

The filled up application along with a DD for Rs1000 in favour of "The Director and Superintendent, Institute of Child Health and Hospital for Children" should be sent to the following address and superscribed as

**APPLICATION FOR FELLOWSHIP IN PEDIATRIC INTENSIVE CARE,
PEDIATRIC EMERGENCY MEDICINE AND PEDIATRIC PULMONOLOGY**

**Director and Superintendent,
Institute of Child Health & Hospital for Children
Halls Road, Egmore, Chennai 600008.**

"Service candidates should submit the application through proper channel."

Last date for submission of application : **10/08/2022, 5 pm**

The date of entrance exam will be : **24/08/2022, 10 am**

Venue: Institute of Child Health and Hospital for Children, Egmore, Chennai. 600008.

Course commencement : **8th September 2022**

The qualifying examination will be of 3 hours duration with total 100 MCQ.

Pediatric Intensive care from General Pediatric and Pediatric Intensive care.

Pediatric Emergency Medicine from General Pediatric and Pediatric Emergency Medicine

Pediatric Pulmonology from General Paediatric and Pediatric Pulmonology

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Indian Academy of Pediatrics Consensus Guidelines on Prevention and Management of Suicidal Behavior in Adolescents

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Justification: Suicide is an important cause of adolescent mortality and morbidity in India. As pediatricians are often the first point of contact for adolescents and their families in the healthcare system, they need guidelines to screen, assess, manage and prevent adolescent suicidal behavior to ensure survival, health and mental well-being of this vulnerable population. **Objectives:** To formulate guidelines to aid pediatricians for prevention and management of adolescent suicidal behavior. **Process:** Indian Academy of Pediatrics, in association with Adolescent Health Academy, formed a multidisciplinary committee of subject experts in June, 2019 to formulate guidelines for adolescent suicide prevention and management. After a review of current scientific literature and preparation of draft guidelines, a national consultative meeting was organized on 16 August, 2019 for detailed discussions and deliberations. This was followed by refining of draft guidelines, and discussions over e-mail where suggestions were incorporated and the final document was approved. **Guidelines:** Pediatricians should screen for mental distress, mental disorders and suicidal and para-suicidal (non-suicidal self-injury) behavior during adolescent health visits. Those with suicidal behavior should be referred to a psychiatrist after providing emergency healthcare, risk assessment, immediate counselling and formulation of a safety plan. Pediatricians should partner with the community and policymakers for primary and secondary prevention of adolescent suicide.

Keywords: *Care cascade, Counseling, Emergency management, Risk assessment, Safety plan.*

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Adolescents form 18% of India's population, and suicide is the third leading cause of adolescent mortality [1]. Only 1% of the pediatric population with mental disorders seeks treatment, due to the scarcity of mental health services and the social stigma [2]. Currently, there is an approximate 75% shortage of mental health professionals in the country [3]. Hence there is a need to stepped care approach to pediatric mental healthcare with active involvement of non-specialists. As pediatricians share a long standing rapport with families, parents often seek their advice for management of adolescent mental health issues. Majority of the adolescent suicides are impulsive and timely intervention can save young lives. Hence there is a need to formulate practical guidelines for pediatricians for management and prevention of adolescent suicidal behavior.

Existing Adolescent Mental Health Status

The National Mental Health survey (2015-2016), reported

a 7.3% prevalence of mental disorder in adolescents, higher in urban metro regions with similar distribution between males and females. The most common disorders were anxiety and depression [4]. Half of the mental illnesses begin by the age of 14 years [5]. In 2021, UNICEF reported a two times increase in prevalence of adolescent mental disorders due to pandemic related stressors [6].

The risk of suicides among adolescents in India is 1.3% [7]. Among high school students, the prevalence of suicide ideation is 6.0-21.7% and of suicide attempts is 0.39-8%. [8]. In adolescents with mental disorders, the estimated risk of suicide is 47-74% [9]. In 2020, one adolescent committed suicide approximately every hour with more girls than boys [10] The actual figures may be higher as in most cases there is inaccurate reporting [10,11]. Hanging, poisoning, drowning and self-immolation were the main modes of committing suicide. Family problems (35%), break-up in romantic relationships (12%), physical and mental illness (12%)

and failure in examinations (10%) were the main causes of suicide in adolescents [10].

Suicide risk identification is a window of opportunity for a pediatrician to contribute to suicide prevention. It is estimated that of all youth presenting with a suicide attempt, 25% have a reattempt and 5-10% commit suicide subsequently. A substantial proportion of youth have had medical visits in the year preceding completed suicide [12]. Adolescents with suicidal ideation might not reveal about their thoughts unless asked. Extreme hopelessness and absence of belongingness with easy access to means may trigger a suicidal attempt [13]. Asking about suicide does not increase the risk for the same. There is evidence to suggest that brief behavioral health interventions with follow-up care have a positive impact on outcomes [14,15]. There is currently inadequate evidence for efficacy of specific suicide prevention interventions [16-18]. A combination of strategies is known to work the best in prevention (**Web Table I**). WHO has recently released guidelines for framing country-specific suicide prevention programs and strategies for promoting positive mental health in adolescents [19,20].

In 2019-2020, guidance for medical officers to manage suicidal behavior and mental disorders in children and adolescents and a manual for caretakers of shelter homes to manage non-suicidal self-injury (NSSI) in female adolescents in Indian settings were published by National Institute of Mental Health and Neurosciences (NIMHANS) [21,22]. Recently, suicide has been decriminalized under the National Mental Health Care Act 2017. The Government of India is currently considering framing a national comprehensive suicide prevention strategy [23].

OBJECTIVES

To empower pediatricians with guidelines to screen and manage adolescent suicidal behavior in clinical practice, and to outline practical strategies for preventing suicides.

PROCESS

The process of forming these guidelines started on 1 June, 2019 with the formation of a national committee of multidisciplinary subject experts in collaboration with Adolescent Health Academy. The experts were selected on the basis of their professional competence and commitment. They are well known in their respective fields with a specialty post graduate and/or doctorate degree with over two decades of professional and research experience. Five sub groups of experts including adolescent health specialists, psychiatrists and pediatricians were formed to evaluate scientific evidence regarding existing status of adolescent mental health, risk and protective factors for suicide, clinical assessment, prevention and emergency

management. Each sub-committee reviewed the existing published literature using the following indexing bodies/databases, but not limited to, Medline, Pubmed Central, Citation index, Sciences Citation index, Expanded Embase, Scopus, Directory of Open access journals (DoAJ). The types of articles that were reviewed included meta-analysis, systematic reviews, original papers, case series, case reports, guidelines from WHO and paediatric professional bodies, international and national statistics in the public domain. Some search words and terms included were: suicide, adolescents, guidelines on suicide prevention and management, non suicidal self-injury, self-harm, suicides in India, suicidal attempt, counselling, etc. After multiple rounds of discussions, the sub-committees prepared draft guidelines pertaining to their respective topics. The draft guidelines were presented and discussed in depth at the National Consultative Meet conducted at Bangalore on 16 August, 2019. During the pandemic, due to the inability of organizing physical meetings, further discussions were continued via digital media. The final document was prepared after consensus through a series of online and email discussions and partial Delphi method. Updates based on revised literature review (up to January, 2022) and suggestions of the team members were incorporated in the guidelines document.

GUIDELINES

Pediatricians should assess all adolescents presenting to a healthcare facility for suicidal behavior and perform a brief risk assessment. If suicidal behavior or risk is detected, pediatrician should refer to a child psychiatrist/psychiatrist after providing emergency care and counselling. Pediatricians should advocate for adolescent suicide prevention measures.

Risk and Protective Factors

All adolescents should be screened for risk and protective factors (**Table I**). Existence of multiple risk factors increases the risk of suicidal behavior and protective factors decrease the risk [24-28]. Suicide occurs due to a dynamic interaction between numerous biopsychosocial factors. Ninety percent of suicidal attempts among adolescents are impulsive [8]. Adolescents have a high emotional reactivity due to differential maturation of the parts of the brain in this phase of life which makes them prone to impulsive behavior, especially in emotionally charged situations and conditions of extreme distress [25]. A major life stressor like a break up of an intimate relationship, academic failure, adverse influences of digital and social media and availability of lethal means of committing suicide can trigger suicide [25]. Adolescents with academic difficulties and learning problems have a 3-times higher risk of suicide compared to those who do not have these issues [26].

Table I Risk and Protective Factors for Adolescent Suicide

| <i>Risk factors</i> | <i>Protective factors</i> |
|--|--|
| <i>Individual</i> | |
| Female sex | Positive coping skills |
| School drop out | Emotional self- regulation skills |
| Previous history of suicidal attempt | High self esteem |
| Death wish/ suicidal notes/ online posts | Conflict resolution skills |
| Non suicidal self- injury | Involvement in hobbies and activities |
| Child abuse/ trafficking | Employment |
| Bullying, cyberbullying | Religious belief |
| Marginalized youth | Good social skills |
| Mental and physical illness | Help seeking behavior |
| Failed intimate relationship | |
| Substance use disorder | |
| Children in conflict with law and in need of care and protection | |
| Gender minority youth: LGBTQIA | |
| <i>School and Peers</i> | |
| Failure in exam | Academic achievement |
| Learning problems | Positive peer relationships |
| Violent peers | Strong school connectedness |
| Lack of school counselling services and social support | Life skill education, suicide and bullying prevention programs |
| <i>Family</i> | |
| Family dysfunction and violence | Family stability |
| Child abuse and neglect | Authoritative parenting |
| Economic crisis, environmental disasters | Strong family connectedness |
| Family h/o suicide, mental disorder, alcohol use disorder | Positive discipline |
| <i>Community</i> | |
| Access to means of suicide | Access to adolescent friendly and mental health services |
| Unsafe media portrayal of suicide | Responsible media reporting |
| | Comprehensive national policy for suicide prevention |

Prepared with material from references 23-28. LGBTQIA - Lesbian, gay, bisexual, queer, transgender, intersex, asexual.

Adolescents living in difficult circumstances e.g., in childcare institutions, street children, exposed to adverse childhood experiences, sexually abused, in poverty, areas of armed conflict, natural disasters, with severe substance use disorder and emotional dysregulation are prone to parasuicidal behavior or non-suicidal self-injury (NSSI) [21]. NSSI behavior is defined as deliberate destruction or alteration of body tissue without suicidal intent. Self-cutting is the most common NSSI [21]. Research indicates that adolescents indulge in NSSI to alleviate feelings of anger, sadness, to distract themselves from problems, to secure attention and as a form of self-punishment. NSSI is a risk factor for suicide [22].

Factors which protect against suicidality are family support, peer and school connectedness, physical and mental well-being, life skills (e.g., problem solving and coping skills) and availability of adolescent healthcare resources. [13].

Risk Assessment

All adolescents should be screened for suicidal behavior

including suicidal ideation, thoughts, attempts and NSSI during clinical encounters and annual health visits using the HEEADSSS psychosocial interviewing framework, in privacy and after explaining the limits of confidentiality [29,30]. Questions should be short, non-judgmental and in developmentally appropriate language. Collateral information should be obtained from parents, peers, school teachers and counselors. Disclosure of suicidality entails sharing this information with a trustworthy caregiver that the adolescent chooses, to discuss further management plan to ensure his/her safety. Pediatricians should maintain medical records regarding documentation of assessment of suicidal behavior and management plan.

Those with suicidal ideation and NSSI should be asked about intent and plan (**Table II**). Adolescents with suicidal thoughts can be classified into three risk groups [31]:

- *Low risk*-thoughts of death only; no plan or behavior.
- *Moderate risk* -suicidal ideation, with limited suicidal intent and no clear plan.
- *High risk*- suicide plan with preparatory behavior

When adolescents do not reveal suicidal behavior, there is a possibility of detecting suicidal risk using ‘IS PATH WARM’ mnemonic developed by the American Association of Suicidology, which can be used to identify warning signs of suicide [32,33] (**Box I**). Those with suicidal thoughts and plan of self-harm in the past one month or with a past history of self-harm in the past one year, currently presenting with extreme agitation, violent episodes, distress and lack of communication are also considered as high risk, even though they may not express suicidal thoughts, intent or plan [34].

All adolescents with suicidal thoughts should undergo detailed history taking and examination to rule out medical, neurodevelopmental and mental disorders. Assessment of emotional and behavioral issues should be conducted. Risk and protective factors for suicide should be assessed.

Additional screening tools: Screening tools may complement but not replace thorough clinical assessment and can be self-administered. Ask Suicide Screening Questionnaire (ASQ) is a 4-item measure that has good sensitivity in identifying youth at risk for suicide [33]. Other screening tools include Columbia Suicide Severity Rating Scale, Beck Depression Inventory and Patient Health Questionnaire- 9 (**Web Table II**).

Criteria for Referral

All suicidal ideation and attempts and NSSI should be taken seriously, and require referral to a mental health specialist. Emergency mental health referral is needed if there is immediate threat to life, and for patients assessed as moderate to high risk and with severe mental distress. Urgent mental health referral within 48 to 72 hours is needed for patients with low risk.

Emergency Management of Adolescent Suicidal Behavior

The potential emergency situations encountered in clinical settings are:

Box I Warning Signs of Suicide (IS PATH WARM)

- I Ideation (Talking or writing or posting online about death, threatening to hurt or kill self, giving away prized possessions)
- S Substance use
- P Purposelessness (Having no reason to live)
- A Anxiety
- T Trapped
- H Hopelessness
- W Withdrawal
- A Anger(uncontrolled)
- R Recklessness
- M Mood changes

Prepared with material from references 31,32.

Presentation with life threatening health effects: As in poisoning, near drowning and hypoxic ischemic encephalopathy following hanging. This situation needs to be handled with triaging, resuscitation, stabilizing and appropriate referral following brief interventional counselling focusing on the physical health needs of the adolescent and assurance of support to the family. The pediatrician inter-ventions should continue through the recovery period to complete the protocol suggestions.

After an event: Parents and adolescent seeking intervention following an attempted suicide or self-harm attempt.

Adolescents categorized as high risk for suicide: Adolescents with warning signs of suicide, past history of suicide attempt, severe mental disorders, substance use disorder, multiple risk factors and refusal to follow the safety plan are considered to be high risk even if they present with only suicide ideation without a plan

A protocol is suggested to provide a minimum care systematic strategy with the intention of effective suicide prevention at first contact and an outline of follow up care. (**Fig.1** and **Box II**). After medical clearance, the cascade of care suggests therapeutic assessment and interventions

Table II Screening Questions for Suicidal Behavior

| <i>Ideation (frequency, intensity)</i> | <i>Intent</i> | <i>Plan</i> |
|--|--|---|
| There are times when situations are unbearable and hopeless, young people think of hurting or killing themselves to end it all. Have you ever thought of hurting /killing yourself? How often do these thoughts happen? How long do they last? What do you do when you have them? What coping strategies do you use? What are the triggering events for these thoughts? | Have you ever thought of acting on your thoughts? How likely do you think that you will act on your thoughts? | Do you have a plan? If so, how would you intend to do it and where? Which means would you use? Do you have a time line in mind? |

Prepared with material available in references 30-33.

covering counseling of the adolescent with focus on inculcating 'hope', safety plan, protective support, lethal means counseling and handling substance use [35,36]. This is followed by a plan for inpatient or outpatient care. National 24×7 toll-free mental health helpline numbers should be shared with the patient and the parents. Subsequent interventions include motivational counseling, addressing treatment barriers, using caring contacts and multidisciplinary collaborative care with psychiatrists, psychologists, psychiatric social worker, educators and counsellors [12].

