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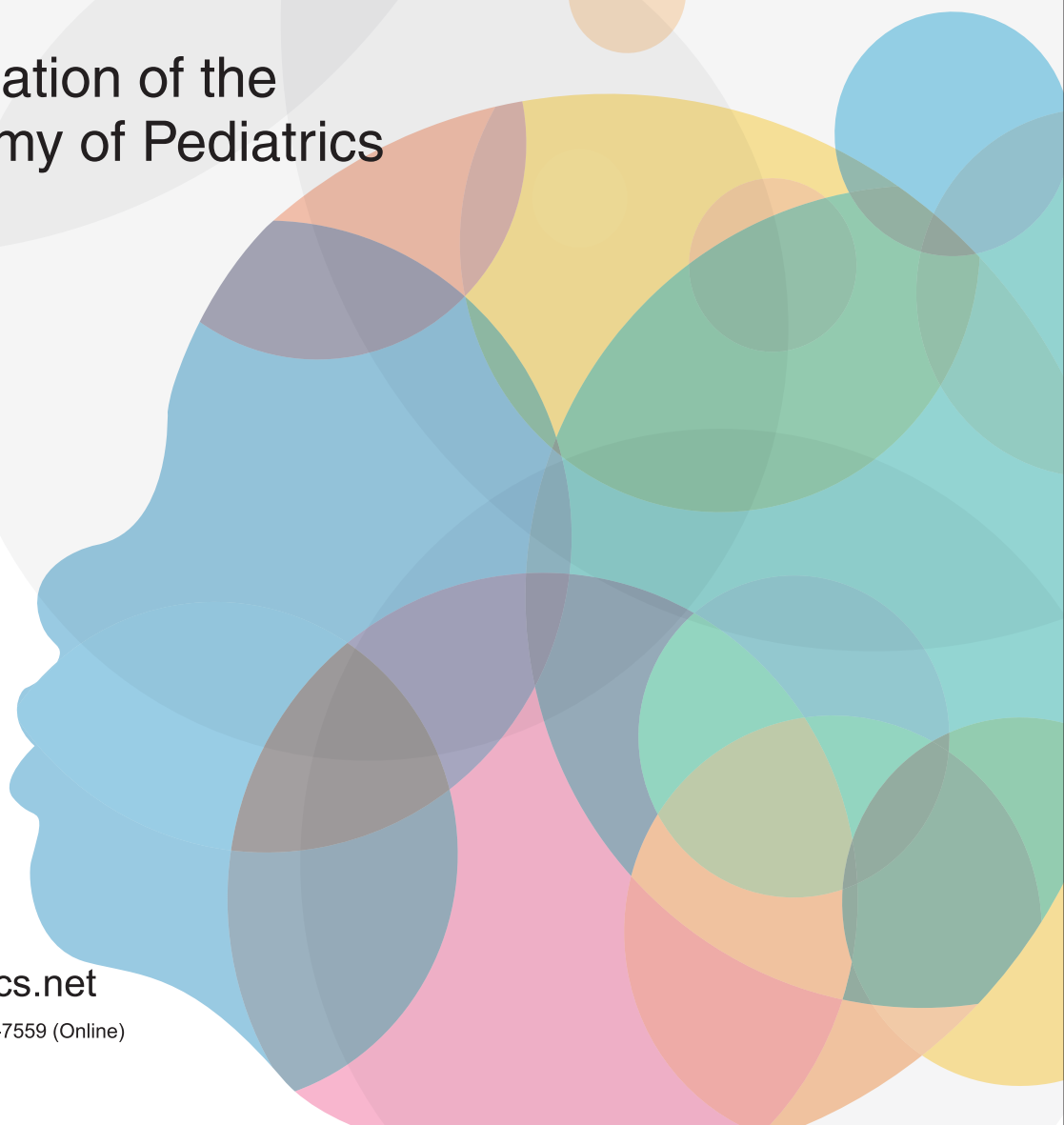
Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 59
NUMBER 3
March 2022



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

IAP Guidelines for pediatric skincare

state that the newborn skin undergoes various structural and functional changes[1*]

Use of appropriate evidence-based skincare practices are important[2]

Protect the infant skin barrier function with safe, appropriate, and evidence-based products

Johnson's® CHOOSE gentle™

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Evidence-based skincare regimen

Cleansing regimen

As mild as pure water to maintain the skin barrier function[3,4]

Helps maintain the skin barrier function[5]

Moisturizing regimen

Improves the skin barrier integrity[6,7]

Helps enhance the skin barrier function for moisture retention[8]

*From birth to the first five years of life

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RA/JB/BMar2021/05

Indian Pediatrics

March 2022 | Volume 59 | Number 3

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Impact Factor 2020 of *Indian Pediatrics* is 1.411

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 33,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

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Yes, It's Time to Send Our Kids Back to School !

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The school is the fountainhead of modern civilization. The unique ecosystem of a school provides the child with stable predictable activity, opportunities for learning and play, and a vibrant social life made up of daily interactions with schoolmates and peers. Within the paradigm of modern nuclear families, the school supplements – and very often complements – the child's overall developmental needs. In the absence of school life, the child will feel lost, and this deficit cannot be compensated easily within the settings of the modern nuclear family. Hence it is very important that continuity of school life is maintained until the child attains maturity.

It is this very important space that the coronavirus disease (COVID-19) pandemic has rather brutally cut short with the series of lockdowns that have been imposed on the population. As a result, the global education system has plunged into a crisis. Though children have been the least vulnerable segment of the population with regard to the pandemic itself, they have also been the most affected due to its other fallouts. Closure of schools and the need for social distancing have resulted in personal isolation. Disruption of normal life and uncertainty regarding the future has evoked a sense of being distraught. For adolescents, the career track seems confused; considering that this is a crucial period for making choices on professional education, the wrong choice can have lifelong adverse implications. The dilemma is palpable.

As many as 1.5 million schools in India remained shut due to the pandemic and successive lockdowns during the last 24 months, impacting 247 million children enrolled in elementary and secondary schools, according to data released by UNICEF [1]. While schools gradually began to offer online education, this is not a perfect solution. Online education is not an option for all as only one in four children has access to digital devices and internet connectivity. Pre-COVID, only a quarter of households (24%) in India had access to the internet and there is a large rural-urban and gender divide [1].

THE NEGATIVE FALLOUT

The negative impact of school closure is manifest in other ways too. It is widely being reported that mental health problems in children have increased with this forced isolation. Among older children and adolescents greater depressive symptoms, anxiety and externalizing behavior have been reported with greater alcohol and substance abuse being reported among males during the pandemic. Children with pre-existing mental health conditions were more significantly affected by pandemic-related changes. Children who were exposed to pre-existing childhood abuse and neglect, as also those living in poverty or in lower socio-economic status were at increased risk of stress and depressive symptoms. Family conflict, again exacerbated by the forced lock in at home, increased the risk of mental distress among children and adolescents.

School drop outs is yet another issue to deal with. Both in developed and underdeveloped countries, higher rate of school drop outs is expected. Education always had persistent issues such as access, continuity, learning gaps, among other issues which result in dropouts; the pandemic has added newer challenges and amplified a few others leading to further increase in drop outs [2]. All these factors will reverse societal progress and have long term impact on society at large. The reasons for closure of schools have been many. Initially it was the sheer novelty of the pandemic and the fact that very little was known about it that made governments to clamp down on schools as a precautionary measure. Even when it was understood that the pandemic had little impact on children, it was feared that schools might become major sources for transmission of the virus to adults. But evidence is now accumulating that school closures alone would prevent a very small percentage of deaths (as opposed to other mitigating interventions) and that schools are not strong drivers of SARS-CoV-2 transmission. These considerations strongly shift the balance, risks and benefits in favor of schools being open except in the most extreme circumstances and as a last resort.

WHAT CAN BE DONE

Being a child focused organization, it is for the Indian Academy of Pediatrics (IAP) to take stock of the situation

and advice the governments as well as all the other stakeholders to create the ground for the reopening of schools. IAP has already come out with Guidelines on School Reopening, Remote Learning and Curriculum in and after the COVID-19 pandemic [3], which give clear solutions to some of the vexing problems relating to school reopening. Many local branches of Indian Academy of Pediatrics have already taken a proactive approach, organized discussion and engaged with the government to facilitate reopening of schools. The following are some of the issues that need to be considered at this juncture:

- The decision to close schools comes with potential risks to children's physical and mental health and their social and academic development, and these must be balanced against the risks of not doing so (such as risk of infection, extended community transmission and its associated harms, mortality, and morbidity - mostly of older segments of the population or children with complex underlying health conditions). Many of these risks are predictable and should be actively and vigorously mitigated when and if school closures are deemed necessary. In future also, school closure should be linked to hospital admissions rather than number of positive cases.
- COVID-19 vaccination should be administered to all adolescents 15 years of age and older who do not have contraindications, using a COVID-19 vaccine authorized for use for their age. School-based health Centers (SBHCs) should be promoted as COVID -19 immunization sites for students and staff. / Parents should be encouraged to complete the routine vaccination of children. However vaccination should not be a prerequisite to attend school.
- Universal masking for children is a must. Mealtime break should be staggered or modified to reduce the risk of spreading COVID-19, especially during periods of high transmission. Timings and number of students per class can be an administrative and logistic decision by school.
- School reopening as the pandemic subsides will necessitate a comprehensive program of support to children and families to address their mental health needs and missed opportunities for learning, socializing, and personal growth. On-site school health services, should be supported if available, to provide pediatric acute, chronic, preventive and behavioral health care. Collaboration with health care workers is essential.

I appeal to all IAP branches across the country to actively engage with their local communities, organize discussion, give proper guidance and develop roadmaps to facilitate reopening of schools. Encouraging parents and giving them the much needed confidence is the priority here. Return to normalcy being the need of the hour, this is the greatest service that we can render to the profession and to the well being of children as well as society as a whole.

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INVITED COMMENTARY

Do We Need To Roll Back Universal Vitamin A Supplementation In India?

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Vitamin A deficiency (VAD) has long been recognized as a common child health problem with a wide range of clinical manifestations from night blindness to severe keratomalacia and blindness. Vitamin A supplementation (VAS) has been closely linked with a reduction in all-cause child mortality by as much as 24% [1,2], suggesting survival benefits in VAD countries. World Health Organization advocated VAS in children aged 6 months to 5 years for settings where VAD is a public health problem with >20% VAD prevalence [3]. The Government of India launched the National Prophylaxis Programme against Nutritional Blindness due to VAD in 1970, targeting children aged 1-6 years with the specific aim of preventing nutritional blindness due to keratomalacia. Survival benefit with VAS was considered relevant to India, and in 2006, the target age group for universal vitamin A supplementation (UVAS) was extended to children aged 6 to 59 months.

In India, some studies showed variable results for under-five mortality reduction with VAS [4] but a Cochrane review in 2017 [5] reiterated that VAS is associated with a clinically meaningful reduction in mortality amongst children aged 6 months to 5 years. Thomas, et al. [6] re-estimated the pooled risk ratio for mortality reduction with universal VAS from Indian studies, and did not find any survival benefit. The results projected by Thomas, et al. [6] should not come as a surprise because right from the beginning it was understood that VAD is not a proximal determinant of death in children in developing countries because they primarily died from infections such as diarrhea, respiratory disease, and measles [7]. VAD presumably alters the incidence, duration, or severity of such infections or the child's ability to withstand their consequences [8]. With effective interventions that reduce the incidence of these infections, the net impact of UVAS on under-five mortality is also expected to be reduced over time.

Thomas, et al. [6] have used a robust methodology while performing the meta-analysis of five Indian trials. However, in order to draw meaningful inferences for making programmatic decisions, there is a need for absolute clarity about the data used for such analysis. Of the five studies, one included only infants, and two trials used a placebo and one 'usual care' for the control groups. The uncertainty of the control group getting or not getting any VAS through the existing health delivery system is an important issue to think about. If they did get, which can be the case in most situations, it makes the cases and controls not so different to draw any conclusions about mortality. One of the trials [4] has acknowledged that some non-trial VAS might have occurred during the study but in such a situation the comparison is between routine versus occasional VAS, which is not a compelling explana-tion to draw conclusions about the survival benefit of VAS.

It is expected that science should inform policy and programs. This study has rightly suggested a targeted VAS approach for the states where the prevalence of VAD is >20% and those with a borderline prevalence of VAD with higher mortality rates. Programmatically, it appears to be an important approach because these states continue to have a high prevalence of VAD despite universal VAS being administered to under-five children for decades. The authors have further suggested surveillance in the other states with VAD prevalence <20%, where VAS can be rolled back. It is this suggestion that needs to be examined programmatically. Firstly, the VAD prevalence estimated by the Comprehensive National Nutrition Survey (CNNS) in 2016-2018 [9] has been conducted in a population getting VAS for decades and if in a majority of states VAD prevalence is <20% it can be interpreted as a partial success of the program. Therefore, one needs to ponder about the possible magnitude of VAD prevalence in these apparently 'better off' states if UVAS was not administered under existing health programs. It needs to be kept in mind that even with UVAS administered for decades, VAD has been reported among 18% of pre-school children in India and the majority of states have VAD prevalence >10% [9]. In this scenario, thinking about rolling back of VAS, particularly when there is no remarkable improvement in dietary intake of vitamin A in

these states over the years, sounds alarming. It is also known that VAD of public health magnitude does exist in clusters or isolated geographical pockets even in 'better off' states because of issues related to poor food availability and food insecurity. How to reach this vulnerable population if VAS is rolled back, and where do we go from here?

Surveillance alone for VAD in the states with VAD prevalence <20% may not make us any wiser to make a decision about the future implementation of the VAS program in India. There is an urgent need to undertake mapping of geographical areas of VAD at the district level and lower down, instead of relying on state averages, in order to know the actual magnitude of VAD within the state. Studies with different doses, strategies, and delivery mechanisms need to be conducted to identify the best alternative to the current VAS program before contemplating rolling back the VAS initiatives in India.

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

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INVITED COMMENTARY

Breastfeeding Support in Health Facilities: A Challenge Less Recognized?

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Optimal breastfeeding is one of the most effective ways to ensure child health and survival [1]. The World Health Organization (WHO) recommends initiation of breastfeeding within first hour of birth and exclusive breastfeeding for the first six months of life [1]. Early initiation of breastfeeding is an important intervention that ensures that the baby receives colostrum and also increases likelihood of successful exclusive breastfeeding [2]. Harmful breastfeeding practices include discarding of colostrum and providing prelacteal feeding. The attitude and practices towards breastfeeding in India is not only determined by awareness of appropriate breastfeeding practices but also heavily influenced by traditional practices and other context-specific factors [3]. Hence, prevalence of optimal breastfeeding practices may vary from community to community and is evident from the regional difference of breastfeeding indices [4].

In this issue of *Indian Pediatrics*, Rasailly and colleagues [5] have studied and compared the practices of timely initiation of breastfeeding, colostrum feeding and use of prelacteal in the tea garden community of Assam (a marginalized community) and native villages of Assam. It is encouraging to find that more than three-fourth of mothers initiated breastfeeding within one hour of birth of their newborn in both tea gardens and villages (76.4% vs 82.6%), which is much better compared to previous reports from the area and even compared to other Indian data [4-6]. However, it is concerning that the practice of discarding colostrum is still highly prevalent in both the settings (39.2% in tea-gardens vs 28.8% in villages), which is worse than the previously reported prevalence from this area [5]. High rate of discarding colostrum, especially in tea gardens, could be attributed to local cultural factor such as negative perception towards use of first milk (colostrum) [6]. One of the striking findings of this study is the near disappearance of harmful practices of providing prelacteal feeding to newborn [5]. This could be an impact of greater institutional deliveries achieved in both the study groups as birthing in health facilities is known to have positive impact on breastfeeding practices including reducing prelacteal feeding [6]. The authors have also demonstrated that institutional delivery was positively associated with early initiation of breastfeeding and giving colostrum [5]. It is a public health success story that both study populations are on verge of achieving universal institutional deliveries with overall 97.5% children being delivered at medical facilities. However, it is observed that a significant proportion of babies did not have timely initiation of breastfeeding despite being born in health facilities and delivery being conducted by trained health care staff. Similarly, nearly 39.2% babies in tea garden and 28.8% in villages were not fed on colostrum despite being delivered at health facilities [5]. Multitude of factors such as cesarean deliveries, obstetric complications, breast-related problems, low birthweight, prematurity or other neonatal factors, lack of knowledge regarding correct technique or positioning of breastfeeding particularly among primigravida, and work overload of existing nursing staff to tackle ever increasing numbers of institutional deliveries may pose a barrier in early initiation of breastfeeding for babies delivered in health facilities [3,6,7].

Findings from this study also suggest that not initiating breastfeeding within one hour was associated with low birthweight and assisted/cesarean section delivery [5]. Prevalence of low birthweight is very high in this population, especially in tea gardens. On the other hand, numbers of delivery by cesarean section mode is also significant in numbers [5]. Hence, these two factors may act as important barrier in the early initiation of breastfeeding in this area. However, there is need to conduct more in-depth research, especially qualitative, to precisely know why such a large chunk of children were not breastfed within one hour of birth or deprived of colostrum despite the fact that 97.5% delivery took place in health facilities. Due to the shift of place of delivery from home to health facilities in India, there is also a shift in the responsibilities of timely initiation of breastfeeding from peripheral health workers and families to the nursing care providers of health facilities where the births take

place, hence identifying these institution level barriers will help in effectively mitigating those factors [7,8].

The institute level barriers might differ in different health care settings depending on adoption and implementation of program in health facilities for promoting, protecting and supporting breastfeeding as defined in BFHI (Baby Friendly Hospital Initiative) target [9]. The findings of the study warrant greater health system efforts for promoting optimal breastfeeding for the children born in health facilities, especially in tea gardens.There should be more sensitization in tea company's hospitals for promoting breastfeeding where deliveries of tea garden women are likely to be conducted. Optimal breastfeeding could be a cost-effective public health intervention for improving health and nutritional status of tea garden children among whom under-nutrition is highly prevalent [10].

Authors also explored the relationship between breast-feeding practices and some important individual and family level variables where they observed some differential relationship in both the settings [5]. This study found that breastfeeding practices were better in homemakers than working women in tea garden, where a substantial number of women work in tea garden as laborer. On the other hand, timely initiation of breastfeeding was associated with nuclear family in villages and joint family in tea gardens [5]. One important limitation of this study is that it did not take into account other potentially important variables associated with breastfeeding such as local cultural and social norms, and individual level enabling variables (e.g., knowledge regarding benefit of optimal breastfeeding, education and counselling on breastfeeding, breastfeeding skill etc.). Therefore, more comprehensive research is needed to better understand the complex relationship between these variables in relation to breastfeeding practices to plan effective context-specific interventions.

Overall, the silver lining is the near disappearance of the harmful practice of prelacteal feeding, and high rate of institutional delivery in the study population. However, significant proportion of women still delay breastfeeding and discard colostrum despite high institutional birth rate. Given a high rate of institutional deliveries in both the study settings, there is a missed opportunity for health care providers to counsel and support appropriate breastfeeding practices [8,9]. Quality improvement measures to optimize breastfeeding recommendations to reality on ground seem crucial.

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

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PERSPECTIVE

The Escalating Health Threats from Ultra-processed and High Fat, Salt, and Sugar Foods: Urgent Need for Tailoring Policy

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With its colonial past, and a glaring problem of poverty and hunger, India oft fails to acknowledge a new, rapidly growing problem of overnutrition. With the economic boost and entry of various foreign players from the food industry, Indian citizens have been increasingly exposed to ultra-processed, high in sugar, salt and fat foods (HFSS foods). The last decade or so has seen an exponential rise in the consumption of such foods, leading to increasing prevalence of overweight- and obesity-related illnesses like diabetes, hypertension, etc. In this scenario, examining the efficacy of policy-related measures in reducing consumption of these harmful foods and preventing the associated health issues is paramount. Across the globe, several countries have explored options from taxation on HFSS foods to restricting marketing to children, as well as different practices for front of the pack labeling. In the context of India and its increasing burden of preventable, diet-related illnesses, the urgent need of instituting these preventive policies at national scale cannot be neglected.

Keywords: *Fast food, Front of pack labeling, Junk food, Obesity, Sugar-sweetened beverages*.

The economic degradation of the Indian subcontinent by several colonial powers was so extreme that it permeated the metamorphosis of independence. The poverty and hunger cycle also took roots in the soil of free India, and the minds of free Indians. And not without reason – according to a Food and Agriculture Organisation report in 2020 [1], 189 million people are undernourished in India, out of a total 746 million globally.

In this historical and current context, it is easy to lose perspective on the rapidly escalating health crisis posed by overnutrition. The number of overweight or obese people in the world has risen to 1.9 billion, while 462 million are underweight. Admittedly, this imbalance skews the other way in children under five, where 45 million children are wasted and 149 million are stunted, compared to near 40 million who were overweight or obese. Yet, it is also true that the low-income and middle-income countries with the highest burden of undernutrition are witnessing swift growth in childhood obesity and overweight [2]. Despite overnutrition being a global issue, there is major inequity when it comes to the readiness of different nations and regions to deal with it.

THE THREAT

The world over, the menace of non-communicable diseases is growing. As per 2021 estimates, they result in death of 41 million people each year, contributing to 71% of deaths globally. Almost three-fourth of these deaths happen in low- and middle-income countries. Children and adolescents are also not exempt from this onslaught and remain vulnerable to obesity, metabolic syndrome, hyperglycemia, hyperlipidemia, hypertension, and diabetes [3]. Contribution of ultra-processed foods, especially consumption of high amount of fats, trans-fats, salt, and sugar to these ailments is now well recognized. The recent Comprehensive National Nutrition Survey (CNNS) under the aegis of Ministry of Health and Family Welfare has documented a prevalence of overweight higher than the national average in 22 Indian states and more than 10% in at least four of them, namely Tamil Nadu, Goa, Delhi, and Arunachal Pradesh [4]. One in 10 schoolchildren is pre-diabetic, 5% adolescents are hypertensive, and 7% are at risk of chronic kidney diseases. Of greater concern is the finding that "metabolic obesity" (either dysglycemia or dyslipidemia) was evident in at least half of the children aged 5-19 years, including in those who were thin or stunted, or conventionally labelled as undernourished [5]. Importantly, triglyceride, glucose and HDL abnormalities were higher among the poor. Thus, the menace of overnutrition has permeated in at least half of the children and adolescents in India, and the threat is being substantially underestimated based on the conventional anthropometric yardstick.

To curb the threat of food-based health abuse, the Indian Academy of Pediatrics released its guidelines on

unhealthy foods and coined a term JUNCS to identify all such foods and beverages under a single umbrella [6]. This nomenclature encompasses junk food (food high in fats, salt, and sugar, also termed as HFSS) [7]; ultra-processed foods (as per Nova classification) [8]; nutritionally inappropriate foods (by virtue of culture or social practices); caffeinated, colored, and carbonated drinks/ foods; and sugar sweetened beverages (SSBs).

Detrimental effects of HFSS diets and ultra-processed foods are now well recognized. A recent systematic review of 43 studies comprising of 891723 participants has demons-trated a robust association of intake of ultra-processed foods with dyslipidemia and metabolic syndrome in adolescents [9]. Another narrative review reported on association between consumption of ultra-processed foods and cardio-metabolic risk [10].

Factors Facilitating Growth of HFSS and Ultra-processed Foods

The speed at which the food industry has grown in India is alarming. At the beginning of the last decade, in the year 2012-13, the reported worth of the fast-food industry was 3400 crores, that was expected to double by 2015-16 to 7000 crores [11]. The ferocity at which the volcano of HFSS foods has erupted can be linked to aggressive marketing, global connectivity, urbanization, and a rise in disposable income.

The advent of social media and networking sites has opened a new avenue for children to be specifically targeted. Both Facebook and Instagram have an age restriction only up to 13 years of age. Targeted advertising to adolescents is a proven marketing strategy of acquiring life-long customers [12]. HFSS and ultra-processed foods are addictive by virtue of being hyperpalatable, and as we have already learnt in the case of nicotine addiction, the ban of advertising to children does not necessarily mean that they are not exposed to such advertisements anyway.

Increased peer pressure to look 'cool' and 'hip' on social media, associated with self-esteem, confidence, and self-worth, has rendered our children susceptible to being influenced. Moreover, nationally known celebrities have ceded some of this control to social media influencers, who may command smaller groups of followers, but due to their availability, access, and personal involvement, may be more effective in shaping their followers' choices. It is important to note also, that some of these influencers predominantly have teenagers in their audiences, offering easy access to HFSS-producing companies to reach them via paid sponsorships, advertisements, and brand collaborations (marketing strategies). In future, it will become harder to isolate and identify online content, which is discreetly promoting unhealthy behaviors in children.

FORMULATING AND IMPLEMENTING POLICES

The battle is not just in the formulation of policies, but in enforcing them as well. The first step; however, is the formulation. The need of the hour is to enable front of the pack labeling (FoPL) on HFSS and ultra-processed foods, making it easy to understand the risks involved with consuming them. Along with it, uniform policies are needed to identify these foods and make aware not only its intended customers, but the various institutions that legislate, execute, and enforce said policies. For instance, in the public interest litigation (PIL) filed by a Delhi-based NGO, the Delhi High Court faced difficulty in defining junk food, as the food industry, represented by the All India Food Processors Association, National Restaurants Association of India, and Retailers Association of India argued that 'junk food' is not defined as such by the food safety law and that there is no justification to formulate a special category called junk food by the court [13]. The PIL had sought to ban the sale of junk food and carbonated drinks in and around the schools and within a 500 yards radius of school premises, as well as a ban on junk food advertisements aimed at children.