Pediatricians should consider any suicide risk as an emergency akin to a coronary ischemic event. They should ensure the following steps, ensuring complete medical documentation [36]:

- i) Stabilize physical health, ensure emergency wound care and completion of age appropriate tetanus immunization schedule and rule out medical problems with acute psychiatric symptoms with altered sensorium like brain tumors, seizures, hypothyroidism, hyperthyroidism, hyperammonia, Wilson disease, hypocalcaemia, drug overdose and substance abuse [37].
- ii) Evaluate mental health status and assess the degree of mental distress, the extent of functioning in the form of ability for self-care, sleep, appetite, educational grades and interpersonal problems like bullying and abuse [30]. Questionnaires like patient health questionnaire-2 and 9 (PHQ 2 and 9), Becks depression inventory, screening for childhood anxiety related emotional disorders (SCARED) and screening to brief intervention tool (S2BI) can be used for screening for depression, anxiety and substance use disorder respectively [38-41]. The final diagnosis of mental disorders is made using the Diagnostic and statistical manual -5 (DSM-5) criteria.
- iii) Identify the protective factors and risk factors with intention to enhance protective factors and reduce risk factors. Classify severity of risk by using a screening tool. The risk for suicide attempt recurrence is assessed by administering a self-report either in person or by writing
- iv) Impart psychoeducation, counsel the adolescent and family, activate psychosocial support and impart lethal means counselling. (**Fig. 1**)
- v) Create a safety plan. This safety plan is a written and discussed treatment plan with the adolescent and family which outlines all the protection supports and contacts in the event of a future situation of suicidal intent (**Box II**)

- vi) Facilitate treatment of identified mental illness
- vii) Enhance resilience with a planned strategy of life skills education using training manuals e.g the NIMHANS adolescent life skill series or the life skill educators' modules [42].
- viii) Impart positive parenting training sessions that include information about normative adolescent development and the vulnerability to risky behaviour under stress. Parents are counselled to provide a secure, supportive and safe home environment, to use effective communication and positive discipline techniques, to encourage a healthy lifestyle and hobbies and to inculcate life skills in their children
- ix) Make a timely referral to a psychiatrist
- x) Retain the adolescent in follow-up with proactive efforts and motivation for a minimum period of 6 months up to a maximum of 2 years. Follow up visits are scheduled once a week for 2 months, once a month in the first one year, and twice in the second year [34].

Suicide Prevention

Pediatricians can play an important role in primary and secondary prevention of adolescent suicide.

Primary Prevention Strategies

These strategies target the risk factors to mitigate the suicidal behavior in clinical and community settings and are detailed below [43, 44].

- i) *Fostering resilience*: During annual health and medical visits, pediatricians can highlight the adolescent's strengths, encourage self-efficacy, teach effective problem-solving skills, and identify protective factors, such as positive religious and spiritual beliefs and thus promote resilience [45]. Life skill education manuals can be used to facilitate these sessions [42].
- ii) *Promoting school, peer and family connectedness*: Pediatricians should screen for family, school and peer connectedness and teach strategies of authoritative parenting, assertive communication and conflict resolution to strengthen these [46,47]. Gender equality and discrimination issues should also be discussed [23]. Partnerships with NGO and medical social workers should be established to enable economic help for deprived families.
- iii) *Intervening on parent psychopathology*: Pediatricians should refer parents (of adolescents) with mental disorder to mental health professionals at the earliest [45]. Pediatricians should partner with schools to plan and



Fig. 1 Cascade for emergency care of adolescent suicidal behavior (Prepared from material available in references 34-37).

| Box II Sample Safety Plan | | | | | |
|---|----------------|--------------------------|-----------|---------------------------|-----------|
| <i>(To be formulated by the adolescent, pediatrician and caregivers)</i> | | | | | |
| a) Warning signs like thoughts, images, persons, situations, events | | | | | |
| 1. | 2. | 3. | | | |
| b) What I can do to distract myself immediately even without involving other people (e.g praying, relaxation, deep breathing, imagery, reverse counting from 100 to 1) | | | | | |
| 1. | 2. | 3. | | | |
| c) Places and people who can help you to distract (e.g grandparents, friends, playground, mall, neighbor, relative, music, painting) | | | | | |
| 1. | 2. | 3. | | | |
| d) People whom I can ask for help. | | | | | |
| 1. Name: | Phone no: | 2. Name: | Phone no: | 3. Name: | Phone no: |
| e) Doctors, clinic, hospital, helpline that I can contact for help. | | | | | |
| 1. Child helpline | Phone no: 1098 | 2. Name: | Phone no: | 3. Name: | Phone no: |
| Reminder: I am precious. My life is precious. The one thing that is very important for me and makes my life worth living for is | | | | | |
| Note: Fill in the points as per your preference and choices. Think about what is practical and will work for you. Keep this safety plan handy for reference on your phone, pasted on your door etc. So that you can remind yourself that you can keep yourself safe at all times. | | | | | |
| Signature of adolescent | | Signature of caretaker/s | | Signature of pediatrician | |

Prepared with material from references 30, 35-37.

implement effective school-based interventions [46]. The school-based interventions include adolescent life skill education to promote overall mental well-being and interactive talks with adolescents, parents and teachers about causes and warning signs of suicide and mental disorders like depression and anxiety. Pediatricians can utilise the ‘Living Life Positively’ manual of National Institute of Health and Family Welfare (NIHFW) to conduct these sessions [47]

Secondary Prevention Strategies

Secondary suicide prevention efforts aim at helping those identified at risk for suicide, screening and treating mental disorders [48,49]. In the outpatient setting, pediatrician can use screening questionnaire for suicidality and other mental health disorders, as previously mentioned. If there are signs of suicidality, the care cascade can be followed. For those with mental disorders, psychotherapy in form of cognitive behavior therapy, dialectical behavior therapy, interpersonal therapy, family therapy and psychopharmacology under the supervision of a psychiatrist is recommended [25,30,34]. Tele health and mHealth are potential methods to manage mental health issues in areas where there are limited mental health resources or where access to health services is restricted [50,51].

Strategies for Advocacy

IAP should update and revive the Mission Kishore Uday program launched in 2019 on adolescent suicide prevention and intervention [52,53]. IAP should organize nationwide

workshops with comprehensive gatekeeper training of pediatricians, parents, teachers and adolescents to disseminate these guidelines

Widespread community level advocacy activities for adolescent suicide prevention and intervention should be planned by IAP, in collaboration with school management and personnel, volunteers of NGOs, community leaders and health workers, religious leaders and adolescents themselves.

Prevention can be universal, selective and indicated [54]. Universal strategy is for entire population and includes suicide awareness programs, education programs for media on suicide reporting practices, and school based crisis response plans and teams. Selective strategies target risk groups (e.g. grade 10 and 12 students) and includes screening programs, gatekeeper training for teachers/parents, school personnel, peers and enhancement of accessible crisis services and referral. Indicated strategies focus on high risk individuals with early warning signs of suicide. Skill-building programs for school/college students and parent support training programs that aim at reducing risk factors, increasing protective factors and imparting life skills.

IAP should advocate for framing a comprehensive national policy for adolescent suicide prevention. This policy should be included in the national adolescent health strategy, Rashtriya Kishore Swasthya Karyakaram on priority basis [23,55]. A national registry should be

Box III Summary: IAP Consensus Guidelines for Adolescent Suicide Prevention and Intervention

1. **Suicide screening:** All adolescents should be evaluated for suicide risk by pediatricians as a part of routine healthcare visit or annual medical checkup. The two basic questions to be asked as part of universal HEEDSSS screening are: *i)* Sometimes when things get difficult, many young people think of death and even hurting/killing themselves. Have you had any such thoughts? If yes, *ii)* Have you actually tried hurting/killing yourself anytime? Additional screening tools may be utilized to assess severity, immediacy of risk and to calibrate further medical interventions.
2. **Assessment:** All adolescents should be assessed for mental wellness, strengths and disorders through HEEDSSS screening and appropriate screening tools on an annual basis. This is in addition to and independent of suicide risk assessments.
3. **Referral criteria:** All adolescents with suicidal behavior should be referred to the psychiatrist. Adolescents with high risk for suicide, psychosis and moderate/severe depression and substance use should be referred on an emergency basis.
4. **Emergency care and management:** The care cascade algorithm should be used to manage an adolescent with suicide risk. The pediatrician should provide first responder services that enables the adolescent and the family to foster hope. They should offer help, counter the feelings of hopelessness, helplessness, worthlessness, shame and guilt and prepare a safety plan.
5. **Collaborative management:** The group recommends that the pediatrician coordinates the care with the psychiatrist, counselor, social worker, educator and a psychologist for physical and mental well-being, resilience building and safety monitoring for a minimum period of 6 months.
6. **Prevention:** All pediatricians should familiarize themselves with life skills training programs that can be implemented on individual and community settings.
7. **Advocacy:** As gatekeepers for child and adolescent health, pediatricians should disseminate the guidelines to healthcare professionals, community, government and non-government agencies.

maintained for collection of accurate statistics regarding adolescent mental disorders and suicidal behavior to evaluate various preventive measures [56]. Media reporting guidelines should be implemented and regulated to avoid suicide contagion (copycat suicide). The availability of child helpline 1098 and the existing mental health services including telecounseling services should be disseminated and periodically highlighted through various media channels. Educational and examination reforms to decrease academic stress on the students should be considered. At a national level, there should be a strategy to reducing the access to means of suicide e.g., regulation of sale of organophosphorus pesticides and prescription medicines.

CONCLUSION

Pediatricians should screen adolescents for protective and risk factors of suicide/suicidal behavior, and conduct a mental health evaluation at annual healthcare visits. During these visits, they should discuss strategies with adolescents and parents to enhance protective factors and over all mental well-being. Mental disorders, if detected, should be treated at the earliest. All cases of suicidal behavior should be referred to the psychiatrist after a risk assessment and brief intervention including immediate counseling of adolescents and parents, and formulating a safety plan. Pediatricians should collaborate with mental health professionals for treatment and follow-up (**Box III**).

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

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ANNEXURE

IAP Guidelines Committee on Prevention and Management of Suicidal Behavior in Adolescents

Chairpersons: MKC Nair, Digant Shastri; **Convener:** Preeti M Galagali; **Writing Committee Members:** Amitha Rao Aroor, Chitra Dinakar, Preeti M Galagali, Piyush Gupta, Chandrika Rao, Latha Ravichandran, Dheeraj Shah. **Members:** PV Arya, CP Bansal, Piyali Bhattacharya Sushma Desai, JC Garg, Atul Kanikar, Satish Pandya, Garima Saikia, RN Sharma, JS Tuteja. **Invited experts:** PS Russell (Child and Adolescent Psychiatrist), Poongodi Bala (Psychiatrist). **Rapporteur:** Kritika Agarwal. **Ex-officio:** Remesh Kumar R.

All members attended the National Consultative Meet at Bengaluru on 16 August, 2019 except CP Bansal, JS Tuteja, and Paul Russel.

Web Table I Evidence Based Strategies for Suicide Prevention

| <i>Prevention strategies</i> | <i>Available evidence</i> |
|---|--|
| <i>Universal interventions</i> | |
| Mitigating unemployment, poverty and inequalities | Implemented by Government authorities. Unplanned studies |
| Restricting access to lethal means of suicide-safer designs of buildings, prisons, stringent firearm rules, limitation to pesticide access. Barriers and safety nets. | Case studies Retrospective observations. Review articles |
| <i>Public awareness</i> | |
| School based interventions, cyber bullying, monitoring bullying, Social media watch, Helplines, Accessible Mental health service | Randomized controlled trials |
| <i>Selective interventions</i> | |
| Gatekeeper training – Health personnel, teachers, priests, volunteers among parents and students | Uncontrolled studies |
| Vulnerable population interventions- Deaddiction, Evaluating depression, social isolation, | Randomized controlled trials |
| Discharge, Contract and follow up for one year minimum, | |
| <i>Indicated interventions</i> | |
| Treatment of mental disorders. | Randomized controlled trials |

Prepared with material available in references 43-45.

Web Table II Screening Tools for Suicide Risk and Common Mental Disorders

| <i>Screening tool</i> | <i>Web link</i> |
|---|---|
| <i>Suicide Screening</i> | |
| Columbia suicide severity rating scale | https://cssrs.columbia.edu/wp-content/uploads/C-SSRS_Pediatric-SLC_11.14.16.pdf |
| Becks depression inventory (BDI) | https://www.ismanet.org/doctoryourspirit/pdfs/Beck-Depression-Inventory-BDI.pdf |
| Patient health questionnaire-9: Modified for teens (PHQ-9) | https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/GLAD-PC_PHQ-9.pdf |
| Adolescent Suicide- Screening Questionnaire (ASQ): | https://www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials/asq-tool/asq-screening-tool |
| <i>Depression screening</i> | |
| Patient health questionnaire-2 (PHQ-2), PHQ-9 and BDI | https://aidsetc.org/sites/default/files/resources_files/PHQ-2_English.pdf |
| <i>Anxiety disorder screening</i> | |
| Screen for child anxiety related emotional disorders (SCARED) | https://www.ohsu.edu/sites/default/files/2019-06/SCARED-form-Parent-and-Child-version.pdf |
| <i>Substance use disorder screening</i> | |
| Screening to brief intervention tool | https://www.drugabuse.gov/ast/s2bi/#/ |

Multisystem Inflammatory Syndrome Associated With COVID-19 in Children (MIS-C): A Systematic Review of Studies From India

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Background: With wide clinical spectrum, multisystem inflammatory syndrome associated with coronavirus disease 2019 (COVID-19) in children (MIS-C) is a relatively novel condition occurring weeks to months' post SARS-CoV-2 infection. The aim was to systematically review data on clinical features, laboratory parameters and therapeutics of MIS-C from India. **Methods:** This systematic review was done as per the PRISMA guidelines, and quality assessment was done using NIH tool for case-series. A systematic search through databases yielded studies whose data was pooled to calculate the mean frequencies with standard deviation using GraphPad software. **Results:** Screening of 2548 articles published till December, 2021, yielded 11 case-series. World Health Organization case definition was used widely. There was a slight preponderance of males (57%), median (IQR) age was 7 (6,7) years, 63% ($n=305$) required intensive care unit admissions, and mortality rate was 10% ($n=261$). Clinical features included fever, mucocutaneous features (72%), and gastrointestinal problems (62%) in majority. Widely used treatment was corticosteroids (76%) and intravenous immunoglobulin (62%) with other options depending on patient's state. An increased level of inflammatory markers and derangement in other parameters corroborated with disease status. Kawasaki disease like features, not reported in many studies, ranged from 4-76% of patients. **Conclusion:** MIS-C presents with a wide spectrum clinical features, increased inflammatory markers and managed as per the disease course and presentation. Future studies monitoring the long-term effects of MIS-C are recommended.

Keywords: *Clinical features, Laboratory markers, Management.*

PROSPERO ID – CRD 42021275503

A minority of children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present with multisystem inflammatory syndrome in children (MIS-C), usually 2 to 4 weeks post-infection, the pathophysiology of which is still unclear. The clinical features of this syndrome overlap with Kawasaki disease (KD), toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome; although the clinical picture keeps on evolving. The exact incidence is difficult to calculate and this entity is relatively rare, approximately 2 per lakh in children under the age of 21 years [1]. Well-accepted case definitions from various organizations are now available for a clinical diagnosis [2]. Data from India suggests similarity in infectivity rates during both the first and the second waves [3].

The current review addresses the question of clinical manifestations, laboratory profile and therapeutic strategies employed for MIS-C in India. Pooled analyses of all these aspects have been reported from various countries and population groups; however, the aim of current study was to gather data from Indian population

and present it in the form of a systematic review.

METHODS

We detailed the following PECO (participants, exposure, comparison and outcome): P: Children with MIS-C, E: coronavirus disease –19 (COVID-19) infection, C: None, O: Types of organ systems involved, common clinical features associated with MIS-C, treatments used, and values of laboratory parameters.

Eligibility criteria for studies: Case series on MIS-C from India published in English till December, 2021 were included. Case definitions as per Centers for Disease Control (CDC), World Health Organization (WHO) and Royal College of Pediatrics and Child Health (RCPCH) criteria were considered. Data related to other coronaviruses were not included and SARS-CoV-2 positivity either by real time-polymerase chain reaction (RT-PCR) or serology was considered essential. Studies on adults (more than 18 years) were excluded.

Search strategy and information sources: The systematic review was conducted as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-

analysis) guidelines updated in 2021. The electronic search was conducted in PubMed, EMBASE and OVID databases. The key terms applied in the databases to search for the relevant studies are listed in **Web Box I**.

Selection process and data collection: Two authors independently did the screening of titles and abstracts. Full text of articles were retrieved, which were further screened by two authors as per the inclusion criteria. Finally, the articles were selected by consensus for inclusion in the review. A structured form to record the details was prepared to extract various parameters from the included studies. The data extraction was done independently by two reviewers, and any conflicts were resolved by discussion or by consulting a third reviewer. Data on age, gender, number of participants, MIS-C case definition, diagnostic criteria, clinical features, treatment regimes, laboratory parameters and features of KD were noted.

Critical appraisal: The quality of case-series was evaluated using the NIH quality assessment tool. Two authors independently did the quality assessment, which was further confirmed by a third author.

Effect measures and synthesis methods: Data on age, gender, SARS-CoV-2 infection confirmation by RT-PCR or serology, intensive care unit (ICU) admissions and mortality was collected from the case-series. Data on clinical manifestations, laboratory parameters and management were also collected. The findings from individual studies were summarized in summary tables, and data for these variables were pooled as relative frequencies and presented as mean and standard deviation. Data analysis and graphical plotting was done using Graph Pad Software (version 5.0, GraphPad Software Inc).

RESULTS

Database search and screening process is depicted in **Fig. 1**. A total of 2548 articles (Pubmed, 238; Scopus, 294 and EMBASE, 2016) were identified in accordance with the key terms from the published literature. Of these, 246 articles were removed due to duplication, and the remaining 2,302 articles were further screened by their title and abstract. Finally, 11 case series were identified for this review. The results of the critical appraisal of the included studies are presented in **Web Table I**.

Out of all the included studies, majority ($n=6$) used the WHO clinical definition for MIS-C; two studies each used the CDC and RCPCH definitions. The details of included case-series are depicted in **Table I**. The data were obtained from different cities across the country (**Web Fig. 1**). Majority of the studies are from the state of Maharashtra followed by Tamil Nadu and West Bengal. The cumulative demographic data comprising of age, gender, SARS-CoV-2

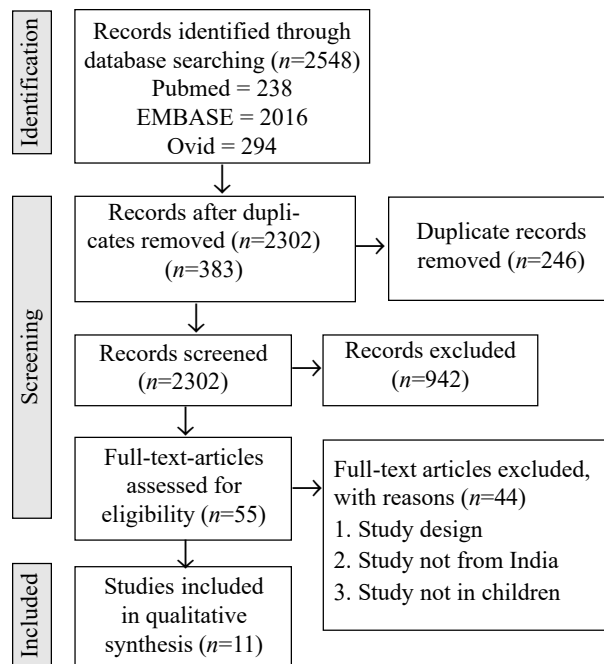


Fig. 1 Flowchart for screening and selection of studies.

positivity (RT-PCR and serology), ICU admissions and mortality on 305 children from different studies is shown in **Fig. 2**. Majority of children were males (57.42%), with median (range) age of 7 year (2 month-16 year). SARS-CoV-2 positivity was confirmed by serology in 71.5%, while rest had a positive RT-PCT. ICU admission was needed in 63.2%, with a mortality rate of 10.8%.

Clinical Manifestations

All children presented with high grade fever with median (IQR) duration of 6.1 (5.2, 7.9) days. The clinical features are presented in **Fig. 3**. The pooled data from all patients ($n=313$) from Indian case-series revealed predominance of mucocutaneous features (72%), with rash (53.5%), conjunctivitis (54.3%) and oral cavity changes (27%) being the most common findings. This was followed by gastrointestinal manifestations in around 62% of cases, including abdominal pain (54.7%) and diarrhea/vomiting (51%). SARS-CoV-2 induces multiple cardiovascular complexities with manifestations in a significant percentage of children (54%). As expected, majority of studies reported complications of the respiratory system (42%) with cough and respiratory insufficiency being the main features. Not all studies reported neurological complications, accounting for around 32% in the remaining studies, which reported headache, seizures and/or altered sensorium being the main features. Features of KD fulfilling the classical definition were reported in six studies ranging from 4-76%. Based on these studies, the median (IQR) age of MIS-C children exhibiting KD like features was found to

Table I Details of Case-Series Included in the Review

| Study ID | City, No. of participants | Disease definition | Age (y) | Males no. (%) | SARS-COV-2 | | ICU admissions (%) | Mortality | KD like features no. (%) |
|----------------------------|---------------------------|--------------------|-------------------|---------------|------------|--------------|--------------------|-----------|--------------------------|
| | | | | | RT-PCR | Serology (%) | | | |
| Jain, et al. [8] | Mumbai, 23 | WHO | 7.2 (0.8 to 14) | 11 (48) | 39.1 | 30.4 | - | 4.30 | 1 (4.3) |
| Dhanalakshmi, et al. [9] | Chennai, 19 | RCPCH | 6 (1.1 to 16) | 8 (42) | 27 | 53 | 100 | 0 | 7 (36.8) |
| Shobhavat, et al. [10] | Mumbai, 21 | WHO | 7 (1.9 to 12) | 10 (48) | 38 | 76 | 100 | 14 | NR |
| Gupta, et al. [4] | New Delhi, 20 | CDC | 1 to 12 | 12 (60) | 98 | Not done | 65 | 60 | 4 (20) |
| Venkataraman, et al. [33] | Chennai, 44 | RCPCH | 7 (0.5 to 14) | 19 (43) | 23 | 100 | 53 | 0 | NR |
| Sugunan, et al. [34] | Thiruvananthapuram, 32 | CDC | 7.5(5 to 9.5) | 21 (66) | 31 | 78 | 94 | 0 | NR |
| Balagurunathan, et al. [5] | Coimbatore, 21 | WHO | 6.9 (4) mean (sd) | 15 (71.4) | 4.8 | 90.4 | 52.4 | 0 | 16 (76.2) |
| Maheshwari, et al. [6] | Delhi, 29 | WHO | 4.1 | 18 (62) | 82.7% | 27.6 | 27.6 | 34.5 | - |
| Angurana, et al. [7] | Chandigarh, 40 | WHO | 7 | 26 (65) | 10 | 66.7 | 85 | 5 | 25 |
| Kashyap, et al. [35] | Faridabad, 12 | - | 6.5 | 9 (75) | 8.33 | 92 | 100 | 25 | - |
| Nathella, et al. [36] | Chennai, 44 | WHO | 7 | 19 (43) | 0 | 100 | 52.7 | - | - |

WHO: World Health Organization [<https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>]; RCPCH: Royal College of Pediatrics and Child Health [<https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance>]; CDC: Centers for Disease Control [<https://www.cdc.gov/mis/mis-c/hcp/index.html>]. - indicates 'data not provided'.

be 6.9 (5.5, 7.3) year. In one of such case-series, around 35% MIS-C cases presented with acute encephalitis-like illness

[4] and 20% had signs and symptoms of severe dengue-like illness.

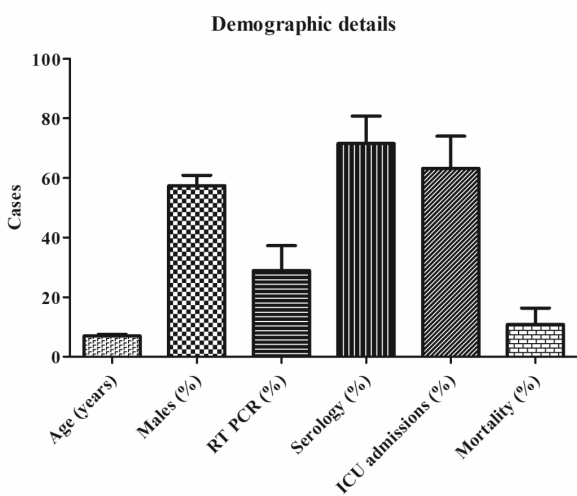


Fig. 2 Demographic characteristics of MIS-C children from included studies (Data is presented as mean with standard error).

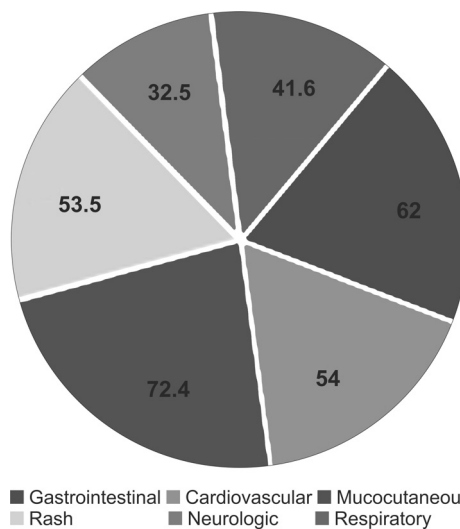


Fig. 3 Clinical manifestations of multisystem inflammatory syndrome associated with COVID-19 (MIS-C) from Indian case series (N=313).

Laboratory Parameters

Due to a lack of uniformity in the reporting format, laboratory investigations of individual studies could not be pooled and are presented in a tabular format (**Table II**). An increase in inflammatory markers, particularly C-reactive protein (CRP) was reported in more than 93% of patients, with values ranging from 96 to 473 mg/L (values reported in only a few studies). Another marker consistently high in studies was IL-6, with median values ranging from 43-527 pg/mL; although, only few case-series reported this marker. The most common hematological abnormalities reported were lymphopenia (44% of patients) and neutrophilia (75% patients, range 99.2-148.8×10⁹/L) with few studies also reporting leuko-cytosis. Thrombocytopenia was also reported in 43% of patients (6 studies). Around 85% of patients had high values of D-dimer (ranging from 1469-10,000 ng/mL). Anemia was also reported in most of the children.

Biomarkers of cardiac dysfunction, troponin and pro-Brain natriuretic peptide (pro-BNP) were also reported to be deranged in many studies [5-7]. Around 82% of affected children had high pro-BNP values (median (range) 8202 (202- 29562) pg/mL), while 34% reported high troponin values (median value (range) 81 (33-348) pg/mL). Sufficient information regarding other para-meters such as creatinine and glutamic pyruvic trans-aminase was not provided in most of the studies. In studies where echocardiography was performed [6,8], left ventricular systolic dysfunction (41%) and coronary dilation (28%) were the most common findings. Arrhythmia and pericardial effusion was also seen in a few patients; however, reported only by two studies [7,9].

Management

The treatment approach followed in the included case-series has been summarized in **Fig. 4**. The data from 10 ($n=233$) studies is presented. Corticosteroids were the most commonly administered therapy (76%) followed by intravenous immunoglobulin (IVIG, 62%). Inotropic and vasoactive support was given to 49% patients. Four studies [5,7,9,10] used anti-coagulative drugs such as heparin and aspirin in 69% of patients. Not all studies have reported the use of antibiotics, but where needed, it was given to around 90% of the cases. Mechanical ventilation was provided to around 29% of patients to manage the respiratory insufficiency. Immunomodulatory agents such as tocilizumab and infliximab were used in around 8% of cases. One study [10] has also mentioned the use of adrenaline or noradrenaline in more than 80% of their patient cohort.

DISCUSSION

Majority of the children reported were aged around 7 years

with a slight preponderance of males. A previous meta-analysis of 56 studies revealed an association of male gender with poor prognosis in COVID-19 in children [11], which has also been reported in adults [12]. A recent systematic review, in contrast, reported mean age of children to be around 9 years [13]. The mortality rate in our analysis was found to be more than 10%, which is much higher than <2% mortality rate reported in a few studies [32,35]. Owing to severe heart failure, cardiac arrest, and refractory hypotension, a higher number of deaths (6.7%) were observed in another study of children with COVID-19. KD-like features were more commonly associated with male gender [14]. A poor prognosis in males could be explained by ACE2 expression, the transmembrane protease, *serine-type 2 (TMPRSS2)* gene, and hyper-inflammatory immunological response in general in males [15].

Fever lasting for an average of 6 days was seen, corroborating with other systematic reviews [16]. As compared to other febrile conditions, children with MIS-C had a higher reported temperature (40°C vs 38.9°C) and a greater duration of fever [17]. We found a preponderance of mucocutaneous features, with less common respiratory features. Respiratory symptoms in children, as compared to adults, were less prevalent, as reported in other studies as well [18]. Evidence regarding oral manifestations in MIS-C has recently come up in a systematic review [19]. These authors reported oral manifestations to appear even earlier than systemic changes [41].

Acute abdomen is the characteristic feature of MIS-C, mostly due to non-surgical intestinal inflammatory pathology. Similar to our findings, gastrointestinal symptoms were observed in around 61% of patients in a recently published systematic review [20]. Another review of 1415 patients from 31 studies across the globe reported predominance of gastrointestinal symptoms and a lesser frequency of patients experiencing respiratory symptoms [21]. This could be explained by a lower expression of ACE-2 receptor gene among children as compared to adults. Another report by Dhar, et al. [22] documented a very high incidence of gastrointestinal symptoms (84%), followed by myocarditis and neurological involvement. More than 50% of children in our review reported cardiovascular changes, corroborating with previous reports [21]. Such symptoms occur concurrently with the peak of cytokine storm with levels of IL-6 correlating with coronary artery dilatation. Cardiac injury could also be caused by a direct viral infection of cardiomyocytes via the ACE2 receptor causing acute myocarditis [23].