The school is one of the primary places where a child may first experience a degree of autonomy when it comes to making decisions about what she or he consumes. It is thus important that certain checks are in place to ensure inculcation of healthy eating practices. Brazil and Australia have been leading the way, the former with its 'school health program' promoting good eating habits, and the latter with its color-coded food options at the school canteen [14,15]. In Australian schools, foods coded 'red' are 'not recommended', 'amber' indicates 'select cate-gory', while 'green' denotes the foods that should be eaten every day. The 'red' foods are present in the menu only twice a term, while the 'green' ones must always be available. In the final judgment of the Delhi High Court on the PIL [13], it directed all schools to implement a system like the color-coding mandated for Australian schools. Although this would be a good start, monitoring systems to ensure continued adherence are sorely needed. Some of the possible strategies are listed in **Box I** and discussed below.

Nutrition Warning Systems

In a developing country like India, with a major chunk of its

Box I Addressing the Threats from HFSS and Ultra-processed Foods

- Nutrition warning systems
- Taxation
- Marketing restrictions
- Consumer involvement
- Awareness

population still illiterate, easily understandable food labeling is critical for behavioral change at a national scale. Studies suggest that nutritional warning systems (NWS) should help the potential consumers to choose healthier options at the point of purchase. Many such like the 'key hole' symbol in Sweden, Norway and Denmark indicating nutritious food, or the 'traffic light' labeling system in the UK indicating high (red), medium (yellow) and green (low) HFSS content in food, or Australia's 'Health-star rating' system, are already in use [15]. National figures have an important role to play: for instance, the USA's 'facts up-front' NWS was developed as a response to the First Lady, Michelle Obama, calling on the food industry to help Americans choose a healthier diet [16]. In India, so far, no concrete policy has been put in place yet to help its populace decipher the complicated numbers and percentages of nutrients listed on the label of an HFSS product.

Compulsory front of the pack labeling (FoPL) has been suggested as an important strategy to reduce the consumption of ultra-processed foods [17]. The four FoPL formats followed by most countries are described below:

i) *The traffic light system*: Used in the UK, Iran and Sri Lanka, it gives traffic light-like colors for salt, sugar, fats, and saturated fats. Green means low, amber means medium, and red means high. It might; however, be misleading for the consumer at times, when a product is simultaneously green and red for different harmful nutrients.

ii) *Summary indicators*: Used in the New Zealand, Australia, France and Belgium, it gives a single, comprehensive indication for overall nutrition in a product, which might be alphabetical (A to E) or numerical (0.5 to 5). This is quite susceptible to industry manipulation, as the rating can simply be improved by adding positive nutrients, which do not in any way reduce the harmful effects of the negative nutrients.

iii) *Reference intake or guidelines daily amount*: These indicate the amount of caloric intake and nutrients in percentage points of the recommended daily intake per serving. Followed by Malaysia and Thailand, it is also adopted voluntarily by the industry in many countries. It is basically a simpler version of the detailed nutrient list provided at the back but is still too difficult to understand for the layman.

iv) *Warning label system*: This is increasingly being viewed as the current best practice, provides easy-to-understand, and nutrient specific warnings. Peru and Chile employ a version of this system, wherein the warning simply states 'high in sugar', or 'high in saturated fats', etc. on a solid black background. On the other hand, Israel uses pictorial icons within their warning labels, for 'high sodium' (a saltshaker), 'high sugar' (a spoonful of sugar), 'high saturated fats' (bread being buttered). In India, the Breastfeeding Promotion Network of India too, has recommended the use of pictures rather than numbers to convey these warnings.

In 2020, a study commissioned by the Food Safety and Standards Authority of India (FSSAI), reported that among 1300 packaged food product samples, only 4.4% adhered to the limits on fat, sugar and salt placed by the WHO. It meant that 95.6% of the products failed on at least one critical nutrient component. These WHO thresholds categorize what products on the market would be required to have FoPL warnings, for the purposes of reducing overweight and obesity and resultant health issues by reducing the consumption of HFSS foods. However, an FSSAI Working Group has considered dilution of these standards for some foods in the Indian context [18]. We caution against the dilution of WHO thresholds, as the formulation of FoPL warning systems could become redundant unless these adhere to the strict, global standards in enforcing them.

The FSSAI should urgently consider adapting and adopting the Nova classification of foods and define ultra-processed foods in the Indian context. This is the first essential step to develop relevant regulations to curb their sales.

Taxation of HFSS and Ultra-processed Foods

Another important area of policy-making includes taxation of HFSS and ultra-processed foods. Even though there is a dearth of real-world evidence for success of taxes on consumption of unhealthy ultra-processed or HFSS foods, several nations have tried one or the other version of it. The results, so far, have been inconsistent. In 2011, Denmark had enacted a 'fat tax' on products containing more than 2.3% saturated fat [19]. Before it could also introduce a similar, proposed 'sugar tax', the Danish Tax Ministry backtracked, and abolished the 'fat tax'. The state had discovered that instead of behavioral modifications in consumption, all they had managed to do was encourage consumers to buy high fat goods from across the border. On the other hand, Mexico's 'soda tax', implemented in 2014, of 1 peso per litre on sugar sweetened drinks proved effective [20]; the probability of converting to a non-consumer of these products amplified by 4.7 percentage points, and of being a low consumer (consuming less than 355 mL a week) increased by 8.3 percentage points. Meanwhile, India's own 'fat tax' implemented by Kerala, a 14.5% surcharge on junk food served in branded restaurants, has been too arbitrary to affect dietary habits [21]. Despite these mixed results, among the comprehensive

umbrella of policies in this regard, taxation, even as a limited pilot project, is worth a serious consideration. It is heartening to observe that the Goods and Sales Tax (GST) Council of India has announced that the category of "Carbonated fruit beverages of fruit drink" and "Carbonated beverages with fruit juice" will be levied 28% GST with additional 12% as compensation cess [22].

Marketing Restrictions

World Health Assembly has endorsed a set of recommendations by the World Health Organization that countries should take steps regarding prevention of advertising unhealthy foods rich in added sugars, trans fatty acids and saturated fats, especially in places that cater to children. There is also a need for restrictions on advertising and marketing of fast food and ultra-processed food in schools, and on television and other media. Use of promotional offers, toys, celebrities, and cartoon characters to market food to children must be strongly prohibited. With the easy availability of online food shopping, there needs to be a restriction on ordering certain items by younger children.

INVOLVE THE STAKEHOLDERS

Even though the formulation of tailored policy is paramount, the involvement of key stakeholders, the consumers, especially children and their caregivers, will go a long way in reducing the consumption of HFSS and ultra-processed foods. It is important that only those stakeholders and policymakers be involved who do not have any potential conflict of interest with the food industry. The environment around the children and their parents needs to be conducive towards making healthier food choices. From the home to the school, to the various avenues of marketing, a compre-hensive push towards the minimally processed food is the need of the hour. For instance, Australian school curriculum is prioritising education on food and nutrition, increasing levels of consumption of healthy foods in school canteens, vending machines, sports clubs, etc. [22]. The spending power of a child, usually desired from the spending power of the parent, needs to be considered as well, especially in a developing economy like India. More stress on balanced meals with only recommended amounts of fat, sugar, and salt, is needed in national schemes like the Supplementary Nutrition Program or Midday-meal scheme (PM-POSHAN), which currently does not focus on simultaneous threat of overnutrition.

CONCLUSION

We are in a quasi-pandemic of sorts – No, not *that* one, the *other* one; slow-moving, non-infectious, non-communicable. A pandemic of over (and inappropriate) nutrition. The major difference between it and the COVID-19 pandemic is that we are better placed to fight the latter. For the former, we have no vaccine, no general awareness, and above all, minimal political will to eradicate it. The Catch-22 situation here is that to create political will, citizens must be made aware of the grave risks associated with the HFSS and ultra-processed foods, and to create such widespread awareness, political will must be strong enough to result in legislation and policies that enable various nutritional warning systems. This is a self-contained circle that allows both parties to be complacent.

The inertia needed to break out of this must come from national-level policies from the government (read FSSAI). If left to their own, the fast-food industry serving these ultra-processed and HFSS foods cannot be expected to self-regulate and act against their self-interest. Alter-natively, waiting for public opinion to organically catch up to these dangers via global osmosis will result in either poor quality or loss of lives due to the inevitable time-lag. This can only be averted by being proactive and urgently formulating tailored national-level policies.

Contributors: The piece was conceptualized by HSS. PG drafted the manuscript that was edited by HSS. Both authors approved the final manuscript.
Funding: Breastfeeding Promotion Network of India;
Competing interests: None stated.

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Indian Undiagnosed Diseases Program (I-UDP) – The Unmet Need

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Genomics is an integral part of many pediatric diseases spanning all sub-specialities. While many genetic disorders are diagnosed with the currently available genomic tests, there still are many patients who do not receive a definitive diagnosis. The Indian Undiagnosed Diseases Program is a multicenter effort to address these challenges and unmet needs of rare disease patients where current available genetic tests have failed to make a diagnosis. It embodies the principles of collaborative effort across multispecialty disciplines, and uses detailed phenotype. Diagnostic methods are tailored to patient specifics and the large genomic data is interrogated with precise, in-house bioinformatics pipelines using patient-specific phenotype to build the diagnostic algorithm. The inception of this research initiative in India is a step towards creating awareness and appreciation of the needs for our undiagnosed cohorts to enable appropriate management in this era of precision medicine.

Keywords: *Collaborative, Evaluation, Genomics, Rare disease*.

Published online: February 01, 2022. PII:S097475591600404

Rare diseases (RD) are conditions that affect a relatively small number of patients. It is estimated that these comprise 5000-8000 disorders and impact about 6-8% of the population [1]. Definitions of rare disorders vary in different countries and India still awaits to adopt a suitable definition [2]. Most of the rare disorders are of genetic origin. While they may be individually uncommon, as a group they substantially contribute to the healthcare burden. Rough estimates show that more than 50 million individuals in India are likely to be affected by rare disorders [3]. The biodiversity of the population groups in India, endogamous marriages, and high consanguinity rates, contribute to the high burden of genetic diseases.

Genetic tests including microarray and next generation sequencing techniques of panel/exome sequencing have made wide inroads into clinical care and there is a dynamic change in medical practice, not only of geneticists, but of many physicians at large. However, a definitive diagnosis is arrived at in only 25-50% patients using standard diagnostic procedures and these tests [4]. Many remain undiagnosed because of limited awareness, the small number of trained geneticists, inadequate representation and thereby the lack of attention, as well as limited access to diagnostic facilities within the healthcare system of the country. Other reasons for the microarray/exome negative undiagnosed cohort include mosaicism at tissue level, structural changes that are not identified by exome sequencing including variants in non-coding regions of the genome or in the regulatory regions. Complex, non-Mendelian patterns of inheritance including genetic and environmental modifiers also contribute to a negative exome analysis. Additionally, it could be a new gene for a clinically recognizable disorder or a previously undescribed syndrome awaiting gene identification [1,4].

Many emerging technologies including genome sequencing, proteomics and metabolomics, with enhanced computational expertise are gaining importance in the landscape of rare disorders. Physicians mostly work in isolation while evaluating a patient, but what is required for these disorders with multidimensional involvement is a multidisciplinary approach with specialists of different disciplines, bioinformaticians and scientists to solve the diagnostic puzzle. In absence of this, the disorders can remain unrecognized and unsolved [1].

The National Institute of Health (NIH), USA initiated an Undiagnosed Disease Program in 2008 for patients for whom diagnosis has eluded them [5]. The success of this program furthered the expansion to multiple sites in the US as well as the initiation of the Undiagnosed Diseases Network International (UDNI), in 2014, to address the worldwide needs of patients with challenging phenotypes and limited information to address this diagnostic conundrum. Many countries, including India, are members of this global call for rare disease patients. Other programs were initiated in many countries, including Deciphering Developmental Disorders in UK [6], Findings of Rare Disease Genes [7] and Care4Rare Canada Consortium [8] in Canada, contributing to the worldwide efforts.