A cytokine driven hyper-inflammatory state is postulated to disrupt the blood-brain barrier without direct viral invasion of central nervous system [24]. Another

Table II Laboratory Markers of MIS-C Patients from Different Case-Series (N=305)

| Study | CRP mg/dL | Ferritin (ng/mL) | Leukocytes (x10 ⁹) | Lympho- cytes %, phils %, | Neuro- cytes %, phils %, | Hb gm/dL | Platelet x10 ⁹ | Creatini- ne (mg/dL) | D-dimer (ng/mL) | ESR | IL-6 (pg/mL) | NT-Pro BNP (pg/mL) | Troponin (ng/mL) | Hepatic dysfunction |
|-------------------------------|-----------------------------|--|-----------------------------------|--|---|-----------------|--|-------------------------------------|--|---------|--|---------------------------------------|------------------------------------|------------------------|
| Jain, et al. [8] | 96.6 | 596.8 (282.2- 1473.5) ^a | 15% | 14.3% | 80 | 10.4 (2.2) | 236.8 (155.9) | 0.47 0.35- (0.6) ^a | 4090 (1824.9- 9958.7) ^a | NR | 230.2 (95.5- 498.7) ^a | 410 (205.5- 21277) ^a | 33.4 (5.7- 185) ^a | - |
| Dhanalakshmi, et al. [9] | 100% | 238 (220- 1230) ^a , 21.4% | - | 36.8% | 68.4% | 31.5% | 15.7% | NR | 92.8% | 81.8% | - | 75% | 16.6% | - |
| Shobhavat, et al. [10] | 98 (89-119) ^a | 710 (422- 1609) ^a | 9.8 (2.8- 14.15) | 80% | NR | 9.6 (9-11.1) | 71% | NR | 2664 (1469.5- 6510) | NR | 215 (43-527) | NR | 53.5 (21.75- 367.9) pg/mL | - |
| Gupta, et al. [4] | 99% | 99% | 15% | 30% | NR | NR | 25% | 5% | 50% | NA | 15% | NA | NA | 60% |
| Venkataraman, et al. [33] | 169 (39-473) | NR | NR | 1386 (330- 2200) /mm ³ | 11658 (9918- 14878) /mm ³ | NR (62-110) | 110 | NR | NR | NR | NR | NR | NR | NR |
| Sugunan, et al. [34] | 94% | NR | NR | NR | NR | NR | 59.3% | NR | 100% | 47% | NR | 87.5% | - | 56/50% |
| Balagurunathan, et al. [5] | 100% | 42.9% | NR | 47.6% | 76.2% | 19% | 38% | NR | 95.2% | 85% | 90.5% | 80% | 30.8% | 35/29 |
| Maheshwari, et al. [6] | 101 mg/L | 335, 28.6% | NR | 38% | NR | 61.9% | 127000 /mL | NR | 80.9% | 45 mm/h | NR | NR | NR | 23.8% |
| Angurana, et al. [7] | 95% | 90% | NR | 65% | NR | NR | 50% | NR | 92.5% | NR | NR | 100% | 65% | 47.5% |
| Kashyap, et al. [37] | 100% | 66.7% | NR | NR | NR | NR | NR | NR | 83.3% | NR | NR | 66.6% | NR | NR |
| Kumar, et al. [36] | 169 (39-473) | 605 (38-2571) ^a | NR | 1386 (330- 2200) | 11658 (9918- 14878) | - | 110 (62-210) x10 ⁹ /L | NR | 4890 (2446- 10000) ^a | NR | NR | NR | NR | NR |

Values in mean (SD) or ^amedian (IQR). % indicates percentage of patients having abnormal values. MIS-C – multisystem inflammatory syndrome in children, NR – Not reported. ^bDefined as (AST>50U/L) (ALT>50 U/L).

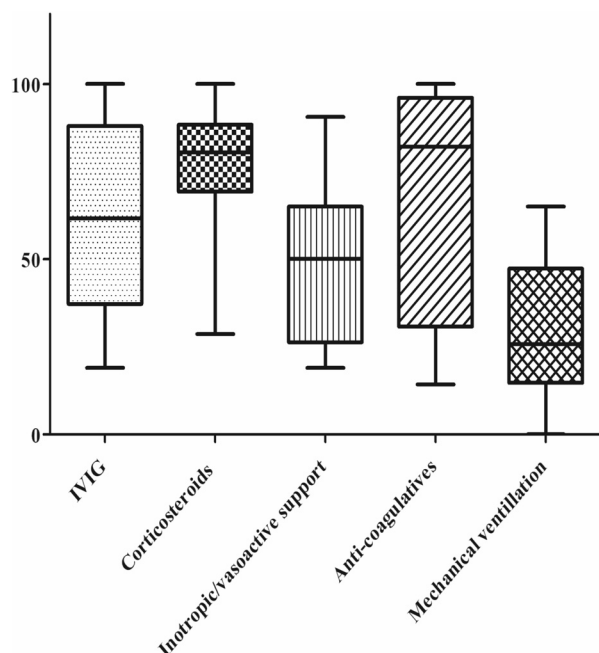


Fig. 4 Therapeutic approaches used for clinical management of multisystem inflammatory syndrome in children (MIS-C) ($N=233$) in Indian case-series.

mechanism could be an induction of autoimmune response owing to a mimicry of viral antigens with self-antigens which occurs following a latent period post-infection [25]. The most commonly observed symptoms include strokes, encephalopathy and seizures. We found only 32% of children manifesting with features of headache, seizures, and altered sensorium. Similarly, another review reported 38% of the cases with neurologic manifestations [26]. The pathophysiological mechanisms behind such complications during MIS-C remain unclear. Another study found neurologic symptoms to be relatively rare [48]. Adults, on the other hand, have quite a high prevalence of such neurological features [27].

The treatment is partly dependent on the presenting condition of patient, and has been evolving with the availability of a wide range of therapeutic options. A recently published review reported frequent use of IVIG and other anti-inflammatory medicines including aspirin, corticosteroids, inotropes and anticoagulation therapies [28]. Unlike adults, the use of antivirals and convalescent plasma therapy was infrequent, as reported in other reviews as well [29]. A better clinical efficacy reported to be achieved with treatment with IVIG together with methylprednisolone as compared to IVIG alone [30].

Higher than normal BNP levels were found in our review, as reported in a meta-analysis of cardiac markers in MIS-C patients as compared to mild or moderate COVID-19

cases [31]; although, troponin and aspartate aminotransferase were not different between these two patient groups.

MIS-C remains a multi-faceted disease and hence poses a difficulty for the treating clinician to decide on the course of its management. New guidelines keep on emerging as the disease evolves over time and as the data on long term effects of MIS-C becomes available. Therefore, we have attempted a compilation of all clinical aspects of MIS-C in the Indian population. Despite following a structured framework to undertake this review, we acknowledge certain limitations. The data was collected from individual case series, because of non-availability of any randomized control trial in our population that could have shed light on the efficacy of various therapeutic regimes. The heterogeneity among the included studies could have led to an over- or under-estimation of some parameters reported in the current review. Data reporting was quite variable among studies. In addition, the effect of various comorbidities and any underlying risks could not be assessed because of insufficiency of data in this regard. We recommend further studies monitoring the long term effects of MIS-C through follow-up evaluations. Many such studies are ongoing and results awaited. Nevertheless, this systematic review provides adequate evidence from Indian population that will help pediatricians in a better management of this disease.

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

Contributors: MS: wrote the protocol, did screening of articles, data extraction and synthesis, compilation and interpretation of results and wrote the manuscript. AA: confirmed the data extraction. HS did the screening; MR, SS: did quality assessment and was confirmed by MS. PP did literature search in databases; MaS: reviewed the manuscript; MeS: conceived the idea, obtained the funding, finally supervised, reviewed and approved the manuscript. All authors reviewed the manuscript.

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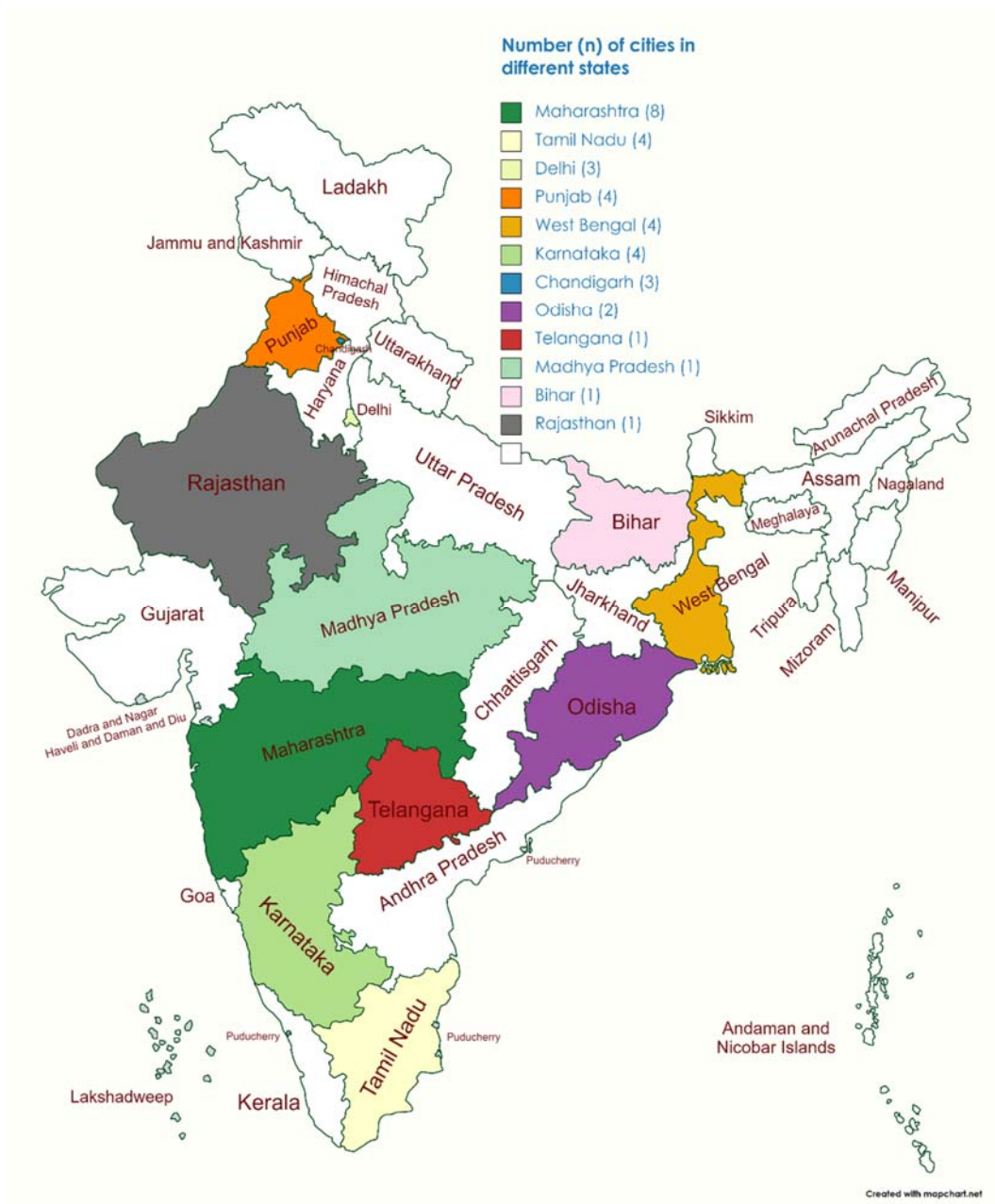
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Web Table I: Critical appraisal of included case-series by NIH tool.

| Study ID | Type of Study | 1. Was the study question or objective clearly stated? | 2. Was the study population clearly and fully described, including a case definition? | 3. Were the cases consecutive? | 4. Were the subjects comparable? | 5. Was the intervention clearly described? | 6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | 7. Was the length of follow-up adequate? | 8. Were the statistical methods well-described? | 9. Were the results well-described? | Quality Rating |
|--|---------------|--|---|--------------------------------|----------------------------------|--|--|--|---|-------------------------------------|----------------|
| Aishwarya Venkataraman et al 2021 | Case Series | yes | yes | yes | yes | yes | yes | No | yes | yes | Fair |
| Anu Maheshwari et al 2021 | Case Series | yes | yes | yes | yes | no | yes | not reported | yes | yes | Fair |
| Haripal Kashyap et al 2021 | Case Series | yes | no | yes | yes | yes | yes | not reported | no | Yes | Poor |
| K. Dhanalakshmi et al 2020 | Case Series | yes | yes | yes | yes | yes | yes | yes | no | Yes | Good |
| Lakshmi Shobhavat et al 2020 | Case Series | yes | yes | yes | yes | yes | yes | yes | yes | yes | Good |
| Muruganatham Balagurunathan et al 2021 | Case Series | yes | yes | yes | yes | yes | yes | yes | yes | yes | Good |
| Nathkella Pavan Kumar et al 2021 | Case Series | yes | yes | yes | yes | yes | yes | yes | yes | yes | Good |
| Sheeja Sugunan et al 2021 | Case Series | yes | yes | cannot Determine | yes | yes | yes | no | yes | yes | Good |
| Shobhna Gupta et al 2021 | Case Series | yes | yes | yes | yes | yes | yes | not reported | yes | yes | Good |
| Shreepal Jain et al 2020 | Case Series | yes | yes | yes | yes | yes | yes | yes | no | yes | Fair |
| Suresh Kumar Angurana et al 2021 | Case Series | yes | yes | yes | yes | yes | yes | yes | yes | yes | Good |



Web Fig. 1 Distribution of studies among different states in India. The number of cities belonging to different states in which studies on MISC were taken is given in the legend.

Web Box I Key Terms Applied to Search for Relevant Studies

(((((((((((((misc) OR ("pediatric multisystem inflammatory disease, COVID-19 related" [Supplementary Concept])) OR (Multisystem Inflammatory Syndrome)) OR (Multisystem Inflammatory Syndrome in Children)) OR (pediatric multisystem inflammatory syndrome, SARS-CoV-2 related OR pediatric multisystem inflammatory syndrome, COVID-19 related OR pediatric multi-system inflammatory syndrome, COVID-19 related OR pediatric multi-system inflammatory syndrome, SARS-CoV-2 related OR MISC associated with COVID-19 OR multisystem inflammatory syndrome, pediatric, COVID-19 related OR multi-system inflammatory disease, pediatric, COVID-19 related OR multi-system inflammatory syndrome, pediatric, COVID-19 related OR PIMS-TS OR multisystem inflammatory syndrome in children MIS-C associated with COVID-19 OR MIS-C associated with COVID-19 OR pediatric multi-system inflammatory disease, COVID-19 related OR multisystem inflammatory disease, pediatric, COVID-19 related OR pediatric inflammatory multisystem syndrome OR MIS-C multisystem inflammatory syndrome in children OR multisystem inflammatory syndrome in children)) OR (COVID-19 related multi-inflammatory syndrome)) OR (COVID-19 Systemic inflammatory syndrome)) OR (pediatric inflammatory multisystem syndrome)) OR ((((((multisystem inflammatory) OR (pims-ts)) OR (children multisystem inflammatory syndrome)) OR (covid children multisystem inflammatory)) OR (multisystem inflammatory syndrome children)) OR (covid multisystemic inflammatory syndrome))) OR ((((((Kawasaki disease) OR (covid-19 kawasaki)) OR (kawasaki disease children)) OR (Kawasaki Syndrome)) OR (kawasaki like disease)) OR (kawasaki like covid children))) AND (India)) AND (("2020/01/01"[Date - Publication]:"2021/06/15"[Date - Publication])) AND (("2021/06/15"[Date - Publication] : "2021/12/31"[Date - Publication]))

OBITUARY

Professor Savitri Shrivastava



1935-2022

Professor (Dr.) Savitri Shrivastava, a pioneer pediatric cardiologist, passed away on the 20th of June 2022, after a long-term illness. She contributed to the growth of pediatric cardiology in all spheres, and was a hero for many established and budding pediatric cardiologists across the globe.

She was born on 1st July, 1935 in Gwalior, Madhya Pradesh where her father was a famous clinician. She followed the tradition of the family and did graduation and post-graduation (Medicine) from GR Medical College, Gwalior; she joined Army Medical Corps initially. She then got the opportunity to do DM in cardiology (AIIMS-1971) and fellowship at the prestigious University of Minnesota, Minneapolis, USA (1975-76). She was entrusted with the responsibility to establish the clinic for pediatric cardiology at AIIMS.

She carried forward the legacy of applying clinical methods, just like her mentor late Professor R. Tandon, and also successfully adopted contemporary noninvasive and invasive procedures. As a teacher, her grasp on the trivet of bedside clinical methods, chest roentgenogram, and electrocardiogram was praiseworthy and exceptional. She was privy to technically evolving echocardiography and she adapted quickly to fetal echo imaging. However, it was the time when cath-intervention procedures like valvuloplasty and percutaneous device closures were about to revolutionize the life of a huge number of patients. India was brilliantly placed in the timeline of history due to her leadership, when the world's first balloon mitral valvuloplasty was done, as the collaborative Indo-US project, in AIIMS Delhi as early as 1984-85 by a team comprised of JE Lock (Boston, Massachusetts), Dr. Savitri Shrivastava and Dr. Khalilullah. It changed the lives of millions of patients suffering from rheumatic heart disease across the world.

She was instrumental in creating three highly acclaimed tertiary care centers for pediatric cardiology (AIIMS, Delhi; SGPGI, Lucknow, and Fortis Escorts Heart Institute, Delhi) and cultivated at least two generations of pediatric cardiologists who became pillars of programs across India and abroad. She was engaged in multiple basic research projects and won multiple medals and awards for her papers. Logical and restrained by nature, she never overtly displayed her emotions but her ethics, clinical excellence, and command of the subject always won the confidence of colleagues and patients' families.

She was married to her passion for children suffering from heart defects, and therefore her legacy includes all those children who could be treated and those clinicians who followed in her footsteps professionally, ethically and spiritually.

Multicenter Studies: Relevance, Design and Implementation

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Multicenter studies are essential in clinical and public health research with several advantages compared to single-center studies. Multicenter studies are attractive and advantageous, allowing quicker recruitment, diverse population coverage and increased generalizability. However, these studies often suffer from methodological, implementation and statistical challenges that can compromise the validity of the study. To meet the technical and interpretative integrity, a multicenter study must be conducted with sound study design, uniform implementation methodology, assured standardization, high-quality data and appropriate statistical considerations. A systematic site selection, rigorous study protocols, stringent quality assurance measures and appropriate analytical approach are indispensable to ensure high internal validity and minimize inter-site variability. For effective implementation of multicenter study, a well-organized coordination center and functional governance mechanism are critical. Transparent and effective network communication among the investigators with cultural sensitivities assists in building productive collaboration. This manuscript summarizes the design, organization, implementation and governance aspects of multicenter studies.

Keywords: Coordination, Design, Implementation, Multisite.

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Many studies face criticism for generalizability and external validity, and fail to inform evidence-based practice and policies [1]. Several studies experience delays in participant recruitment requiring period extensions and sometimes additional funding [2]. Increasingly, multicenter studies are being conducted in the clinical and public health sectors. The multicenter collaboration is attractive for both researchers and funders in view of faster participant enrolment, enabling the conduct of larger studies over a shorter duration, and enhanced generalizability of the results. The multicenter or multisite research differs from the single-site research for several reasons. There are limited documentation on the design, methodology and implementation aspects of multicenter studies from India and developing countries. This paper addresses key concepts related to multicenter research.

MULTICENTER RESEARCH AND ITS RELEVANCE

Single-center studies face challenge of generalization and external validity, which can be achieved by study replication at same site with different populations or sub-populations or at other sites. However, alterations/modifications in the context, time-frame and the research question or objective(s) may challenge the replication. While single-center research is conducted at one center/site, a multicenter research involves more than one site for data collection. Multicenter research is different from multi-institutional research. Usually in multicenter

research multiple sites collect same/similar data with common objective and protocol. In multi-institutional research, investigators from multiple institutions participate, which may be conducted at single site or multiple sites. Although in simpler terms, multicenter study is multiple single-center studies with same protocol, methodology, with combined data analysis, there are several design, implementation, analysis and regulatory aspects which need attention. The salient differences between single-center and multicenter studies are summarized in **Table I**.

The multicenter research may be undertaken for most types of the study designs, observational (cross-sectional, case-control, cohort), clinical trials (randomized or non-randomized) or quasi-experimental, qualitative or mixed methods, community or hospital or laboratory based. Although the core framework of multicenter research for different study designs remains the same, some variations according to the design or objectives or activities may be needed.

TYPES OF MULTICENTER RESEARCH

Although there is no formal classification of multicenter studies, the taxonomy proposed by Elkin and Edward [3,4], can be expanded into four types based on the design and conduct.

- i) *Centrally designed and coordinated studies*, where the study sites are selected through headhunting or

Table I Differences Between Single-center and Multicenter Research

| <i>Domain</i> | <i>Single-center study</i> | <i>Multicenter study</i> |
|---------------------------------|--|---|
| <i>Structure</i> | | |
| Number of sites | Single study site/ population/ geography | More than one study site/ population/ geography |
| Investigator(s) | Single or multiple investigators at a single site | Multiple investigators, one or more investigators from each site and/or institution |
| Institutions | Single or more institutions | Multiple institutions, single or multiple institutions at each site |
| Ethics review | Single committee review and reporting | Multiple committee review and reporting Longer time needed |
| <i>Design</i> | | |
| Question/ Objective | Population and contextual diversity is not considered | Population and contextual diversity is part of the question |
| Population | Single, may have sub-groups/ populations Homogenous | Multiple, may have sub-groups/populations at each or some sites Heterogeneous |
| Generalizability and validity | Not generalizable Internal validity good | Higher chance of generalizability and external validity |
| Sample size | According to the research question (usually smaller) | May need consideration of the inter-site/population variability (larger) |
| Protocol | Simple | More complex |
| Bias | Personal bias more | Personal bias less Chances of recruitment and evaluation variability |
| Statistical analysis | Weaker | Stronger, needs consideration of the inter-site variations |
| Timeline | Usually longer duration of participant recruitment | Usually shorter duration of participant recruitment |
| <i>Conduct</i> | | |
| Research staff | Research staff at one site | Research staff at multiple sites |
| Training | Training of research staff and/or investigators at one site Easier and convenient | Training of research staff and/or investigators at all sites Need standardization and uniformity |
| Communication & coordination | Convenient and simpler Study coordinator not mandatory | Structured communication needed Study coordinator is mandatory |
| Data collection & management | Data verification, entry and checking easier | Need systematic process of data verification, entry and checking |
| Supervision & quality assurance | Direct supervision possible Monitoring is easier | Direct supervision not possible Monitoring is complex Systematic protocol adherence and quality assurance review needed |
| Protocol adherence | Greater, less variation/deviation anticipated | Lesser, more variation/deviation anticipated |
| <i>Others</i> | | |
| Budget | Lower | Higher than single-center research Additional for coordination, quality assurance, data management |
| Translation | Limited chance, needs replication or additional multi-center study | Higher chance, if conducted designed and conducted appropriately |
| Dissemination | Authorship is easy to handle | Authorship and sequence challenging May consider group authorship |

peer-review/peer-referral wherein the collaborators/ investigators are variably involved in the decision-making;

ii) *researchers consortium*, wherein the researchers collaborate and jointly design the study;

iii) *hybrid architecture*, wherein the study adopts variable combinations of centrally designed and consortium arrangements; and

iv) *contribution to common database*, wherein the investigators/institutions contribute to a common

database, but may not collaborate and follow uniform protocol.

According to design, the multicenter study may be of two types. *i)* uniform multicenter study wherein the same research question(s) and protocol are pursued across all sites/institutions; or *ii)* combinational multicenter study, wherein the study has multiple research questions and different sites/centers focus on different research questions. The sites/centers pursuing the same research question follow uniform protocol.

ADVANTAGES AND CHALLENGES OF MULTI-CENTER RESEARCH

The direct advantages of multicenter research include ability to recruit large number of participants quickly, document population and sub-population diversity, statistical power, generalizability, higher relevance and practice and/or policy translation chances. The indirect benefits include higher funding appeal, networking, better academic and peer recognition.

There are several inherent challenges including sustained commitment, leadership, interpersonal skills and communication, rigorous quality assurance and careful planning apart from regulatory and administrative aspects. The advantages and disadvantages of the multicenter studies are summarized in **Table II**. As the principal investigator is ultimately responsible for the study and outcome, careful planning and anticipation of the potential challenges are essential to ensure successful conduct of the multicenter research.

DESIGNING A MULTICENTER STUDY

Multicenter study designing considers various aspects: *i) research question:* variation in the disease and outcome according to the population, socio-cultural, environmental and other relevant programmatic factors; *ii) population generalizability:* if the research and/or intervention attempts to explore relevance and applicability across different populations; *iii) timeline:* if the research mandates recruitment of larger sample size in a limited

Table II Advantages and Disadvantages of Multicenter Studies in Various Domains

| <i>Advantages</i> | <i>Disadvantages</i> |
|---|---|
| <i>Methodology</i> | |
| Attractive and captures population diversity | Complex study design |
| <i>Collaboration and network</i> | |
| Availability of diverse technical expertise | Challenging to coordinate with multiple investigators, institutions and processes |
| Collaborative decision making | Personality problems and need to meet individual site/ investigator interests |
| Capacity building | |
| <i>Implementation</i> | |
| Limits ad hoc and unstructured implementation | Protocol adherence and uniformity requires stringent quality assurance |
| Enables simultaneous implementation at multiple sites | Logistics challenges including manpower, training, supplies, data and sample transfer, financial management |
| <i>Validity</i> | |
| Better external validity and generalizability | Challenges in internal validity and variation across sites |
| Lesser personal biases | Heterogeneity in participants and practices |
| <i>Sample size</i> | |
| Quicker recruitment | Unequal recruitment across sites leading to a reduction in power |
| Large sample size achieved in a shorter time-period | |
| Increases the sample’s diversity | |
| <i>Data management and analysis</i> | |
| Less data manipulation and fishing | Data management and cleaning challenges |
| Allows comparison across sites/groups and detect variations | Statistical analysis requires additional attention |
| | Handling the site-specific effects and variations may be challenging |
| <i>Cost</i> | |
| May be cost-effective for the time needed to answer the research question | Redundancy of staffing and resources at low recruiting sites may increase the cost |

timeframe; iv) *resources*: if adequate fund and manpower resources are available; v) *coordination center capacity*: adequate capacity of the investigator and coordination center; vi) *funder requirements*: if the funder(s) have preference for multicenter studies and geographic specifications.

PLANNING AND IMPLEMENTING A MULTI-CENTER STUDY

The broad steps for planning and implementing the multicenter study are detailed below.

Proposal development: The design of multicenter study is primarily guided by the research question, disease/risk factor epidemiology, target population, sample size, timeline and budget. It also depends on the clinical, social, policy and geographical factors and the funder interests.

Sites and investigators selection: Selection of the study sites and investigators are critical for success of the multicenter studies. The sites with sub-optimal caseload or access to the population, insufficient site investigator(s) experience and commitment, challenge the study performance and increase the cost. Although, there is no definite guideline for study site and investigator selection, studies have adopted different procedures like convenient headhunting, peer-referral, snowballing, and systematic selection process including open/closed calls for expression of interest. Studies have also used several criteria for site selection, like caseload, population access and institutional support (research, ethics, administrative and financial management). Inappropriate site and investigator selection may lead to implementation problems including lower recruitment, poor quality data, operational challenges and timeline delay. Publications on methods of site selection are not abundant. The various examples of site and investigator selection are summarized in the supplementary material.

Team building: Once the study sites are finalized, team-building efforts are to be made with opportunity for technical contribution from the investigators on the study protocol and implementation plan for ensuring common vision sharing. Physical meetings or tele-/web-conferences may be organised to achieve this. This is essential to keep the investigators and site research teams motivated.

Standard operating procedures: For effective conduct of multicenter studies, detailed standard operating procedures (SOP) for different components of data collection and implementation are needed to ensure uniformity. The SOPs must include various components of study conduct including recruitment, consenting, tests/measurements, investigations and laboratory methods,

questionnaires filling, data collection and data handling. The SOPs should also include training, communication, travel, administration and financial management. The investigators and research team must be orientated on these SOPs to avoid conflict and misunderstanding.

Research staff selection: The engagement of competent research staff is critical for protocol adherence and quality data collection. For the selection of staff, minimum qualification, terms of reference and selection guideline should be followed. Attention to attrition prevention and replacement pipeline should be given to minimize disruption in study conduct. Assembling the central coordination team with competent members is also critical for conduct of multicenter research.

Investigators and research team training: The investigators and research staff must undergo common training on the study methodology, participant recruitment, data collection, investigations and/or laboratory procedures, as appropriate. Additional targeted orientation/training of the investigators may be needed. Training modules (presentations, audio-visual and written manuals) must be developed for uniform training. The engagement of common trainers can bring uniformity in training. Need based periodic refresher orientations may be considered. The complex design studies and qualitative data collection may need longer and additional training.

Data collection and management: Data transmission from the study sites to the coordination site/data management center must be planned adequately to ensure timeliness. More and more studies are using electronic mode of data collection. Direct data entry using mobile/tablet/dedicated devices may be performed using either open-source platforms or customized software. Studies may collect the data on paper forms followed by computer data entry. Adequate care must be taken to ensure participant anonymity and confidentiality during data transmission. The transfer of data on hardcopy from study sites and data verification may take sizable time and add cost, which must be factored into the timeline to avoid delays and stretch the budget.

Quality assurance: Quality assurance is a continuous, independent and systematic monitoring and documentation process to ensure protocol adherence, correct and timely data collection. Various quality assurance measures can be adopted in multicenter studies, like protocol finalization and concurrence, regional training of teams, monitoring of data collection, data entry (use of software and digital tools like intelligent character recognition), site visits by monitors, and review of case record forms. The quality assurance plan and tools must be carefully developed according to the methods, data types,

anticipated rigor, feasibility and cost involved. The methods may include virtual and/or physical methods, internal and/or external laboratory checks. The site's performance must be communicated appropriately to encourage good practices and address the gaps and challenges.

Analysis and interpretation: The data analysis of a multicenter study is usually undertaken centrally by a data management center. The statistical analysis plan is usually developed and agreed by the investigators. This ensures appropriate data analysis and minimizes the chances of data fishing and inappropriate analysis. The analyzed data is shared with the investigators for agreement prior to submission of the report to the funder and dissemination.