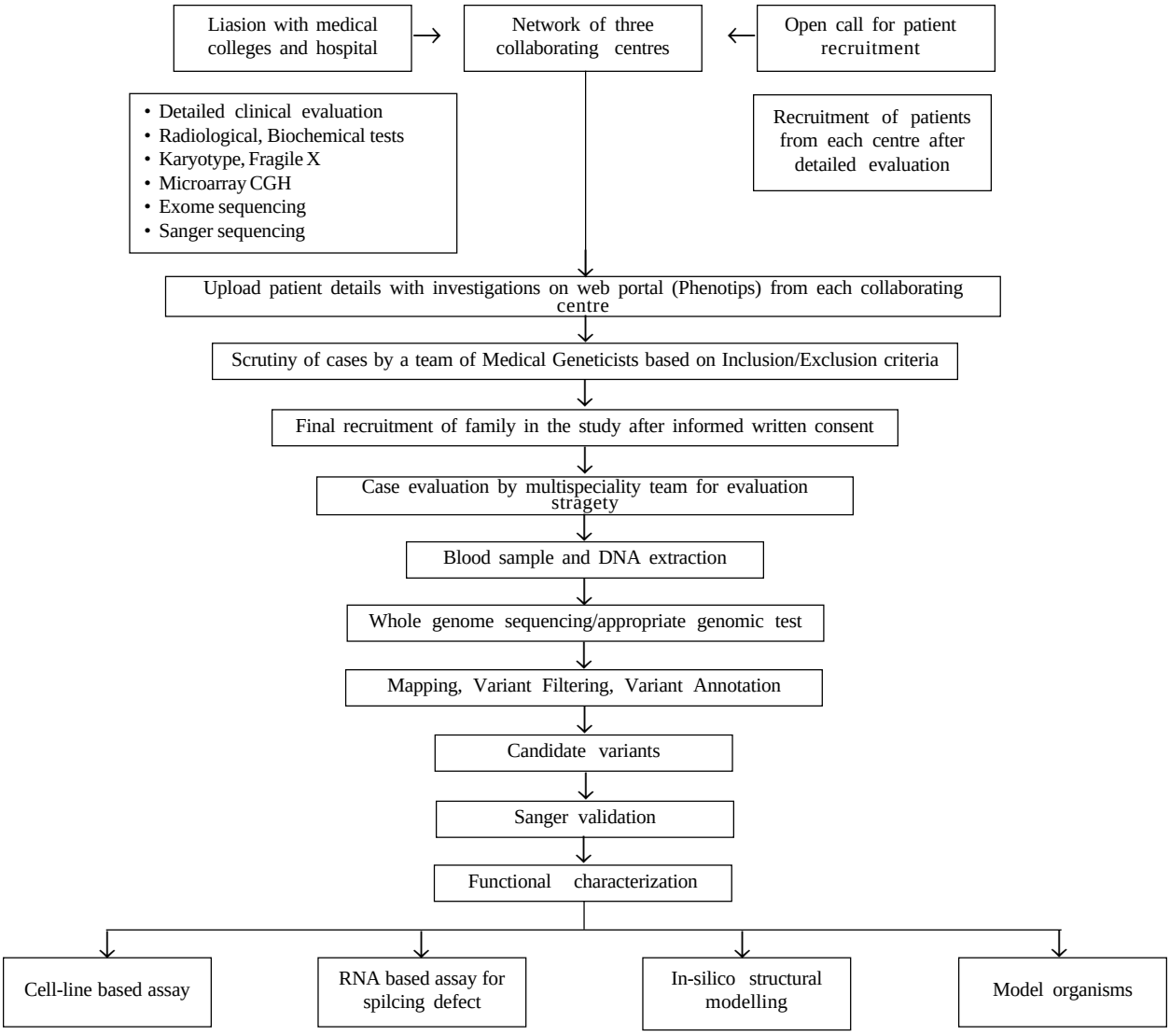

Fig. 1 Flowchart of work planned in I-UDP project.

There is a vast unmet need for rare disease gene discovery in India despite many novel genes having been described in the country [9]. These patients have long diagnostic odysseys, multiple physician visits, repeated laboratory tests with accumulated old documents, and families are spent emotionally and financially to understand the reason for their child's disorder [10,11].

There are two important concepts in working with patients with RD. Firstly, functioning within a multi-disciplinary, multi-specialty expert group allows precise phenotypic characterization. Secondly, delineating clinical features in a standardized vocabulary of clinical phenotypes, the Human Phenotype Ontology (HPO) [12], enables deep phenotyping for appropriate database search, as well as a bench-to-bedside approach to gene prioritization and discovery. Enabling a rare disorder diagnosis requires exchanging thoughts on phenotypes, and understanding etiological pathways, methods of gene identification and tools used for this to help in resolving some of these challenging cases.

The Indian Undiagnosed Diseases Program (I-UDP) was conceptualized on similar lines. This research project, funded by the Indian Council of Medical Research, commenced in February, 2021 with three participating sites - genetic units at Sir Ganga Ram Hospital, New Delhi; Sanjay Gandhi Postgraduate Institute (SGPGIMS, Lucknow, UP) and two centers at Hyderabad, Centre for DNA Fingerprinting and Diagnosis (CDFD) and Nizam's Institute of Medical Sciences (NIMS). The methodology involves a review of the submitted cases by the team of I-UDP. The challenging cases are

discussed first by a group of relevant multidisciplinary experts, followed by video conferencing between the participating sites. The aim is to enable a case-specific tailored approach and formulate a highly collaborative and coordinated format for clinical evaluation, detailed and standardized docu-mentation of patient phenotype with close bedside and bench collaborations (**Fig. 1)**. The undiagnosed diseases program enables a one-time, one patient, focused opinion, assessment, and advanced genetic testing. The strengths of this program are collaboration across multiple centers with multidisciplinary experts working together to enhance case-specific diagnostic algorithms, and allows access to all physicians in India to apply for inclusion of their patients with challenging genetic disorders in this program. This collaborative effort is expected to harness novel methods for providing diagnoses to patients, and also help science by identification of new genetic etio-logies using vast clinical material in India.

This initiative on rare and undiagnosed diseases is a great opportunity for identification of patients with rare disorders. Today, precision medicine requires gene mutation information, as a definite diagnosis has far reaching consequences for appropriate disease management, prognosis, recurrence risk and future reproductive options [13]. Additionally, the family looks to a closure of their prolonged diagnostic quest.

The I-UDP is important for patients who are spent emotionally and financially to find an answer to their disorder, the scientific community of doctors and researchers to further understand biology, and for our country, where the recent Rare Disease Policy 2021 [2] emphasizes the cognizance by the government about rare disorders and possibility of funding for treatment in the near future. In India, the realization of the important role of patient-parent organizations in supporting families with genetic disorders is coming forth and we want to use this opportunity of the change in landscape of patient care in the country. With the discovery of novel genes and identification of disease mechanisms and pathways, there is possibility of a future silver lining of therapies and precision medicine in the years to come.

Contributors: All authors were involved in the preparation of the manuscript.
Funding: Indian Council of Medical Research grant (33/9/2019-TF-Rare/BMS). *Competing interests*: All authors are working at participating institutions in the program.

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RESEARCH PAPER

Efficacy and Safety of Pidotimod in Persistent Asthma: A Randomized Triple-Blinded Placebo-Controlled Trial

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Received: May 09, 2021; Initial review: July 05, 2021; Accepted: December 16, 2021.

Objective: To study whether addition of pidotimod to inhaled corticosteroid (ICS) therapy enhances control in children with persistent asthma, as compared to ICS therapy alone.

Design: Triple-blinded, randomized controlled trial.

Setting: Allergy and Asthma Clinic, Department of Pediatrics, at a tertiary care hospital between May, 2018 and June, 2019.

Patients: 79 children (5-12 years) with newly diagnosed persistent asthma as per Global Initiative for Asthma guidelines.

Interventions: Children received 7 mL twice-a-day for 15 day, followed by 7 mL once-a-day for 45 days of either pidotimod (*n*=39) or placebo (*n*=40). In addition, both groups received inhaled budesonide via metered dose inhaler and spacer, throughout the study. Children were followed up every 4 weeks for a total of 12 weeks. At each follow-up visit, peak expiratory flow (PEF) and asthma symptom score and medicine adverse effects were recorded.

Main outcome measures: Change in PEF at 12 weeks compared to baseline. Secondary outcomes were PEF at each follow-up visit, asthma symptom score at each visit, change in asthma symptom score at 12 weeks, and adverse event profile.

Results: The median (IQR) change in PEF (from baseline to 12 weeks) was 13.0% (0.8%, 28.3%) in pidotimod group (*n*=35) vs 17.7% (4.3%, 35.2%) in placebo group (*n*=35) (*P*=0.69). All the secondary outcomes were also comparable between the two groups. There were no significant adverse effects observed.

Conclusions: Addition of pidotimod for 8 weeks to standard ICS therapy did not enhance asthma control compared to placebo.

Key words: *Immunostimulants, Management, Prophylaxis.*

Trial Registration-CTR1/2018/04/013405

Published online: January 09, 2022; ***PII:*** S097475591600398

In children with asthma, inhaled corticosteroid therapy is the mainstay of pharmacologic management for reducing recurrent asthma attacks, preventing airway remodeling, and preserving lung function. Pidotimod, a synthetic immunomodulator, reportedly enhances innate and cell mediated immunity [1] by stimulating maturation of dendritic cells that activate natural killer cells, macrophages and neutrophils. It also increases T-helper 1 (Th-1) mediated release of Interferon-gamma (IFN-γ), thus increasing immuno-globulin-A (IgA) production, protecting the respiratory tract against microbes. In asthma, there is a reduction in regulatory T cells, which normally inhibit T-helper 2 (Th2) cells [2]. Pidotimod decreases Th2-mediated IL4 release, reducing IgE production, which could prevent asthma exacerbations [1]. Pidotimod also decreases the in vitro expression of CD30 affecting the Th-1/Th-2 balance in atopic asthma [3].

Pidotimod has been explored for the prevention of respiratory tract infection in children with allergic rhinitis [4], bronchopulmonary diseases [5], recurrent respiratory infections [6], Down syndrome [7], and even healthy toddlers [8]. Since respiratory tract infections often trigger asthma exacerbations, pidotimod could theoretically enhance asthma control, and perhaps reduce exacerbation severity or frequency. However, there is no well-designed study that has examined this hypothesis. This randomized controlled trial was conducted to evaluate whether the addition of pidotimod to inhaled corticosteroid therapy enhances asthma control in children with persistent asthma.

METHODS

This study was conducted in the Allergy and Asthma Clinic, Department of Pediatrics, PGIMER Chandigarh, from May, 2018 to June, 2019. All children aged 5-12 years, newly diagnosed with persistent asthma, defined as per the 2017 Global Initiative for Asthma (GINA) guidelines [9], were eligible. Those who had received inhaled corticosteroid preventer therapy for any duration more than 2 weeks during the preceding six months, those suffering from co-morbid conditions (cystic fibrosis, chronic lung disease or congenital lung dysplasia) and those prescribed immunomodulator therapy for any other condition, were excluded. The study was approved by the Institute Ethics Committee, and the trial was registered on the Clinical Trials

Registry India (CTRI) platform. Children were enrolled after written informed consent from their parents. Additional written assent was obtained from children older than 8 year.

Pre-trial analysis of approximately 600 children with persistent asthma in our institution showed that the mean (SD) PEF (% of predicted) in newly diagnosed children with asthma was 65.3 (12.7)%, increasing to 79.8 (11.7)% at the end of 4 weeks of ICS therapy, i.e., approximately 15% increase from baseline. In order to detect an additional 10% increase in PEF (% of predicted) in the intervention group, we estimated a sample size of 34 in each group i.e., total 68, with an alpha error of 0.05 and power of 80%. Anticipating 10% attrition, the sample size calculated was 75.

Each enrolled child underwent a detailed evaluation of demographic features, clinical history, history of atopy, family history, clinical examination, and asthma severity categorization, as per the GINA guidelines [9]. Computer generated, random sequence was created in blocks of 4, 6 or 8, by a faculty member not connected with the trial procedures. Transparent plastic bottles containing either pidotimod (400 mg per 7 mL) or placebo were used. The placebo was the vehicle in which pidotimod was dispensed, hence was identical to pidotimod in appearance, colour and taste. Each bottle was labeled with a sticker showing only the enrollment number and dosing instructions. This was done at a central location in our institution by personnel not connected with the study. Children were dispensed bottles as per the enrolment number; thereby assuring allocation conceal-ment. The randomization code was revealed only after data analysis.

At enrolment, baseline peak expiratory flow (PEF) and Asthma symptom score [10] were recorded. PEF was measured as per the American Thoracic Society recommendations [11], using mini Wright peak flow meter (mini Wright Cat No 3103001). Percentage was calculated against the predicted, as per Indian norms of Parmar, et al. [12] developed at our institution, and updated periodically. PEF measurements were performed by a single, trained technician. Each child performed the procedure thrice, and the best reading was used for analysis.

Asthma symptom score was measured using a tool validated in Indian children [10]. It comprised of six items, each item received a daily score of 0 for absence and 1 for presence; thus the weekly score could range from 0 to 42. An average score was calculated for four consecutive weeks by adding the weekly score of preceding four weeks and dividing it by 4.

All children were prescribed inhaled corticosteroid therapy (budesonide 200-600 µg/day), depending on the severity, delivered by metered dose inhaler through a spacer. In addition, children received bottles containing the study drug labeled with the enrolment number and dosing instructions. The dosage was 7 mL twice a day for the first 15 days, followed by 7 mL once a day for the next 45 days as per the manufacturer's instructions. Budesonide was continued throughout the study period and beyond, as per the GINA 2017 guidelines [9].