Results dissemination: The investigators in consultation

with the funder and technical experts/advisors (if engaged), plan the dissemination through journals, presentation in appropriate scientific and program/policy platforms, policy briefs, white papers and mass communication channels. The investigators (or publication committee) must decide about these well in advance along with the credit sharing and authorship to avoid conflicts [5]. The overall study results should be published prior to site-specific result publication.

Study governance: The multicenter studies require different governance, management and coordination mechanisms. The project governance and management depend on the complexity of the study, domains, size and geography of the network. Although various governance mechanisms are used, different groups may be organized

| Box I Key Areas and Specific Functions Therein of the Coordinating Center in Multicenter Studies | |
|--|---|
| <p><i>Proposal development</i></p> <p>Planning the proposal (hypothesis, objectives, methods, data collection procedures, sample size estimation, outcomes and analysis outline)</p> <p><i>Ethics and regulatory</i></p> <p>Prepare documents for submission to ethics committees</p> <p>Prepares and submits documents for regulatory approvals and tracking</p> <p><i>Protocol and data collection tool development</i></p> <p>Develops the detailed study protocol, Standard Operating Procedures and data collection tools (including piloting and refinement)</p> <p>Prepares/adapts the data collection software</p> <p>Prepares monitoring tools and quality assurance checklists/guides</p> <p><i>Training</i></p> <p>Prepares training materials, operational manuals for all study activities</p> <p>Schedules and conducts training of the investigators and research staffs</p> <p>Ensures training of new staff and refresher training, as needed</p> <p><i>Data management</i></p> <p>Prepares data handling, storage, transmission guidelines</p> <p>Supplies the intervention/drug/materials for clinical studies</p> <p>Tracks data collection, entry, transmission, review of the entered data</p> <p>Conducts the data verifications and resolves queries with sites</p> <p>Maintains the database and backup</p> <p><i>Quality assurance</i></p> <p>Prepare the quality assurance plan</p> <p>Schedules and conducts quality assurance activities (calls/visits)</p> <p>Prepares reports, submits to committees and provides feedback to sites</p> | <p><i>Data analysis</i></p> <p>Prepares the data analysis plan</p> <p>Conducts data analysis (pooled data, segregated for regional/sites)</p> <p>Ensures methodological inputs and analysis</p> <p>Generates analysis results for reports and manuscripts</p> <p><i>Communication</i></p> <p>Schedules periodic calls/meetings of the investigators and committees</p> <p>Prepares minutes of the meetings and communicates to all concerned</p> <p>Communicates the progress reports, updates, etc.</p> <p><i>Administrative and finance management</i></p> <p>Ensures execution of agreements between the sites/institutions</p> <p>Tracks expenses and ensures timely fund transfer to the sites</p> <p>Provides administrative support for study activities (including human resource hiring, material/equipment procurements, logistics, etc.)</p> <p>Tracks technical and financial reports from the sites</p> <p><i>Dissemination/Publication</i></p> <p>Prepares the publication plan and dissemination plan</p> <p>Prepares/coordinates with responsible investigators for manuscripts</p> <p><i>Compliances</i></p> <p>Coordinates with funding agency for contract and deliverables</p> <p>Coordinates with regulatory authorities and government agencies to ensure compliances</p> <p><i>Documentation and archival</i></p> <p>Ensures documentation and safe archival of the study materials (including biological samples) as per regulatory norms and study need</p> <p>Ensures disposal of the study materials (paper documents or biological samples) as per the prevailing norms</p> |

CCC: central coordination center; DCC: domain coordination center; RCC: regional coordination center; SS: study site.

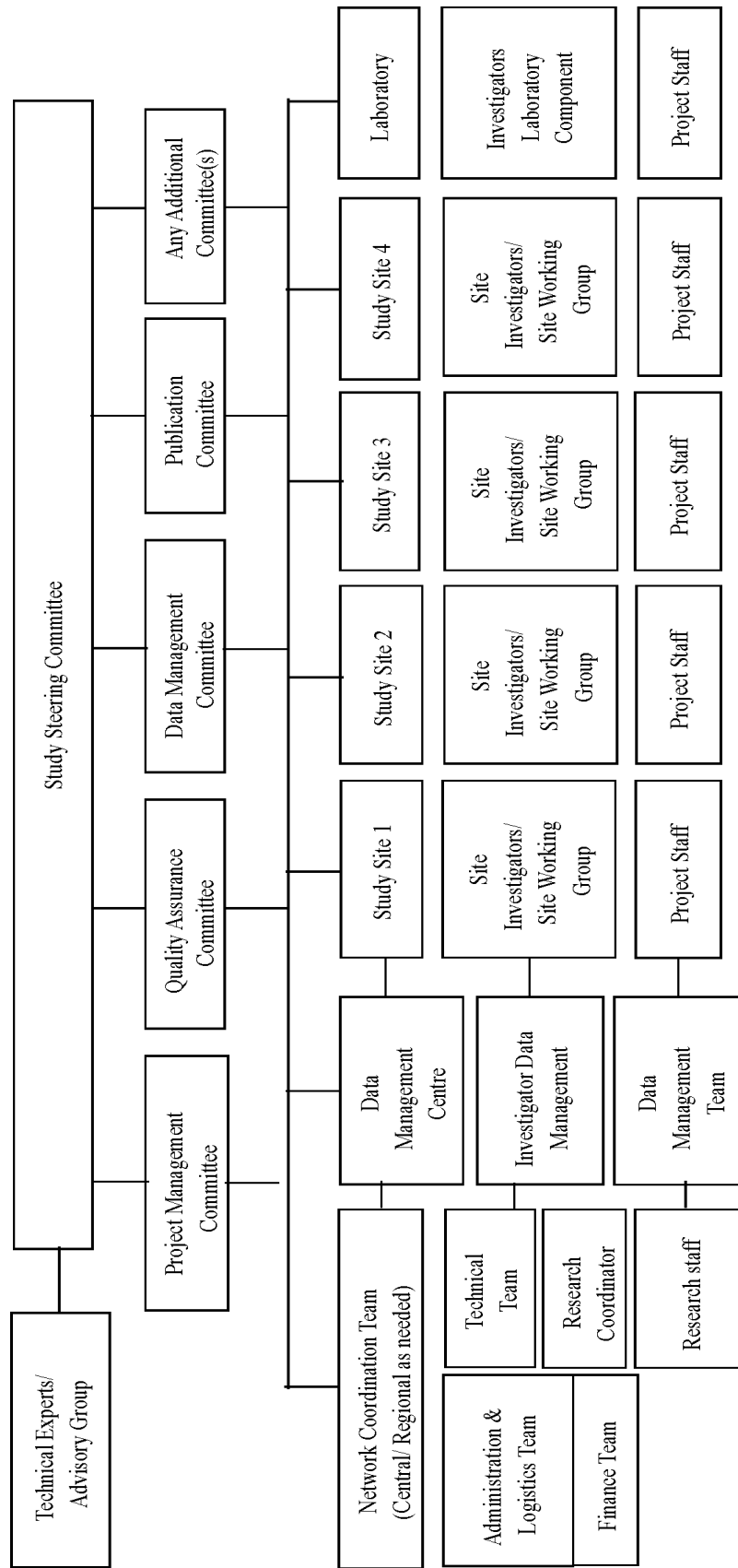


Fig. 1 Suggested governance model of multicenter studies.

including Steering Committee, Project Management Committee, Quality Assurance Committee, Data Management Committee, Publication Committee, etc. [6]. The compositions of these committees are decided by the investigators and communicated to all concerned (Fig. 1). A competent techno-managerial coordination team is important for day-to-day operations of the study and to address the routine queries and challenges [7]. The roles and responsibilities for the coordination center are given in Box I. For largescale multicenter studies, regional coordination centers (RCCs) or domain coordination centers (DCCs) may be needed to support the central coordination center (CCC) for the technical and/or logistics aspects. The different models of multicenter network coordination are shown in Fig. 2. It is worthwhile to note that no specific model suits all types of multicenter studies and need-based customization is needed.

Communication: Transparent and honest communication with rapid turnaround is critical for maintaining the network’s interest and confidence. The CCC must be efficient and proactive in communication, and clarifying queries.

SPECIAL ISSUES RELATED TO MULTICENTER STUDIES

Ethical aspects: The study protocol must be approved by the institutional ethics committees (IECs) of all participating institutions. The time taken for IEC approvals may range from one month to more than two years [8]. For some multicenter studies by the author’s group, IEC approvals took 18 months, which delayed the timeline. The budget should account for the IEC review charges. Several countries (United States, Canada, Australia and Uganda) mandate common ethics review system for federally funded multicenter research [9,10]. The Indian Council of Medical Research (ICMR) has issued similar draft guidelines [11,12]. Adoption of common IEC review process by author’s group for a multicenter study in India with facilitation from ICMR, assisted in completing the ethics approvals in three months. Common IEC review would make approvals quicker, reduce the inefficiencies, redundancies, and cost.

Data ownership and sharing: Data ownership is an important aspect of multicenter studies. The data collection, management and sharing must follow the ICMR Ethical Guidelines and ensure that no data with identifiers are shared outside the site institute [11]. The list of participants with identifiers must reside at the recruiting institutions.

Statistical aspects: While multicenter studies assist in quick enrolment and generalizability, the extreme

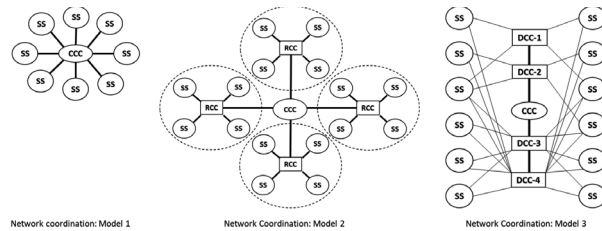


Fig. 2 Suggested models of network coordination for multicenter studies. Network coordination model 1: Spoke and hub network: All study sites (SS) coordinated by the central coordination center (CCC), which may or may not be a SS itself. Network coordination model 2: Regional cluster model: Few SS are coordinated by the regional coordination center (RCC) based on geography/logistic feasibility. The CCC coordinates with and through the RCCs for study implementation. Network coordination model 3: Domain cluster model: The SS (or laboratories) are coordinated by the domain coordination center (DCC) based on the activities undertaken by the SS/laboratories. The CCC coordinates with and through the DCCs for study implementation.

imbalances in enrolment across sites may challenge the power and sensitivity of the results. The total sample size calculation using standard formulas by default considers balanced enrolment across sites and doesn’t account for the number of sites and recruitment variations. It has been observed that with increase in number of centers, the size of the average treatment difference decreases systematically and hence the power decreases. Usually, during analysis, the multicenter studies ignore data clustering and many do not report center-wide recruitment variations, selection bias and representativeness [1]. Ignoring the centers in design and analysis can result in incorrect *P* values, confidence intervals, biased estimates from unrecognized confounders, and heterogeneity of effect of treatment or exposure across centers. Experts suggest applying unweighted and weighed methods of analysis for multicenter clinical studies based on the presence of treatment-by-center interaction. Using coefficient of imbalance and design effect are suggested during sample size estimation and power calculation [13,14].

Multisite qualitative research: The multicenter qualitative research through data collection from multiple sociocultural and geographic settings using similar methods and procedures enhance transferability and trustworthiness of findings to other contexts by comparing data across sites, but retaining the site-specific understandings. The multicenter qualitative research needs special attention to the selection of appropriate researcher teams and training to ensure common understanding and methodology adherence. The study tools and collected data need appropriate translation to retain the meaning and sentiments. The analysis combines

within-site and between-site analyses to identify the similarities and variations at and between the sites and overall interpretation [15]. Data triangulation and

respondent validation processes can be used to assess and resolve the variations among sources, contexts, methods, and investigators.

Table III Challenges of Multicenter Studies and Potential Strategies to Address Them

| <i>Domains</i> | <i>Challenge</i> | <i>Potential strategy to address</i> |
|------------------------------|--|--|
| Protocol | Consensus and agreement among the investigators | Discussion and feedback from all investigators during the drafting and detailed standard operating procedure Technical experts/advisors inputs Piloting of data collection forms and processes |
| Ethics approval | Variable formats, documents and frequencies | Common ethics review process Enquiry about the ethics requirements Assist in preparing documents and orient investigators |
| Study staff | Selection of the study staffs Retention | Standard selection criteria and terms of reference Qualification compatible compensation Frequent engagement with the site study staff |
| Training | Uniformity and consistency Contextualization | Preparation of detailed training modules/tools Training of the site investigators Participation core team members in site-level trainings Periodic refresher trainings for site research teams |
| Data collection | Varying record-keeping practices Data collection- transmission lag High staff turnover | Adaptation and/or additional site-specific templates to capture the desired information based on piloting Uniform data collection forms and data entry templates Consider electronic data collection or site level data entry Securing permissions for optimal access to records Frequent data quality checks and internal audits/reviews |
| Data management and analysis | Data sharing Data analysis | Prepare case record forms to ensure confidentiality Form data management committee formation with the protocol for data access and sharing Prepare data analysis plan and develop consensus |
| Monitoring | Participant recruitment and retention | Prepare recruitment or data collection targets for each site Regularly monitor progress, reporting and tracking Check the problems and address them in real-time |
| Quality assurance | Protocol adherence Data quality | Prepare monitoring and quality assurance review/visit schedule by coordinating team and/or external monitors Periodic data review and resolution with study teams |
| Finances | Budget and institutional procedures | Awareness about the norms and guidelines Common and site-specific discussion Execute agreement with institutions and/or investigators |
| Communication | Uniformity in communication Compatibility of investigators External communication | Conduct tele-/vision-calls regularly with full site teams Additional need-based meetings for sites/teams Collegial tone of the discussion and create opportunities for informal interaction and discussion Identify spokesperson for external communication and prepare protocol and material Review and approval of the interim presentations and communications by committee |
| Coordination | Study governance and coordination | Discuss and agree on study governance and coordination Formation of committees with terms of reference |
| Publication | Authorship | Formation of publication committee and SOP Consider group authorship for publications |
| Timeline | Meeting timeline | Adequate planning- activities, timeline and budget Suitable study site and investigator selection |

International partnerships: The multicenter studies with international partnership(s) must comply with the regulations on data and biological material sharing (Health Ministry Screening Committee) and receiving foreign funds (Foreign Contribution Regulation Act). Explicit agreement on the technical credits and authorship must be discussed and agreed upon in advance.

The challenges encountered by multicenter studies and the potential strategies to overcome them are summarized in **Table III**.

CONCLUSION

The multicenter studies have the ability to accelerate participant recruitment, data collection in a shorter timeline, reach a larger population and better validity. These have several advantages compared to the single-center studies and higher potential for clinical practice, program and policy translation. For successful implementation of multicenter studies, careful study design, including the statistical and operational aspects, appropriate site and investigator selection, rigorous protocol adherence, stringent data quality assurance and dedicated coordinating mechanism are essential. However, ignoring the heterogeneity in recruitment, implementation rigor and other contextual factors may challenge the power and generalizability. To ensure generalizability and retain power, the number of sites, variability and sample size distribution across the sites are to be considered at the design phase, not as an afterthought.