Children were followed up every 4 weeks, for a total of 12 weeks. At each follow-up visit PEF, asthma symptom score, and any adverse effects to the medication were recorded. The bottle from the previous visit was returned to the investigator, who measured the volume of syrup remaining, in order to determine the compliance.

The primary outcome was the change in PEF at 12 weeks, defined as PEF (% of predicted) at 12 weeks minus PEF (% of predicted) at baseline, expressed as a percentage of the baseline PEF (% of predicted). The secondary outcomes were PEF (% of predicted) at each follow-up visit, asthma symptom score at each visit, change in asthma symptom score at 12 weeks, and adverse event profile. The parents of the enrolled children were requested to record any perceived side effects, especially rash, abdominal pain, vomiting, nausea and headache. These data were reviewed at each follow-up visit.

Statistical analysis: Statistical analysis of data was performed using IBM SPSS software version 23. Inter group means were compared using the Student t test, whereas medians were compared using Mann-Whitney U test. Proportions were compared using Chi-square test. PEF (% of predicted) and asthma symptom scores were compared within each group using Wilcoxon signed rank test.

RESULTS

A total of 100 children were potentially eligible to participate in the trial during the study period. Of these, 21 were excluded on the basis of exclusion criteria and 79 children were randomized (pidotimod 39, placebo 40). Seventy children completed the study per protocol, as 9 children (pidotimod 4, placebo 5) did not attend the first follow-up visit (**Fig. 1).**

The baseline characteristics of children in both groups were similar with respect to age, duration of symptoms, type of symptoms, asthma severity, baseline PEF and Asthma symptom score as depicted in (**Table I)**. The most common associated comorbidities were allergic rhinitis (25.3%), allergic conjunctivitis (6.3%) and atopic dermatitis (5.1%).

The median (IQR) change in PEF at 12 weeks was 13.0% (0.8, 28.3) in the pidotimod group vs 17.7% (4.3, 35.2) in the placebo group (P=0.69). Similarly, PEF (% of

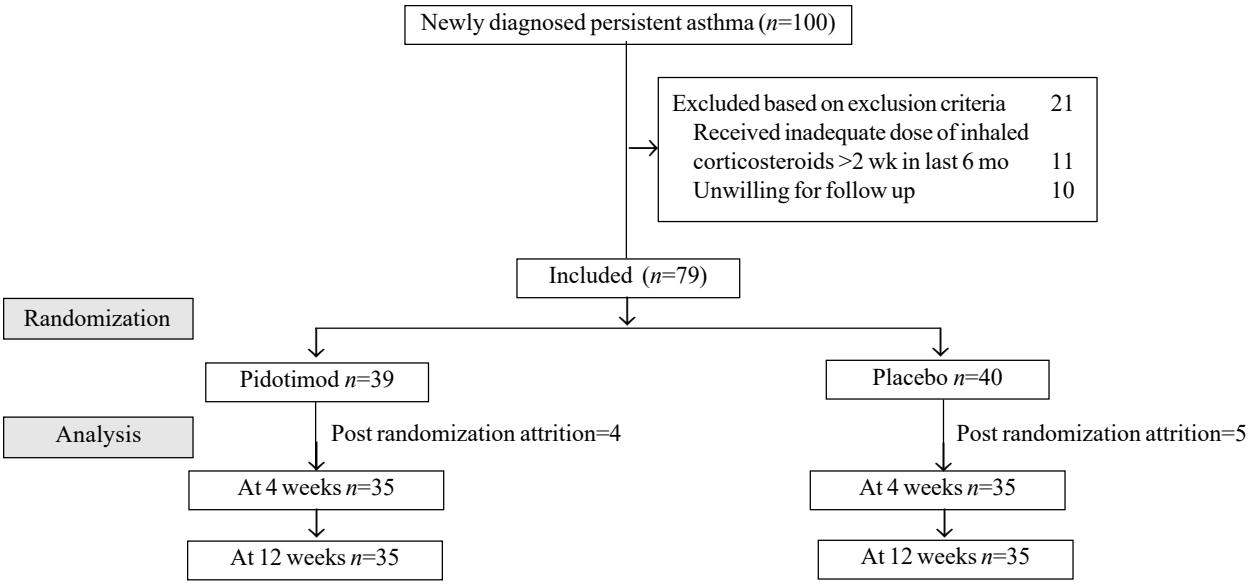

Fig. 1 Flow of participants through each stage of the trial.

predicted) at each follow-up visit was comparable between the groups (**Table II**). The median Asthma symptom score declined from 21.0 to 1.75 in the pidotimod group and 21.0 to 0.0 in the placebo group at the end of 4 weeks, and the difference was not statistically significant. The score was also comparable between pidotimod and placebo groups at other time-points (**Table II**).

Only two children in each group (5.7%) complained of mild abdominal pain during the first week of enrolment. This was observed for one day in those in the pidotimod group, and for two days in those in the placebo group. The pain resolved spontaneously and did not require discontinuation of the medication. None of the other children complained of any other side effects. Three children in each group experienced a mild exacerbation within the first four weeks. These were managed with addition of inhaled salbutamol for 2-3 days, and none required oral steroids or hospital admission. The highest Asthma symptom scores (out of 42) of these six children on any given day were 7, 9, 10 (Pidotimod group) and 7, 7, 8 (Placebo group).

Table I Baseline Characteristics of Children With Persistent Asthma Enrolled in the Study

Characteristics	*Pidotimod group (n=39)*	*Placebo group (n=40)*
Age (y), mean (SD)	7.95 (2.33)	8.20 (2.42)
Male sex[a]	30 (77)	32 (80)
Duration of cough (mo)	32.0 (8,61)	36.5 (11,72)
Wheeze on auscultation[a]	18 (46.2)	22 (55.0)
Asthma classification[a]		
Mild persistent	17 (43.6)	17 (42.5)
Moderate persistent	21 (53.8)	19 (47.5)
Severe persistent	1 (2.6)	4 (10)
PEF (% of predicted)[b]	76 (66,87)	73 (60,89)
Asthma symptom score[b]	21 (21,28)	21 (21,28)

Values in median (IQR) or [a]no. (%).[b]Values at baseline. PEF: Peak expiratory flow.

DISCUSSION

This placebo-controlled trial showed that the addition of pidotimod (for 8 weeks) to inhaled corticosteroid therapy did not enhance asthma control. Even though pidotimod

Table II Primary and Secondary Outcomes in Children in the Pidotimod and Placebo Groups

Outcome measures	*Pidotimod group (n=35)*	*Placebo group (n=35)*	*P value*
Change in PEF[a]	13% (1, 28)	18% (4, 35)	0.69
PEF (% of predicted)			
At 4 wk	84 (79, 97)	95 (77,105.5)	0.61
At 8 wk	87 (79, 100)	94 (82, 103)	0.52
At 12 wk	93 (78.5, 104)	98 (92, 103)	0.43
Asthma symptom score			
At 4 wk	1.75 (0, 8.0)	0 (0, 7.0)	0.59
At 8 wk	0 (0, 2)	0	0.24
At 12 wk	0 (0, 2)	0	0.41

Values in median (IQR). [a]change from baseline after 12 wk of treatment. PEF-peak expiratory flow.

was safe compared to placebo, there was no additional benefit.

A Chinese trial in 60 children with allergic rhinitis and asthma, comparing pidotimod plus symptomatic treatment, versus only symptomatic treatment, showed that pidotimod improved mean PEF as compared to controls, but this benefit was observed only after one year of treatment [13]. In contrast, our study was limited to only 8 weeks of therapy and 12 weeks of follow-up. Another placebo-controlled rando-mized trial in 60 children with allergic rhinitis accompanied by asthma, suggested that pidotimod decreased the inflam-matory reaction, and improved pulmonary function parameters [14]. However, the details of this study in terms of enrollment criteria, case definitions, dosing, etc. were not available, hence the results could not be compared to the present study.

In contrast to asthma, there is more data available on the effect of pidotimod on acute respiratory infections. In a multicentric placebo-controlled randomized trial, children who received pidotimod had fewer acute respiratory infection (ARI) episodes as compared to controls, and pidotimod use was not associated with significant adverse effects [15]. A clinical trial in children aged 2-10 year with >6 annual respiratory infections showed that pidotimod (used in the same regimen as in our study) significantly reduced the incidence of infections, and of asthma episodes [16]. However, the authors did not explore the frequency of asthma episodes.

Another prospective study in children with frequent episodes of ARI, where pidotimod was taken for 6 months, showed reduced frequency of ARI episodes [4]. However, the absence of a control group makes interpretation difficult. Since respiratory tract infections trigger exacerbations, and/or vitiate asthma control in many children with asthma, it follows that reduced frequency of infection should result in better asthma control. Although, we did not examine the frequency of ARI episodes (home-based, self-reporting of acute respiratory infections can be unreliable), we did not observe any benefit of pidotimod on asthma control. In yet another recent trial, pre-school children (3-6y) with recurrent respiratory infections, were randomized to four arms viz., pidotimod plus bifidobacteria, pidotimod plus placebo, bifidobacteria plus placebo or double placebo, administered during the first 10 days of the month for four consecutive months. Those who received pidotimod (with or without bifidobacteria) had less frequent colds and more symptom-free days [17].

A recent meta-analysis [18] to assess the effects of pidotimod on recurrent respiratory infection in children <14 years, identified several low-quality trials, mostly from China. Those receiving pidotimod had less frequent respiratory tract infection, shorter durations of fever and cough during episodes, and reduced antibiotic usage. However, there were several methodological issues compromising the credibility of the systematic review [18].

A narrative review of 32 studies (24 in children including four studies in asthma), suggested that pidotimod decreased IL-4, and IgE levels, resulting in improved FEV1% and PEF. Those receiving pidotimod also had lesser days with infection compared to the control group [19]. However, the variability in definitions of asthma in these studies, methodological differences, and duration of follow-up, made them incomparable with our study. Another review in children with acute respiratory infections, suggested that pidotimod reduced reinfection (odds ratio 0.20, CI 0.12, 0.33), duration of antibiotics (mean difference -2.65, CI -3.68, -1.6) and absenteeism [mean difference (-2.99, CI -4.03, -1.95) [20].

Although the body of evidence on a potential role for pidotimod in various childhood respiratory conditions is growing, the evidence pool is compromised by poorly-designed trials, inappropriate methodology, and a gap between laboratory results and clinical results. This calls for well-designed studies to address the knowledge gaps.

The strengths of this study were a triple-blinded randomized control design minimizing the risk of bias. Considerable precautions were taken to ensure allocation concealment and blinding. Objective parameters of asthma control were used to assess immediate, short-term as well as longer-term asthma control. These objective parameters included patient-centric observations by parents (recorded in the home-based asthma symptom diary), physicians (performing clinical examination) and respiratory technician (performing PEF). Each type of outcome assessor was unaware of the outcomes recorded by the others. Thus, the combination of patient reported observations combined with professional assessments, minimized observer bias. Frequent follow-up visits ensured that outcome data were collected at least thrice after enrolment. The study was adequately powered to detect statistically significant differences in the primary outcome. Children were enrolled all-round the year, minimizing season bias.

The study limitations include a relatively short period of pidotimod use (8 weeks). This regimen was chosen based on the manufacturer's dosing recommendation, and the absence of sufficient prior data supporting benefit or harm. Spirometry could not be performed in most children, as the instruments available in our institution provide reliable results in those above 8 years of age. Determination of safety was based on parental report of a pre-defined set of symptoms, rather than telephonic or home-based active surveillance.

WHAT IS ALREADY KNOWN?

- Pidotimod is an immunomodulator that improves innate and cell-mediated immunity and helps mount an immune response, thus potentially preventing recurrent respiratory tract infections.

WHAT THIS STUDY ADDS?

- This trial showed that addition of pidotimod for 8 weeks to standard ICS therapy did not enhance asthma control, compared to placebo.

Our study concluded that addition of pidotimod for 8 weeks to standard inhaled corticosteroid therapy did not enhance asthma control, compared to placebo. There were no remarkable safety issues observed.

Acknowledgements: Mr. Deepak Dhawan, Respiratory Technician, Advanced Pediatrics Centre, for performing PEF measurements in the enrolled children. Mrs. Deepika Rechal, Research Nurse, for assistance with enrolment and follow-up of children in this study.
Ethics Clearance: Institute's Ethics Committee, PGIMER; No. NK/4232/MD/481 dated 20 March, 2018.
Contributors: RD: enrolled patients, collected data, interpreted them, and drafted the manuscript; JLM: conceived and designed the study, supervised data collection, revised and finalized the manuscript. He will act as guarantor of the study; MS: was overall in-charge of patient management and helped in manuscript writing. The final manuscript was approved by all authors.
Funding: M/s Wockhardt Limited (Mumbai, India) provided pidotimod and identical placebo, free of cost; *Competing interest*: None stated.