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Erratum

Please note the following corrections in the article titled “Clinical and Genetic Profile of Children With Short Stature Presenting to a Genetic Clinic in Northern India” published in *Indian Pediatr.* 2022;59:463-66. **Table I**, referred to on page 464, was not published with the article, and is as under:

Table I Etiology of Short Stature in Children Presenting to a Genetic Clinic (N=455)

| Condition | No. (%) |
|--|-----------|
| Proportionate short stature (n=142) | |
| Recognizable syndrome | 93 (65.5) |
| Chromosomal disorders | 26 (28) |
| • Turner syndrome [45,X (n=4), mos 45,X/46,X,i(Xq) (n=4), mos 45, X/46,XX (n=2), 46,X,i(Xq) (n=2)] | 12 (53) |
| • William syndrome | 7 (22) |
| • Wolf Hirschhorn syndrome, 46XX DSD SRY+ 22q deletion syndrome/ Smith Magenis syndrome/ Cri du Chat syndrome | 2 each |
| Single Gene disorder | 29 (30) |
| • Prader Willi syndrome | 8 (27.6) |
| • Rasopathies: Noonan syndrome | 7 (24) |
| • Cardiofaciocutaneous syndrome | 2 |
| • Russell Silver syndrome/Primordial short stature syndromes/ DNA repair defects (Fanconi anemia/Cockayne syndrome) | 2 each |
| • Coffin Siris syndrome/ Rubinstein Taybi syndrome/ Cornelia de Lange syndrome/ Noonan-NF1 syndrome/ Wolfram syndrome/ Carbonic anhydrase deficiency | 1 each |
| Not tested | 38 |
| Clinically undefined syndromes | 39 (27.4) |
| Chromosomal disorder [Karyotype (n=3) (der8p13, der14p11, +mar chromosome), Microarray (n=6) (8q21 del, 7q35 del, 20q13dup 9q34.3 del, 16p13dup 21q22del, 11q22dup, 15q13 del) | 9 (23%) |
| Single gene disorder (histiocytosis lymphadenopathy plus syndrome) | 1 |
| Skeletal dysplasia [OI (n=3), Stickler syndrome/ MED/ SEMD (2 each), cleidocranial dysplasia (n=1)] | 10 |
| Negative NGS + Microarray | 3 |
| Partially tested (negative karyotype or microarray, could not be re-evaluated) | 12 |
| Not tested | 14 |
| <i>Disproportionate short stature (n=84)</i> | |
| Lysosomal storage disorders ^a | 38 (45) |
| MPS II | 14 (37) |
| MPS I/IVA | 7 each |
| Mucopolysaccharidosis type II | 4 |
| MPS III/MPS VI/Sialidosis | 2 each |
| Skeletal dysplasias ^b | 37 (44) |
| Achondroplasia+Hypochondroplasia | 20 (39) |
| Osteogenesis imperfecta | 3 |
| Ciliopathy/pseudoachondroplasia/PPRD/metaphyseal dysplasia | 2 each |
| Slender bone dysplasia/ SEMD/Desbuquois dysplasia/metatropic dysplasia/ Stickler syndrome/CDP | 1 each |
| Unclassified ^c | 9 |

-+Mos: mosaic, i(Xq): isochromosome Xq, DSD: Disorder of sexual differentiation, NGS: next generation sequencing, del: deletion, dup: duplication, mar: marker chromosome, MED: multiple epiphyseal dysplasia, SEMD: Spondylo-epi-metaphyseal dysplasia, PPRD: progressive pseudorheumatoid dysplasia, CDP: chondrodysplasia puncta. ^a Enzyme analysis=86.8% (n=33), Molecular confirmation=73.6% (n=28); ^b Skeletal survey=89% (n=33), Molecular confirmation=86.4% (n=32); ^c Suspected skeletal dysplasia, could not be classified on skeletal survey.

Appropriate corrections have been done in the web version at <https://www.indianpediatrics.net/june2022/463.pdf>

Ocular Features and Autism Spectrum Disorder: A 10-Year Retrospective Review

We reviewed the medical records of our pediatric ophthalmology and strabismus clinic of our hospitals for the period 1 January, 2009 to 31 December, 2018, to identify children with autism spectrum disorder (ASD). We found that refractive errors (62%) and strabismus (63%) were the most common ocular manifestations in children with ASD. With timely management, amblyopia and strabismus could have favorable outcome. As amblyopia was significantly associated with intellectual disability ($P=0.02$), early ophthalmic monitoring via multidisciplinary approach is warranted.

Keywords: *Amblyopia, Intellectual disability, Refractive errors, Strabismus.*

Autism spectrum disorder (ASD) is a spectrum of neurodevelopment disorders with impairment of social communication and social interaction with restricted repetitive pattern of behavior, interest, or activities [1,2]. The incidence of ophthalmic disorders in ASD has been reported up to 71% [3,4].

Ophthalmic examination of children with ASD could be challenging due to their suboptimal cooperation for examination and any impairment of vision may affect eye contact training in ASD children. We conducted this study to explore the demographics, ocular manifestations, and treatment outcomes of pediatric patients with ASD. This is because identifying and treating the underlying eye conditions timely and appropriately can facilitate training of children with ASD.

This retrospective study was approved by the local institutional review board and was conducted in accordance with the Declaration of Helsinki. Medical records of all consecutive cases attending pediatric ophthalmology and strabismus clinic of Kowloon East Cluster of Hong Kong over 10 years, from 1 January, 2009 to 31 December, 2018, with the following diagnoses, were reviewed (International Classification of Diseases and Related Health Problems, 9th and 10th revision): "Autism", "Asperger's disorder" and "Pervasive Developmental disorder" [5]. Our study included ASD patients with or without intellectual disability (ID) who were referred for ophthalmological assessment. ID was diagnosed with a score below 70 on Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV).

The Record showed that all patients had undergone complete ophthalmic examination by pediatric ophthalmologists and optometrists. The best corrected visual acuity (BCVA) was measured with Snellen or Sheridan-Gardiner visual acuity test for verbal patients, and preferential looking (Cardiff Acuity card) for non-verbal patients. Amblyopia was diagnosed only in verbal patients, with BCVA of 20/40 or worse in at least one eye or at least 2 lines of difference between two eyes. Successful

treatment of amblyopia was defined as BCVA difference in less than 2 lines between eyes or BCVA better than 20/40 after treatment. Cycloplegic refraction was performed in accommodative esotropia or those with poor cooperation [6].

A total of 100 patients aged 1 month to 11 years [80 boys, median (IQR) age 1 (1,4) year] were identified. The mean follow up period was 4.94 years (3 months to 16 years). Ten patients were born prematurely (at 36 weeks of earlier) and 13 were preverbal. Coexisting developmental delay ($n=32$), ID ($n=24$) and attention deficit and hyperactivity disorder ($n=31$) was present. The most common reasons for ophthalmic referral were ocular misalignment (58%), followed by refractive errors (15%) and poor vision (8%). The most common eye problems reported were strabismus (63%) and refractive errors (62%) (Table I).

Amblyopia was identified in 26 patients, with a mean (SD) presenting age of 2.69 (1.85) years. Strabismus (34.6%) and anisometropia (30.8%) were the leading causes. All cases were treated with spectacles and part-time patching, except for three cases who declined treatment. Eighty seven percent of children were successfully treated with patching. Three cases had failed treatment, including 2 cases with poor compliance and 1 case with underlying optic atrophy.

A total of 63 cases presented with strabismus, out of which 46 (73%) had exotropia. The average angle of deviation at near was 29.6 +/-15.7 Prism Dioptre (PD) and 33.3 +/- 11.7 PD at distance. Esotropia was found in 23.8% patients with strabismus, with an average angle of deviation at near and distance of 27.4 +/- 14.1 PD and 24.4 +/- 15.3 PD, respectively. For esotropia, fully or partially accommodative esotropia was the most common (80%). Success rates for strabismus surgery were 75% for exotropia and 80% for esotropia. We reported higher frequency of exotropia than esotropia in all ASD patients with strabismus in our series, which is consistent with the findings from the Multi-Ethnic Pediatric Disease Study (MEPEDS) for Asian children [7].

Most cases ($n=83$) in this study were reported by psychiatrists to have poor eye contact, including 4 without any eye contact during psychiatry consultations. However, only 4 cases had structural abnormalities (chronic retinal detachment, congenital nystagmus, bilateral optic atrophy and Leber Congenital Amaurosis) while the other 79 were structurally normal and without any history of epilepsy. Poor eye contact in ASD could be attributed to an abnormality in the orbitofrontal-striatum-amygdala circuit in response to social stimuli [8].

The rate of amblyopia (26%) in the present study is comparable to other studies (10-19%) [4,9], but much higher than the general pediatric population (1.81%) [7]. The most common causes of amblyopia were strabismus (34.6%) and anisometropia (30.8%) which is similar to a recent study [4]. Amblyopia was significantly associated with ID or developmental delay when compared with normal ASD patients (37% vs 16.7%, $P=0.02$,

Table 1 Ophthalmic Diagnosis of Patients With Autism Spectrum Disorder (N=100)

| <i>Ophthalmic diagnosis</i> | <i>No.</i> |
|-----------------------------------|------------|
| Squint | |
| Exotropia | 46 |
| Intermittent exotropia | 45 |
| Sensory exotropia | 1 |
| Esotropia | 15 |
| Fully accommodative esotropia | 7 |
| Partially accommodative esotropia | 5 |
| Abducens nerve palsy | 1 |
| Non-accommodative esotropia | 2 |
| Superior oblique palsy | 2 |
| Refractive errors | |
| Myopia | 36 |
| Hyperopia | 14 |
| Astigmatism ^a | 46 |
| Anisometropia | 16 |
| Amblyopia | |
| Strabismic | 9 |
| Anisometropic | 8 |
| Deprivational | 4 |
| Bilateral ametropic | 4 |
| Unknown | 1 |
| Others^b | |
| Retinopathy of prematurity | 2 |
| Ptoxis | 3 |
| Nasal lacrimal duct obstruction | 3 |
| Epiblepharon | 8 |
| Nystagmus | 2 |
| Chalazion | 2 |
| Iris abnormality | 2 |

^a34 patients with coexisting myopia/hyperopia. ^bOne each had congenital cataract, Leber congenital amaurosis, vernal keratoconjunctivitis, retinal detachment, optic atrophy, and suspected glaucoma.

Chi-Square test). This higher prevalence of amblyopia in ID or developmental delay has also been reported and may have been contributed by the higher incidence of refractive errors and strabismus in this population [10].

Our study is limited by its retrospective nature which may be subject to missing data and we did not include healthy control in our study. We encountered the incidental finding of unilateral chronic rhegmatogenous retinal detachment of a preverbal moderate ID case. This highlights that presentation of severe but potentially treatable conditions could be delayed in ASD, due to communication and language problems. This together with our findings of significant association of amblyopia with ID or developmental delay in ASD have brought out a strong message that general practitioners, psychiatrists and pediatri-

cians should have a low threshold for ophthalmology referral, especially if there is any concern of the vision of ASD patients. We propose that visual screening should be offered to all ASD patients with ID or limited language ability around age of four years old, using a multidisciplinary approach with pediatricians, psychiatrists, optometrists, nursing specialists, and play therapists. This would allow early detection and treatment of any potentially treatable condition.

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Old is Often Gold in Typhoid Fever

A 9-year-old, well-nourished girl, unimmunized for typhoid was admitted with history of fever for one month and vomiting for one day. On examination, she had mild splenomegaly. After sending samples for laboratory workup, keeping a possibility of enteric fever, she was empirically started on intravenous ceftriaxone (100 mg/kg/day). Her Widal test came positive (TO and TH titres, 1:320). Her blood culture report (collected on day 5) grew *Salmonella typhi*, which was resistant to ceftriaxone. Since she was still febrile, antibiotics were changed to azithromycin (15 mg/kg/dose once daily for 7 days) as per sensitivity pattern (sensitive to azithromycin, chloramphenicol and cotrimoxazole). She turned afebrile on day 9 of admission, and was discharged. She remained well for four days and was then readmitted with fever of 72 hours. Her repeat blood culture also grew *S. typhi*, which showed the same sensitivity pattern as before. Having not achieved defervescence with macrolides despite adequate dosing, she was prescribed chloramphenicol (100 mg/kg/day for 14 days) with monitoring of blood counts. She achieved defervescence after five days of chloramphenicol and was well at her one-month follow-up visit.

Typhoid is hyperendemic in India with an incidence rate of 500-700 per 100,000 population, with children below 15 years accounting for >55% of the affected. Without treatment, case fatality rate was 10-30%, dropping to 1-4% with appropriate therapy [1,2]. The emergence of antimicrobial resistance is a significant challenge, and this was the first case of laboratory-confirmed ceftriaxone resistance seen by us in recent times. Azithromycin, despite sensitivity in vitro, did not lead to resolution of symptoms. Clinical non-response in enteric fever

was also seen in 10% children in a recent study [3]. The antimicrobial susceptibility pattern in enteric fever from Chandigarh from 2018-2020 denotes chloramphenicol, cotrimoxazole and ampicillin sensitivity as 95%, 94.7% and 100%, respectively; and ceftriaxone, azithromycin and ciprofloxacin sensitivity as 94.7%, 100% and 9.5%, respectively; (personal communication, Dr Madhu Gupta). Similar findings have been reported from other regions of India [4]. We wish to highlight the growing evidence on cyclical use of antimicrobials i.e., revisiting old-generation antibiotics for effective clinical management can prove a useful weapon in our armamentarium, while following principles of antibiotic stewardship.

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Exercising Prudence in Requesting Advanced Genetic Tests

The genetic diagnosis of monogenic disorders has become simpler in recent years with the evolution of techniques which permit massive parallel sequencing of deoxyribonucleic acid (DNA) isolated from blood or tissue samples. The techniques, referred to as next generation sequencing (NGS), are widely available in our country and the cost of testing is probably among the lowest in the world. This has led to indiscriminate use of these diagnostic tests resulting in sub-optimal yield. We highlight the danger of inappropriate use of genetic testing in two infants whom we encountered recently.

The first infant was referred to us at 4 months of age for

respiratory symptoms and poor weight gain. He had dysmorphic features including low set posteriorly rotated ears, depressed nasal bridge, anteverted nares, a long philtrum and retrognathia. An echocardiogram diagnosed hypertrophic cardiomyopathy. The clinical suspicion was a rasopathy. The infant had previously been evaluated by an orthopedician who had suspected achondroplasia and advised genetic testing (clinical exome sequencing). This did not reveal any significant variant. We requested the laboratory to re-evaluate the genetic data based on the additional clinical information. This showed a heterozygous pathogenic variant in the *RAF1* gene (c.776C>G (p. Ser259Cys) Transcript NM_002880.4) consistent with a rasopathy.

The second infant was referred to us for cardiac evaluation in the newborn period. She had dysmorphic features including thick eyebrows, pointed nose, coarse facies and a long philtrum. The echocardiogram showed moderate valvular pulmonic stenosis and

a persistent arterial duct. Based on the coarse facies and eyebrows, Cornelia de Lange syndrome (CdLS) was suspected, and genetic testing was suggested (whole exome sequencing). However, the clinical details were not provided to the laboratory appropriately. Based on the clinical indication provided as low birth weight, no pathogenic or likely pathogenic variant was detected on NGS. We requested a reanalysis of the sequence after providing all the clinical information. This detected a heterozygous pathogenic variant in the *NIPBL* gene (c.1859_1860dup (p. Ala621Ter)) (Transcript ENST00000282516.13) consistent with the clinical diagnosis of CdLS.

Although the ability to correctly identify variants has improved greatly during the last decade [1], identification of variants continues to be limited by the lack of accurate clinical information. The American College of Medical Genetics (ACMG) has published guidelines on reporting of secondary findings unrelated to the clinical phenotype, but this is limited to certain critical genes where knowledge about the genotype can help in early diagnosis and management of diseases [2]. Hence the clinician should take utmost care in providing all available clinical information to the genetic laboratory. NGS cannot be used to diagnose disease caused by genomic imprinting such as Prader Willi syndrome as well as trinucleotide repeat expansions including Fragile X syndrome.

Commercial genetic testing in our country is at present not regulated by any central body and the onus on appropriate utilization of this exciting technology lies with the clinicians. Professional bodies including the Indian Academy of Pediatrics (IAP) should take leadership in educating its members of the dangers associated with inappropriate use of advanced genetic testing by conducting workshops and training sessions. Genetic testing should be accompanied by a pre-test counselling of the family about the limitations of the testing methodology and what to expect from the testing process as well as a post-test counselling about the implication of the results.

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Monkeypox: A New Global Threat

As per the latest update issued by the WHO on 29 May, 2022 within a span of two weeks since the first case of Monkeypox was reported from United Kingdom, a total of 257 laboratory confirmed cases and around 120 suspected cases have been reported to the WHO. These cases are reported from 23 member countries spread across four WHO regions, which are not endemic for monkeypox virus. And this number is expected to increase further with the surveillance in non-endemic and endemic countries. Maximum number of the cases are reported from the United Kingdom and Canada; followed by Portugal, Spain and United States of America. Most of the reported cases have involved mainly, but not exclusively, men who have sex with men (MSM). A major worrisome cause is the absence of travel history to endemic areas in the confirmed monkeypox cases. This sudden unprecedented rise of the monkeypox cases in the non-endemic areas has raised a concern – Is this the rise of another global threat??

This pox like illness was first discovered in 1958, when an outbreak occurred in a colony of Asian monkey's kept for research, hence named as Monkeypox. But it is more commonly found in squirrel, rat, and shrew species than monkey, occasionally spilling over into the human population, where it spreads mainly through close contact. According to the Head of the genomics lab at the National Institute of Biomedical Research (INRB) in Kinshasa, Democratic Republic of the Congo (DRC), the cause of the increase in the number of cases is due to the invasion of the forests by humans. The availability of full genome sequence of the virus by INRB and a lab in Goma can help in the development of newer treatment options in the future. Till then the news of the availability of a vaccine for high risk contacts of cases in USA and promising results of an under trial drug by University of Oxford gives a new hope to us. (*Science.Org 1 June, 2022*)

CRISPR: Newer Technology to Detect Tuberculosis

In 2020, approximately 9.9 million people fell ill due to tuberculosis, including 1.1 million children. In spite of the fact that tuberculosis (TB) is a curable and preventable disease, it is the second most common infectious cause of death causing 1.5 million deaths in 2020 globally.

The current diagnostic methods which use sputum based tests, have suboptimal detection rates because *i*) getting a good sputum sample is difficult, especially in children, *ii*) in immunocompromised HIV patients and cases having extrapulmonary disease can have low bacteria load in the sputum, which can lead to false negative results. In order to find the solution for this problem a team of researchers in New Orleans, USA evaluated the use of CRISPR-based assay to detect the cell-free DNA from live *Mycobacterium tuberculosis* bacilli (*Mtb-cfDNA*).

The CRISPR-based fluorescence assay to detect *Mtb-cfDNA* demonstrated >90% sensitivity and specificity in a pooled adult and pediatric group, including children with HIV (adult TB - 96.4% sensitivity and 94.1% specificity; pediatric TB - 83.3% sensitivity and 95.5% specificity). Simultaneously, they have also demonstrated that the blood levels of the *Mtb-cfDNA* start falling within a month of treatment and gets cleared off after the end of treatment i.e. 6 months, thus highlighting the role of CRISPR-based fluorescence assay to detect *Mtb-cfDNA* in monitoring the treatment. Wide availability of this technique will be of much help in detecting TB in paucibacillary conditions and monitoring the treatment in high disease burden countries. (*The Lancet Microbe 31 May, 2022*)

Acute Hepatitis of Unknown Etiology in Children

According to the WHO Multi-country Disease Outbreak news, there are recent reports of acute hepatitis of unknown etiology in children. Between 5 April and 26 May 2022, in total six hundred fifty cases have been reported from 33 countries located in the five WHO regions. Out of these 650 cases, 374 (54%) were from WHO European region countries. Majority of these cases had severe hepatitis and a higher percentages developed acute liver failure. Liver transplant was required by 38 (6%) children and 9 (1%) deaths were reported.

The key findings of the Joint Surveillance Report by the WHO's Regional Office for Europe (EURO) and the European Centre for Disease Prevention and Control (ECDC) showed that three-fourth of the children who have acute hepatitis of unknown etiology have age less than 5 years, 60% samples were positive for the Adenovirus and only 12% were positive for SARS-CoV-2 on PCR among those tested. Based on the case definition, the common causes of acute hepatitis in children viz., hepatitis A-E viruses, have been excluded during the initial laboratory testing.

Due to the lack of a definitive etiology and high positivity rates in the samples tested for Adenovirus, multiple possible explanations like emergence of a novel adenovirus, SARS-CoV-2 co-infection, and increased susceptibility amongst the unexposed children are arising. Possibility of the presence of this condition in the countries not reporting cases at present cannot be ruled out completely due to the variable testing capacity among different countries. But these countries must collect and store all possible samples from the cases meeting the case definition criteria, for future investigations. Until more information is available, WHO has recommended to follow the standard precautions, and to implement contact and droplet precautions for suspected or probable cases in the health facilities. (*WHO.int 27 May, 2022*)

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Combination therapy of albendazole and praziquantel vs albendazole monotherapy in children with persistent neurocysticercosis (J Child Neurol. 2022;37:366-72)

Persistent lesions after the first course of albendazole poses a clinical dilemma in choosing the next line of treatment in neurocysticercosis. This study examines the safety and efficacy of albendazole and praziquantel in combination for complete radiologic resolution in children with persistent neurocysticercosis when compared with albendazole monotherapy and placebo. The majority (62%) of children in the combination therapy group showed complete resolution of the persisting lesion at the end of 6 months compared to the albendazole alone group (26.3%). Percentage reduction in the lesion's mean area at 6 months was highest in the combination group compared with other groups. The combination therapy did not result in any adverse drug reaction compared with albendazole monotherapy. Thus, a combination of praziquantel and albendazole is an effective and safe regimen for persistent neurocysticercosis.

Italian league against epilepsy guidance on alternatives to valproate in girls and women of childbearing potential with idiopathic generalized epilepsies (Seizure. 2021;85:26-38)

Idiopathic generalized epilepsy is one of the commonest epilepsy syndromes in adolescent girls and requires long-term anti-seizure medication (ASM) therapy. Valproic acid (VPA) is often the drug of choice in most generalized epilepsy syndromes. However, the use of valproate in young girls is associated with a risk of reproductive adverse effects. In contrast with focal epilepsies, for which several alternative ASMs are available, suitable options for the treatment of idiopathic generalized epilepsy (IGE) are limited. With the exception of absence seizures, the literature lacks high quality studies on ASMs in IGEs. This guideline recommends based on available literature and expert consensus, that in young girls, levetiracetam, lamotrigine and ethosuximide should be considered the first-choice drugs in generalized epilepsy syndromes, instead of valproic acid.

Modified zipper method, a promising treatment option in severe pediatric immune-mediated neurologic disorders (J Child Neurol. 2022;37:505-16)

The treatment of severe immune mediated disorders with the customary step-ladder approach (gradual escalation of immunomodulation) is often unsatisfactory (as against an aggressive approach). In this study a modification of the "zipper method"—a treatment strategy alternating intravenous immunoglobulin (IVIG) and plasma exchange (PLEX), was used for severe immune-mediated disorders. The modified zipper method comprised longer intervals between PLEX-IVIG cycles (48 hours instead of 24 hours), more cycles (7-10 instead of 5), a consistent plasma volume exchange (instead of the original multistep approach), and variable infusion times for IVIGs (4-8 hours). The modified zipper method was applied as an individual treatment

approach once standard therapy failed. The follow-up ranged from 6 months to 2 years. Four children (9-15 years) with (1) Miller-Fisher syndrome, (2) Bickerstaff brainstem encephalitis, (3) common Guillain-Barre syndrome, and (4) severe acute disseminated encephalomyelitis were treated by the modified zipper method. Results for duration of mechanical ventilation hospital stay and time to unaided walking outperformed previous studies with IVIG/PLEX alone or IVIG + PLEX combinations unlike the zipper method. They conclude that the 'modified zipper method' is a low mortality, a short mechanical ventilation time, a short hospital stay, and has an excellent outcome in children with severe Guillain-Barre syndrome or acute disseminated encephalomyelitis.

Breastfed infants with spells, tremor, or irritability: Rule out vitamin b12 deficiency (Pediatr Neurol. 2022;131:4-12)

Vitamin B12 deficiency in infancy has important and often under-recognized neurological manifestations. In this Norwegian study of 85 infants with vitamin B12 deficiency, 80% presented with spells (37%) of apneas, motor seizures, or absences within the first two months of life. Tremor (29%) and irritability (18%) were the most common findings at the first examination. Serum total homocysteine (a surrogate marker of Vitamin B12 deficiency) $\geq 10 \mu\text{mol/L}$ was found in 77% of cases compared to 28% of controls. None of the mothers were vegetarians, but 25% reported a previous history of vitamin B12 deficiency and 7% had celiac disease. The dose of nitrous oxide given during labor was significantly associated with infant serum total homocysteine level at diagnosis. This shows that spells, tremors and irritability are common findings in infantile vitamin B12 deficiency.

Efficacy and tolerability of melatonin vs triclofos to achieve sleep for pediatric electroencephalography: A single blinded randomized controlled trial (Eur J Paediatr Neurol. 2021; 34:14-20)

Sedation for electroencephalography (EEG) requires induction of natural sleep rather than the use of pharmacological sedatives, since these medications have effects on the pattern of electrical activity thereby affecting interpretation of the EEG. Oral triclofos has been used for this purpose but the availability of this drug has been erratic. Melatonin is an attractive alternative with its specific effect on shortening sleep latency and increasing total restful sleep time. This study compares melatonin and triclofos for effectiveness in this context. Among 228 children, the proportion of successful EEG was 89.4% in melatonin and 91.2% in triclofos group. First dose was effective in 64% in melatonin and 63.15% in triclofos group. Augmentation dose was needed in 25.4% in melatonin and 28% in triclofos group. Adverse effects were observed in 6.14% of melatonin and 8.65% of triclofos group. Study results indicate that melatonin is a safe alternative to triclofos.

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Rhizomelic Chondro-Dysplasia Punctate (RCDP)

An 8-month-old boy presented with developmental delay and decreased vision. On examination, a length of 62 cm (-4.44 WHO-Z-score) with an upper: lower segment ratio of 1.81:1, micrognathia, malar hypoplasia, flattened bridge, bulbous nose, rhizomelia, and bilateral cataract were noted (Fig. 1). The clinical diagnosis of skeletal dysplasia was made, and differentials of Zellweger syndrome, rhizomelic short stature with punctate calcification (RCDP), and Marinesco-Sjogren syndrome (MSS) were differentials considered. Zellweger syndrome was ruled out as no characteristic facies, cortical malformation, and MSS as there is no cerebellar atrophy. A skeletal survey showed flared rounded iliac wings, flattened acetabula, bilateral coxa vara, and stippled calcification in epiphysis with metaphyseal flaring (Fig. 2). A novel homozygous variation; c.500A>C (p.Asp167Ala) in exon 4 of the *GNPAT* gene was detected suggesting RCDP type 2.



Fig. 1 Clinical photographs of the child showing *a*) bilateral cataract; *b*) shortening of bilateral humerus and thighs.



Fig. 2 *a*) Chest radiograph showing bilateral short humerus (asterisk) with metaphyseal flaring (thin white arrow) and punctate cartilaginous calcifications in epiphysis (thick long white arrow). *b*) Frontal radiograph of bilateral hip joints, thigh, and knee joints showing bilateral short femurs (asterisk) with distal metaphyseal flaring (thin white arrow). Punctate cartilaginous calcifications in the femoral epiphysis and patella regions (thick long white arrow). Flattening of acetabulum and squaring of iliac bones seen (white arrowhead). *c*) Lateral radiograph of the thoracic and lumbar spine shows mild coronal clefting of vertebral bodies (thick short white arrows).

RCDP is characterized by rhizomelia and stippled calcifications, and cataracts. Neuroimaging for brain malformation, skeletal survey, phytanic acid levels, and exome sequencing aided the diagnosis. We managed the child with multi-disciplinary symptomatic care, cataract extraction, and a phytanic acid restricted diet.

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Pediatric Tendinous Xanthomas

An 8-year-old non-obese girl, born of non-consanguineous marriage, presented with skin-colored papules and nodules on the hands for two years. The lesions were firm, non-tender and were localized to the extensor aspect of interphalangeal and metacarpophalangeal joints (**Fig. 1**). There was no joint pain or restriction of mobility. Complete blood count, serum uric acid, renal, liver and thyroid function tests were normal. The patient had elevated total cholesterol (630 mg/dL) and low density lipoprotein cholesterol levels (528 mg/dL). The corresponding levels in her father were 324 mg/dL and 210 mg/dL, respectively. Triglyceride and high density lipoprotein levels were normal in both the patient and her father. Skin biopsy showed diffuse dense nodular infiltrate of foamy histiocytes in the dermis consistent with the diagnosis of xanthoma. Genetic mutation analysis for familial hypercholesterolemia could not be done.

Tendinous xanthomas are caused by altered lipid metabolism, which results in cholesterol deposits in ligaments, tendons or periosteum. These are frequently seen in familial hypercholesterolemia due to mutation in low density lipoprotein receptor, apolipoprotein B or proprotein convertase subtilisin/kexin type 9. Tendinous xanthomas localized to the hands should be differentiated from rheumatoid nodules, multicentric reticulate histiocytosis, knuckle pads,




Fig. 1 Skin-colored papules and nodules on the metacarpophalangeal and interphalangeal joints of both hands diagnosed as pediatric tendinous xanthomas.

pachydermodactyly, tophaceous gout and subcutaneous granuloma annulare. Early diagnosis and treatment of hyperlipidemia by dietary modification and lipid lowering drugs can reduce the risk of cardiovascular morbidity.


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- GERD: Gastro Esophageal Reflux Disease.



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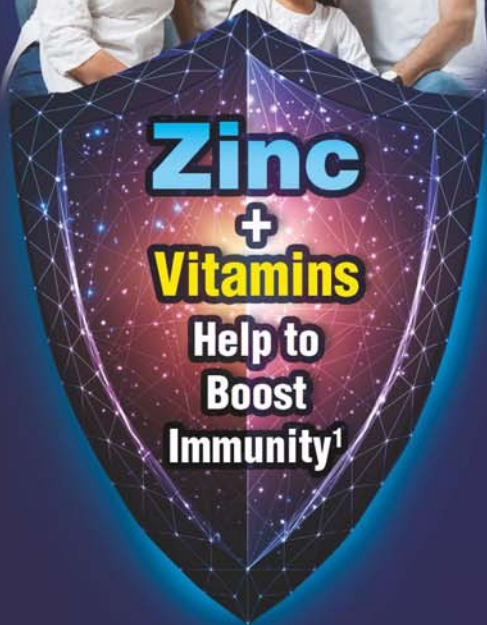
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