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RESEARCH PAPER

Association of Vitamin A Status With Under-Five Mortality in India

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Received: May 25, 2021; Initial review: August 05,2021; Accepted: September 03, 2021.

Objective: To re-estimate the survival benefit from Vitamin A supplementation (VAS) in India using meta-analysis and to correlate mortality and vitamin A deficiency (VAD) in children aged 6 month to 5 year. **Methods:** Pooled risk ratio (fixed effects model) for mortality reduction with VAS was calculated from available Indian studies. Computed mortality rates in 6 months to 5 years children in Indian states were regressed on VAD prevalence estimates of the states. **Results:** There was no reduction in risk of all-cause mortality with VAS (RR=0.96; 95% CI: 0.89, 1.03). When regressing mortality on VAD in high or low VAD prevalence states, the regression coefficients were discordant. **Conclusion:** No survival benefit was observed for VAS in India from the available literature. The targeting of VAS programs should be given serious consideration.

Keywords: *Deficiency, Policy, Prevalence, Universal supplementation.*

Published online: September 22, 2021; ***PII:*** S097475591600372

The World Health Organization's (WHO) recommendation for high-dose vitamin A supplementation (VAS) in children aged 6 months to 5 years, is for settings where vitamin A deficiency (VAD) is a public health problem, with ≥20% VAD prevalence as evaluated by a low serum retinol concentration [1]. This was assumed to be national condition in India, where universal VAS has been implemented for many years now. An additional and important consideration for implementing universal VAS was a Cochrane analysis [2] that showed a 12% reduction in 6 months to 5 year mortality with VAS [RR (95% CI) 0.88 (0.83, 0.93)]. This survival benefit was assumed to be relevant for India as well.

The recent Comprehensive National Nutrition Survey (CNNS) showed that the serum retinol levels based national VAD prevalence in children was 15.7% (95% CI: 15.2%, 16.3%); which was significantly less than the cut off for identifying VAD as a public health problem [3]. Secondly, the potential survival benefit of VAS would be more relevant to India if it was calculated from Indian studies. The purported survival benefit [2] also merits re-evaluation based on contemporary data, given the impressive decline in child mortality in recent years. Here, we evaluate the potential reduction in under-five mortality attributable to VAS from Indian data, and examine current estimates of 6 months to 5 years mortality (which is the age range of the survival benefit attributed to VAS), in different Indian states in relation to their VAD prevalence [3].

Invited Commentary: Pages 189-90.

METHODS

Meta-analysis of Indian studies: For the meta-analysis, we identified VAS studies conducted in India from the included trials in the Cochrane review [2]. Studies evaluating fortification or weekly low dose supplemen-tation were excluded. Raw data from the identified studies was extracted from the original publications and confirmed from the Cochrane review input [2]. We performed meta-analysis using Review Manager (RevMan) version 5.4.1 software [4]. The pooled effect size of risk ratio (RR) was estimated by inverse variance weighted average, as in the Cochrane review [2]. All study details regarding context, participants and quality are available in the original Cochrane review [2]. A sensitivity analysis was performed with a random effects model.

Association of child mortality with VAD: Infant mortality rate (IMR) estimates for 2018, the last year (2016-2018) of the CNNS that provided the state-based VAD prevalence values [3], were obtained from the Sample Registration System bulletin [5]. IMR data were complete for all States and Union Territories of India. Neonatal mortality rate (NMR) and under 5 years mortality rate (U5MR) data for 2018, for 22 of 30 states (including Jammu and Kashmir), were shared by the Ministry of Health and Family Welfare,

Government of India. Missing state values for NMR and U5MR were imputed from a linear regression of each on the IMR. Mortality in children aged 6 months to 5 years was computed using the following equations (all mortality estimates are per 1000 live births): 6 months to 5 years mortality = U5MR - 0 to 6 month mortality; 0 to 6 month mortality = NMR + [0.5 × (IMR-NMR)], conservatively assuming that 50% mortality in the 1 -12 month age group occurred before 6 months of age.

VAD prevalence estimates in different states were obtained from the CNNS [3], conducted in 30 states and Union Territories of India from 2016 to 2018, using a multistage stratified probability proportion to size sampling design. Serum retinol measurements were made on 9563 children aged 1-5 years. Serum retinol levels were adjusted for C-reactive protein (CRP), as a marker of inflammation using a new probability method [6]. Linear regression analysis of 6 month to 5 year mortality on VAD prevalence was performed for all states, and separately for states with prevalence <20% (upper limit of 95% CI<20%) and for the remaining states.

The potential reduction in under-five mortality that could accrue was estimated by applying attributable fraction derived from the meta-analyzed RR estimates of 6 months to 5 years children to U5MR.

RESULTS

Meta-analysis of Indian studies: Five trials were included in the meta-analysis [7–11]. One study was excluded, as the intervention comprised a small weekly dose of vitamin A [12]. There was no beneficial effect of VAS on mortality with the fixed effects model (**Fig. 1**; RR=0.96; 95% CI: 0.89, 1.03; *P*=0.23; I^2=56%; Heterogeneity *P*=0.06). The findings were similar with the random effects model (RR=0.84; 95% CI: 0.56, 1.26; *P*=0.40).

Association of child mortality with VAD: The R^2 for the regression of NMR against IMR was 93% and for the regression of U5MR against IMR was 98.4%; both regressions had good fits. Missing NMR and U5MR values in 8 states were predicted from these regressions. The calculated national 6 month to 5-year mortality rate was 8.5/1000 births, and for states ranged from 6 to 41/1000 live births (Kerala and Madhya Pradesh, respectively). VAD ranged from 0.7% to 40.8% [3].

Mortality was not associated with VAD prevalence when all states were considered [β= 0.08 (95% CI:-0.04, 0.20)]. However, mortality was negatively associated (**Fig. 2**) with VAD in states with VAD prevalence not <20% β (95% CI) = -0.27 (-0.49, -0.05)]. At the national level, there was no predicted mortality gain that would accrue from VAS, using the pooled RR from the Indian studies of survival benefit with VAS.

DISCUSSION

In present day India, the motivation for continuing the universal high-dose VAS is suspect, particularly when based on a purported survival benefit. Globally, the effect of VAS on reducing child mortality has attenuated [13], and the drop in child mortality rates and the incidence of morbidities associated with VAD [14] all point in this direction.

The present meta-analysis of Indian studies also showed no evidence of survival benefit of VAS. Even if the survival benefit from global studies that were conducted when VAD was rife [2] were used, the absolute risk reduction for 6 months to 5-years national mortality would be 1/1000 live births (95% CI: 0.6, 1.4), translating to a reduction of U5MR (per 1000 live births) from 36 to 35 (95% CI: 34.6, 35.4). The absolute U5MR reduction with this assumption ranged from 0.3 to 1.9/1000 live births across states. Under real life programmatic settings, it is unlikely that any survival benefit will accrue, even with this optimistic assumption.

There are several reasons to conclude that the relation

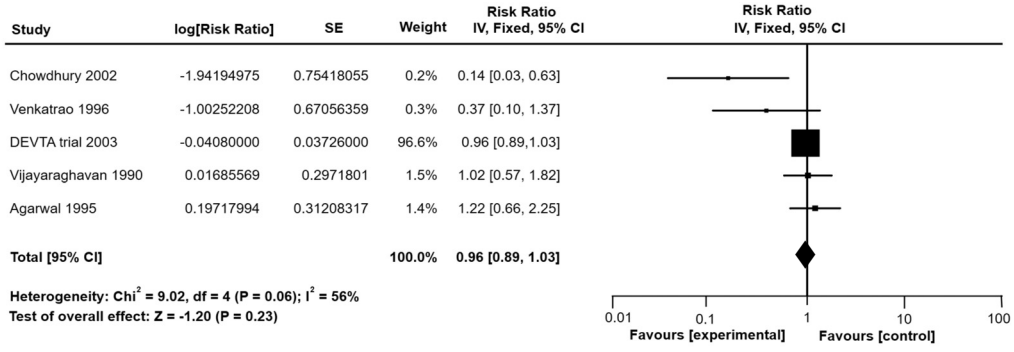
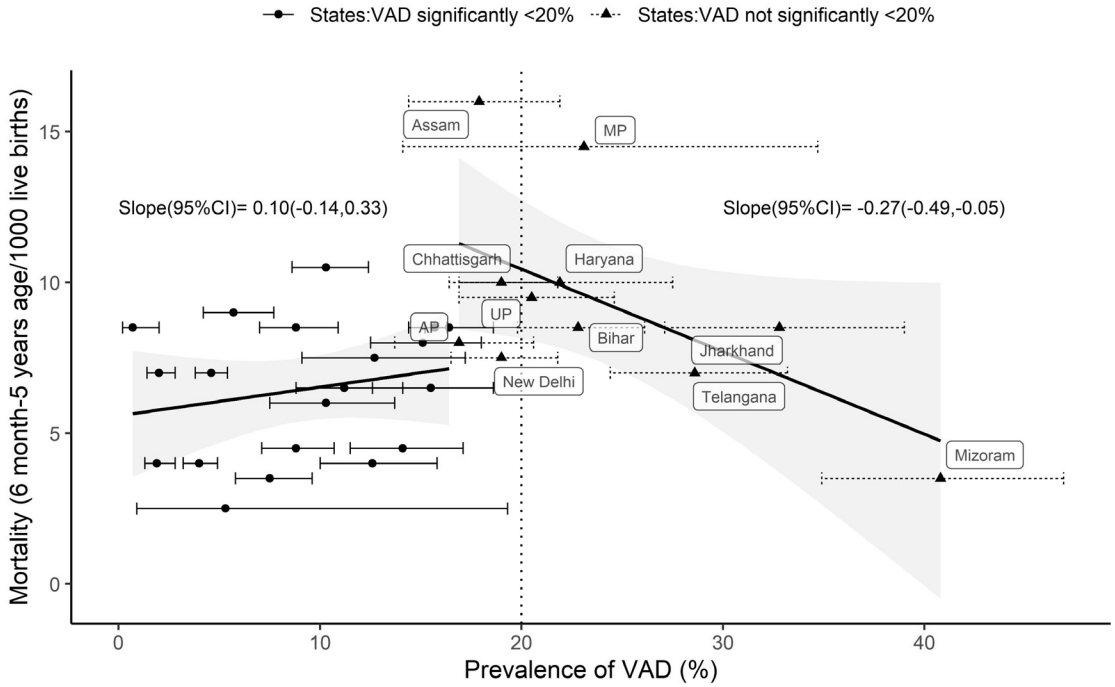


Fig. 1 Fixed effects model meta-analysis of the effect of mega dose vitamin A supplementation on mortality in under-five children in studies conducted in India.

between mortality and VAD does not exist in the present context. Overall, there was an absence of any association between mortality and VAD, when all states were considered. Next, there was discordance in the sign of the regression coefficient of mortality on VAD prevalence, when VAD prevalence was either high or low. Finally, the association of mortality with VAD was counter-intuitively negative in states with higher VAD prevalence. Limitation of this analysis is the use of state level estimates with the likelihood of the ecologically inference fallacy, if individual effects are interpreted based on these aggregate data.

The next step then, is to consider the roll back of the national VAS program, into a targeted program for defined states [3]. The definition of these states could be first, based on the >20% prevalence of VAD cut-off, or for those with higher mortality. A state-based analysis of VAD by Reddy, et al. [3] showed that only three states (Mizoram, Telangana and Jharkhand) had significantly >20% VAD prevalence (based on the lower 95% CI limit being >20%). There were 19 states with VAD prevalence significantly <20% (upper 95% CI limit being <20%). Therefore, in the most rigorous sense, only Mizoram, Telengana and Jharkhand qualify for continuation of VAS, as their VAD prevalence was significantly greater than 20%. Second, one could consider those states whose VAD prevalence was not significantly lower than 20% (where their 95% CI included 20%) in addition to higher (greater than national value) mortality rates. This occurred in the states of Assam, Bihar, Chhattisgarh, Haryana, Madhya Pradesh and Uttar Pradesh (**Fig. 2**). A targeted VAS approach could be considered in these nine states, with surveillance in the other states where VAS can be rolled back.

A similar roll-back approach has been suggested in a recent re-assessment of the need for national VAS programs across different countries [15]. This analysis suggested the cessation of VAS programs based on VAD and mortality data as the first step, which would help targeting limited resources, and then ensuring VAS coverage where required. Further, the decline in child mortality from diarrhea and measles (the morbidities that significantly contribute to VAD-related mortality) is probably because of improvements in nutritional status, water and sanitation, and vaccinations, and the explicit role of VAS in this decline is not clear [16]. In agreement and in conclusion, the Indian national VAS program cannot be justified on the basis of recent estimates of national VAD prevalence, nor based on a survival benefit. There is now a need for serious consideration of a targeted approach to



AP: Andhra Pradesh; UP: Uttar Pradesh; MP: Madhya Pradesh; VAD: vitamin A deficiency. Circles: States with VAD prevalence significantly <20% (data points represented by circles, upper limit of 95% CI<20%). Triangles: States with VAD prevalence not significantly <20% (data points represented by triangles, upper limit of 95% CI not less than 20%). Error bars indicate 95% CI of VAD prevalence. Dashed vertical line corresponds to the 20% prevalence mark of VAD.

Fig. 2 Prevalence of vitamin A deficiency and 6 month to 5 year mortality in Indian states.

VAS in India, and a potential basis for the targeting of this program has been suggested.

Acknowledgements: Jeswin Baby and Aswathi Saji in mortality estimation.
Ethics clearance: This study was conducted with publicly available secondary data. The details of ethics clearance for data collection are reported elsewhere.
Contributors: HPS,UK: were involved in the data acquisition, analysis, drafting the work; SG: involved in analysis and interpretation of data, revising the manuscript critically for important intellectual content; TT,AVK: involved in conception of the work, analysis and interpretation of data, revising the manuscript critically for important intellectual content and final approval of the version to be published.
Funding: None; *Competing interest*: None stated.

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ERRATUM

Please note the following correction in the Recommendations section titled "Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets" published in Indian Pediatr. 2020;59:142-58.

The 10th line in the abstract should be "Vitamin D supplementation in doses of 400 IU/day is recommended during infancy; however, the estimated average requirement in older children and adolescents (400-600 IU/day) should be met from diet and natural sources like sunlight." in place of "Vitamin D supplementation in doses of 400 IU/day is recommended during infancy; however, the estimated average requirement in older children and adolescents (400-600 IU/day, respectively) should be met from diet and natural sources like sunlight."

Appropriate corrections have already been done in the web version at https://www. indianpediatrics.net/feb2022/173.pdf on March 2, 2022.

ERRATUM

Please note the following correction in the 'Reviewers for 2021' published in Indian Pediatr. 2022;59:173-74. The name of Dr. Bhavna Dhingra, who reviewed articles for the journal during this period, was missing from the list.

Appropriate corrections have already been done in the web version at *https://www. indianpediatrics.net/feb2022/142.pdf* on March 2, 2022.

RESEARCH PAPER

Correlates of Breastfeeding in Villages and Tea-Gardens in Assam, India

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Received: July 05, 2021;
Initial review: August 19, 2021;
Accepted: December 03, 2021.

Objective: To observe and compare breastfeeding practices in villages and tea-gardens. **Methods**: Analytical cross-sectional study among mothers of infants in a health and demographic surveillance site in Dibrugarh, Assam. **Results**: 1435 mothers (855 from tea-gardens, 580 from villages); and 1437 infants (857 from tea-gardens, 580 from villages), were included in study. Mean maternal age was 25.1 (4.4) years in tea-gardens and 25.8 (4.9) years in villages. Timely initiation of breastfeeding was higher in villages (82.6%) than tea-gardens (76.4%). Feeding colostrum was higher in villages (71.2%) than tea-gardens (60.8%). **Discussion**: Factors affecting breastfeeding were different in villages and tea-gardens. Timely initiation of breastfeeding was associated with nuclear family in villages and joint family in tea-gardens. Hence, interventions promoting breastfeeding practices should be tailored instead of one-size-fits-all approach.

Keywords: *Assam, Health and Demographic Surveillance System (Dibrugarh-HDSS).*

Published online: January 05, 2022; ***PII:*** S097475591600391

Globally, only about 40% of infants below 6 months are exclusively breastfed [1], and there is a low awareness of optimal breastfeeding-practices [2]. There is evidence suggesting endorsement of early initiation of breast feeding as a cost-effective intervention, which would reduce 1.45 million deaths translating to 22% neonatal deaths in developing countries [3]. Infant mortality rate (IMR) in Assam was found to be 48/1000 live births with a huge rural-urban disparity (20 in urban vs 58 in rural) [4].

In India, the breastfeeding practices are influenced by the traditions, customs, rituals and taboos [5]. Tea-garden community, socio-culturally different from the native village population, is a distinct community in Assam constituting 18% of total population. Studies on practice and determinants of breastfeeding, which is expected to be different in different communities would be of immense importance to acknowledge and address the barriers that may exist. This study was undertaken to observe and compare the breastfeeding practices among mothers of infants in villages and tea-gardens of Dibrugarh district of Assam.

METHODS

This was a cross-sectional study based on the data collected during a baseline survey for establishment of a Health and Demographic Surveillance System in Dibrugarh district (Dibrugarh-HDSS) of Assam by Indian Council of Medical Research, Regional Medical Research Centre, North-Eastern region (ICMR-RMRC NE). Dibrugarh-HDSS covers 60 villages and 20 tea-gardens with a total of 1,06,769 individuals (22,536 households). For this communication, all mothers living in the study area with children under one year of age were included; 1437 infants born to 1435 mothers during March, 2019-February, 2020 were recorded in Dibrugarh-HDSS. Mothers of infants providing informed consent were included.

Invited Commentary: Pages 191-92.

Data were collected using a structured, interviewer-administered, app-based questionnaire in a unique geo-tagging- enabled mobile application in tablets provided to the trained surveyors. The questionnaire was first translated to Assamese language and then retranslated to English, to maintain consistency of questions.

The breastfeeding practice variables (time of initiation, colostrum and pre-lacteal feeding) and history of delivery were obtained from the mothers. All the documents pertaining to the history of childbirth were examined. The family information was obtained from the head of the family or the key informant.

Statistical analysis: Data collected through mobile tablets were stored in ICMR-RMRC server, which was then

extracted in Excel-format and further exported to SPSS (ver. 26.0, IBM) for analysis. For descriptive statistics, frequencies and cross-tabulations were generated. Bivariate regression analysis was done to find the risk-factors associated with the dependent-variables and Odds Ratio(OR) with 95% confidence-intervals were obtained. Significance was considered when $P \leq 0.05$.

RESULTS

We report 1435 mothers (580 in villages and 855 in tea-gardens) with 1437 infants (580 in villages and 857 in tea-gardens) in the study area. The mean maternal age was found to be 25.4 (4.7) years [25.1 (4.4) years in tea-gardens vs. 25.8 (4.9) years in villages]. **Table I** represents the socio-demographic characteristics of the mothers.

Most of the deliveries were institutional and attended by doctors in both the groups. There were more non-institutional deliveries in tea-gardens as compared to the villages (3.9% vs 0.9%). Almost similar proportion of women in both communities had adequate antenatal checkups. There were significantly higher number of assisted births or Caesarean sections in women from the villages than tea-gardens (21.9% vs 10%). The incidence of low birth weight was also found to be higher among tea-garden than village community (34.3% vs 24.5%). **Table II** demonstrates that a significantly higher proportion of infants had delayed initiation of breastfeeding and did not receive colostrum in tea-gardens (23.6%) than villages (17.4%).

Table I Socio-demographic Characteristics of the Study Participants

Characteristics	*Village (n=580)*	*Tea garden (n= 855)*
Age of mother (y) [a]		
≤ 20	52 (9.0)	59 (6.9)
21-30	416 (71.7)	689 (80.6)
31- 40	105 (18.1)	102 (11.9)
> 40	7 (1.2)	5 (0.6)
Religion[a]		
Hindu	543 (93.6)	820 (95.9)
Muslim	32 (5.5)	20 (2.3)
Others	5 (0.9)	15 (1.8)
Nuclear family[b]	472 (81.4)	587 (68.7)
Educational status of mother[b]		
Illiterate	56 (9.7)	308 (36.0)
Upto primary	121 (20.9)	212 (24.8)
High school and above	403 (69.4)	335 (39.2)
Maternal occupation [b]		
Working mother	1 (0.2)	151 (17.7)
Homemaker	579 (99.8)	704 (82.3)
Institutional delivery[c]	575 (99.1)	824 (96.1)
Delivery attended by[b]		
Doctor	366 (63.2)	379 (44.2)
General nurse midwife	64 (11.0)	187 (21.8)
Auxilary nurse midwife	108 (18.6)	240 (28.0)
Birth order[c] *(n=1437)*		
First	299 (51.5)	395 (46.1)
Second	222 (38.3)	313 (36.5)
Male sex	306 (52.8)	440 (51.3)
Full term delivery[d]	556 (95.9)	839 (97.9)
Normal delivery[b]	453 (78.1)	771 (90.0)
Low birthweight[b]	142 (24.5)	294 (34.3)

Values in no. (%). [a]P<0.01, [b]P<0.001, [c]P=0.001,[d]P<0.05.

Fig. 1 shows the OR of different variables on timely initiation of breastfeeding and colostrum feeding. Overall, time of initiation of breastfeeding was found to be associated with maternal education, occupation and delivery being conducted by a doctor. In villages, belonging to joint family and delivering a mature newborn were associated with timely initiation (**Web Table I**). Whereas, in tea-gardens, being a homemaker and belonging to a nuclear family were associated with timely initiation of breastfeeding.

DISCUSSION

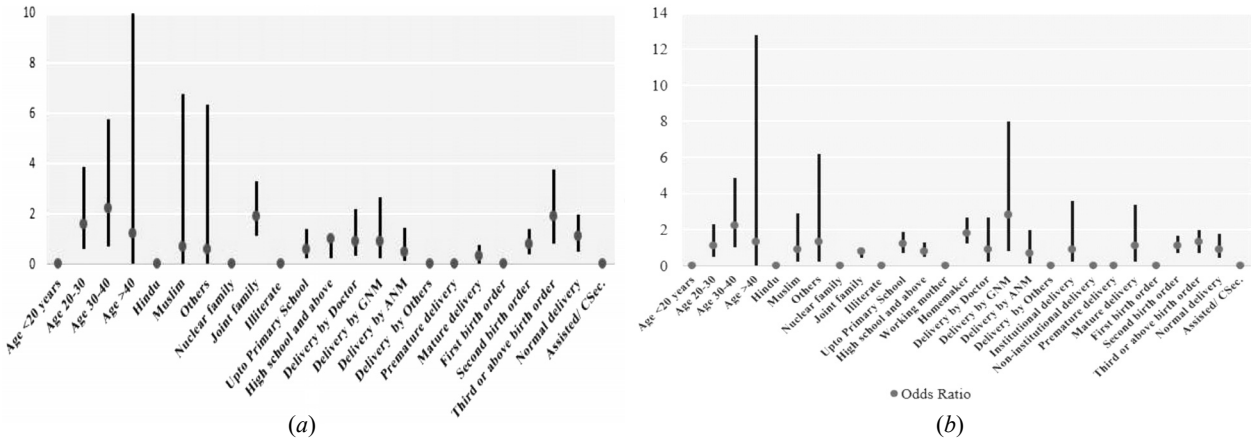
Of the 1435 mothers with 1437 infants surveyed, the proportion of institutional deliveries was low in tea-gardens. The lack of health awareness and education may be considered as factors for low rate of institutional deliveries, which also indicates poor utilization of health services [6,7]. However, this is far better than the state average in both groups [8]. There were a small proportion of births attended by non-medical staff in both groups of women (7.2% in villages vs 6% in tea-gardens). There were significantly higher numbers of cesarian sections in villages as compared to tea-gardens. This might be attributed to poor awareness and utilization of services among the tea-garden community [6].

Timely initiation was significantly poorer in mothers from tea-gardens as compared to their village counterparts (76.5% vs 82.6%). Both these figures are; however, better

Table II Breastfeeding Practices Among the Study Participants

Characteristics	*Village (n=580)*	*Tea garden (n=855)*
Breastfeeding initiated[a]		
Within 1 h	479 (82.6)	655 (76.5)
1-24 h	71 (12.2)	170 (19.8)
>24 h	30 (5.2)	32 (3.7)
Pre-lacteal feed given	3 (0.5)	1 (0.1)
Colostrum given[a]	413 (71.2)	521 (60.8)

Values in no. (%).[a]P<0.001.



(*a*) (*b*)

Fig. 1 Distribution of different factors determining timely initiation of breastfeeding in villages (1*a*) and in tea-gardens (1*b*).

than that made by other studies in Assam [5,9]. Many women did not know that they can breastfeed immediately after childbirth [10]. This might be the reason behind some children having delayed initiation of breastfeeding. Mothers, whose delivery was attended by trained medical staff had more odds of initiating breastfeeding timely. In our study, initiation of breastfeeding was independent of maternal education or occupation, in contrast to findings of Gupta, et al. [10].

We found encouraging figures for the proportion of infants fed on pre-lacteals. Only 4 (0.3%) infants were given pre-lacteals. These figures are better than other studies done in Dibrugarh [11,12]. About three-quarters of the mothers fed colostrum to their newborns. (60.8% in tea-gardens vs 71.2% in villages). This is, however, lower than that found by other studies done in this area (86-91.8%) [11,12]. This focusses on the need to explore factors responsible for lower rates of giving colostrum like poor knowledge, common beliefs/myths regarding colostrum, etc. among study communities.

Other studies conducted in this research area have had almost similar findings related to colostrum feeding of babies [9,12-14]. Similar to previous authors [14] we found that the breastfeeding practices were better in homemakers than working mothers [14]. However, the specific impact of these factors in our study needs further exploration. This contrasting findings related to practices in joint families may be attributed to various socio-cultural factors like family structure, values, beliefs, etc. to explore which, further research is warranted. We found that the educational status of mother did not influence the initiation of breastfeeding differing from that found that higher educational achievement influences breastfeeding practices [15]. Complex relationships between education, occupation and breastfeeding practices need to be studied.

The major limitation of this study is the varying recall periods of mother, which may lead to bias. We can conclude that the breastfeeding practices are comparatively better in the villages than tea-gardens which implies that breastfeeding promotion activities in tea-gardens need to be intensified. The study commu-nities had different set of factors determining the breast-feeding practices and thus, it is implied that interventions to promote breastfeeding practices should be tailored to the needs of each population. The institutional deliveries in tea-gardens are comparatively lesser than that in villages. Efforts to promote optimal breastfeeding practices should, in addition to increasing institutional deliveries, focus on the identification of factors that influence the practice and how they can be addressed in a participatory manner. The findings of our study will be useful to plan intervention strategies in the communities for improvement of breast-feeding practices.

Ethics clearance: Institutional Ethics Committee (Human) of Regional Medical Research Centre, North Eastern Region; No. RMRC/Dib/IEC(Human)/2017-18/3710 dated March 20, 2018.
Contributors: RR,PKB: conceptualized the study and finalized the study design; PKB,KB, PC,NB: carried out data collection and analysis was done by PKB, KB, JP and MD. All the authors contributed in data interpretation, draft preparation and review of draft. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Funding: Indian Council of Medical Research; No.5/7/1596/2018-RBMCH. *Competing interest*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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WHAT THIS STUDY ADDS?

- The determinants of breastfeeding are different for specific communities in Assam; hence, intervention to improve breastfeeding practices should be tailored to the community rather than a unitary approach.

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NEWS IN BRIEF

Gene Therapy for the Limb-Girdle Muscular Dystrophy

Dysferlinopathy caused by recessive pathogenic variation in the *dysferlin* gene (DYSF) is designated as Limb-Girdle muscular dystrophy 2B (LGMD2B) or LGMD R2 dysferlin-related. Defective *dysferlin* gene (DYSF) leads to lack of sarcolemmal protein dysferlin, which impairs sarcolemmal muscle repair by reducing secretion of the enzyme acid sphingomyelinase (ASM), ultimately leading to muscle degeneration. Gene therapy is one of the treatment modalities which acts on muscles by, making them capable of producing the missing proteins. But in case of LGMD2B, the large size of the mutated gene and body wide delivery to reach all muscles in the body are the significant challenges in front of researchers. Recently a team of researchers from Center for Genetic Medicine Research at Children's National Research Institute (CNRI), Washington developed a liver specific Adeno-associated virus (AAV) vector with a proposed mechanism that a single *in vivo* dose of an AAV vector produces a secreted version of human acid sphingomyelinase (hASM) in the liver, which then reaches muscles through blood and restores the membrane repair capacity of patient cells to healthy levels. The team demonstrated that hASM-AAV treatment restored myofiber repair capacity, attenuated fibro-fatty muscle degeneration, increased myofiber size, and restored muscle strength in LGMD2B mouse model. Translation of this research into clinical therapy in near future will be of much help to the patients of LGMD 2B.

(*Journal of Clinical Investigation 07 January, 2022*)

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Web Table I Results of Binary Logistic Regression Analysis of the Factors Associated with Giving Colostrum to the Infant

Independent variables	*Adjusted Odds Ratio (CI)**		
	Overall	*Village*	*Tea garden*
Maternal age (y)			
20-30	1.1 (0.3-3.6)	2.6 (0.3-21.9)	0.2 (0.02-2.5)
30-40	1.1 (0.3-3.8)	3.0 (0.3-26.2)	0.2 (0.02-2.5)
>40	1.1 (0.2-6.2)	1.8 (0.1-28.6)	0.5 (0.03-10.3)
Religion			
Muslim	2.0 (1.1-3.6)	3.1 (1.5-6.5)	1.2 (0.5-3.0)
Others	0.8 (0.3-2.1)	1.8 (0.3-11.1)	0.6 (0.2-1.9)
Joint family	0.5 (0.4-0.7)	0.99 (0.6-1.6)	0.4 (0.3-0.5)
Maternal education			
Up to primary school	0.9 (0.6-1.2)	0.7 (0.3-1.3)	1.1 (0.8-1.6)
High school and above	0.6 (0.5-0.8)	0.6 (0.4-1.2)	0.8 (0.6-1.1)
Mother - homemaker[a]	1.3 (1.03-1.7)	-	1.8 (1.4-2.4)
Trained birth attendant			
Doctor	0.3 (0.2-0.5)	0.4 (0.2-0.8)	0.1 (0.05-0.3)
GNM	0.6 (0.3-1.1)	0.6 (0.3-1.4)	0.3 (0.1-0.8)
ANM	0.7 (0.4-1.2)	0.7 (0.3-1.5)	0.4 (0.1-1.0)
Institutional birth[a]	3.3 (1.4-7.7)	-	5.3 (1.7-16.7)
Preterm delivery	0.7 (0.4-1.3)	0.4 (0.2-0.9)	1.0 (0.4-2.9)
Birth order			
Second	0.9 (0.7-1.2)	0.9 (0.6-1.4)	0.9 (0.7-1.3)
Third or above	1.2 (0.8-1.7)	1.8 (0.9-3.2)	0.9 (0.6-1.5)
Normal delivery	1.4 (0.9-1.9)	1.5 (0.9-2.5)	0.9 (0.6-1.6)

[a]The numbers of mothers in villages who are employed and also that of women having non-institutional deliveries are negligible and hence the OR could not be obtained for these variables in villages.

RESEARCH PAPER

Immunoglobulin Profile and Lymphocyte Subsets in Preterm Neonates

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Received: July 15, 2021;
Initial review: September 21, 2021;
Accepted: November 05, 2021.

Objective: We documented the immunological profile of neonates and mothers, and lymphocyte subsets at birth. **Methods**: Consecutively born preterm neonates (26 to 31 weeks gestation) at our level III neonatal unit, fulfilling the inclusion criteria were enrolled. Immunoglobulin levels were assessed in maternal blood and in cord blood along with T cell subsets. **Results**: A total of 115 neonates were enrolled. The mean cord levels for IgG, IgM and IgA, respectively were 5.34, 0.10 and 0.04 g/L and of B, T, NK and NK-T cells were 14%, 71%, 10% and 1%, respectively of total lymphocyte population. Cord IgG and IgA levels showed a significantly rising trend with increasing gestation (*P*=0.005 and 0.02, respectively) but not IgM and T cell subsets. Maternal immunoglobulins were similar in all gestations. **Conclusion**: The cord IgG and IgA increased with increasing gestation but not IgM in neonates.

Keywords: *B cells, Gestation, NK-T cells, T cells.*

Published online: January 05, 2022; ***PII:*** S097475591600389

Preterm neonates, born before 37 completed weeks of gestation, constitute 11% of total births with those born before 32 weeks comprising about 16% of preterm births [1,2]. Preterm neonates are seen to develop sepsis more often; one of the factors being immature immune system. Previous studies on immuno-globulin profile in preterm neonates have documented reduced immunoglobulin concentrations in preterm as compared to term babies. Studies on lymphocyte subsets and immunoglobulins in preterm neonates have had varying results [3-15]. Literature is scanty regarding immuno-globulin and lymphocyte subsets at very low gestation. Hence, our aim was to study the immunoglobulin profiles and lympho-cyte subsets in very preterm neonates at birth, which may have clinical implications.

METHODS

The study was conducted in a tertiary care referral hospital as a single center, observational study in neonates and their mothers after obtaining written informed consent from parents. The study was approved by the institute research ethics committee. All consecutively born neonates with gestation of 26 to 31 week during the study period of 1 year were enrolled. Neonates with severe perinatal asphyxia, suspected or proven chromosomal anomalies, intra-uterine infection and definite immunodeficiency in sibling or parent, and mothers with chorioamnionitis, multifetal gestation, acute febrile illness 4 weeks preceding delivery, on long-term steroids, recent vaccination and TORCH (toxoplasma, others, rubella, cytomegalovirus and herpes) infections were excluded. The gestational age of the baby was assessed from the first day of last menstrual period or first trimester ultrasonography, whichever was available. Postnatally gestational age was confirmed by New Ballard score. Demographic details, gravidity, mode of delivery, HIV (Human immunodeficiency virus) status, TORCH serology and any other infections during pregnancy were recorded for the mother. Neonatal details included birth weight, sex, APGAR and antenatal steroids. Various morbidities during the hospital stay including respiratory distress, sepsis, shock, total parenteral nutrition, neonatal jaundice, feed intolerance and hypoglycemia were recorded.

Each mother's venous blood (2 mL) was collected prior to delivery for immunoglobulin profile (IgG, IgM and IgA). Five mL of cord blood was collected for immunoglobulin profile (IgG, IgM and IgA) and lymphocyte subsets (B cells, T cells, NK cells and NK-T cells). Samples were centrifuged within 24 hours of collection and the separated serum was then stored in refrigerator at -80^{0}C and processed later for immunoglobulins. Lymphocyte subsets were assessed within 24 hours of collection. Serum IgG, IgA and IGM were estimated by endpoint nephelometry on a semi-automated nephelometer MININEPH (The Binding Site).

Lymphocyte subsets (T, B and NK, NK-T cells) were estimated using monoclonal antibodies against CD45, CD3, CD19 and CD16/56. Lymphocytes were gated using CD45 and side scatter, and the lymphocyte subsets were estimated in the gated lymphocyte population. Fifty μL of EDTA anti-coagulated blood was pipetted into a FACS tube and 10 μL

each of fluorochrome labelled CD45, CD3, CD19 and CD56/16 were added to the tube and vortexed for proper mixing of the antibodies with the test sample. The tube was then incubated in the dark for 15 minutes. Following incubation, 1 mL of lysing solution was added to the tube and incubated in the dark for 10 minutes. The tube was then centrifuged at 1200 rpm for 10 minutes, the supernatant was discarded, and the stained cell pellets were washed twice with Phosphate buffer saline (PBS) and suspended in 500 µL of PBS before sample acquisition on a flow cytometer (Navios 2 laser 6 color flow cytometer, Beckman Coulter). Following sample acquisition, data analysis was performed using the Kaluza flow cytometry data analysis software. Lymphocytes were gated on CD45 vs side scatter and the different subsets in the gated lymphocytes were estimated using dot plots and histograms.

In the absence of previous data in very preterm neonates, it was decided to enrol a convenience sample of 25 mother-infant pairs at each gestational age.

Statistical analysis: Statistical analysis was done using SPSS version 22. Comparisons were made by using student *t* test, Mann-Whitney *U* test, Chi-square test and Kruskal-Wallis test as appropriate. A *P* value of <0.05 was considered significant.

RESULTS

A total of 115 neonates and their mothers were enrolled in the study (26 to 27 weeks-18, 28 weeks-22 and 25 each from 29-31 weeks). The demographic details of the neonates are given in **Table I**. The immunoglobulin profile of neonates and their mothers are presented in **Web Tables I** and **Table II**. The lymphocyte subsets of the neonates are given in **Table III**.

The immunoglobulin profile (IgG, IgM and IgA) of mothers and neonates with and without sepsis did not differ significantly. The same was true for lymphocyte subsets in the neonates.

DISCUSSION

The present study noted increasing values of IgG and IgA with gestation. The lymphocyte subsets were not significantly different among the preterm neonates of 26 to 31 week gestation. There was no difference in immunoglobulin profile of neonates and mothers and lymphocyte subsets of

Table I Demographic and Clinical Characteristics of Preterm Neonates (*N*=115)

Variables	*26 wk (n=10)*	*27 wk (n=8)*	*28 wk (n=22)*	*29 wk (n=25)*	*30 wk (n=25)*	*31 wk (n=25)*
Birthweight (g)[a]	846 (169)	913 (121)	1076 (198)	1112 (231)	1189 (217)	1369 (264)
Male	5 (50)	5 (62)	13 (59)	10 (40)	13 (52)	11 (44)
SGA	1 (10)	0	1 (5)	6 (24)	9 (36)	8 (32)
Suspect sepsis	7 (70)	5 (63)	12 (55)	18 (72)	20 (80)	10 (40)
Proven sepsis	0	1 (13)	2 (9)	2 (8)	1 (4)	1 (4)

Values in no. (%)or [a]mean (SD). SGA-small for gestational age.

Table II Immunoglobulin Profile of Mothers of Neonates With Gestational Age of 26-31 Week (*N*=115)

Variables (in g/L)	*26 wk (n=10)*	*27 wk (n=8)*	*28 wk (n=22)*	*29 wk (n=25)*	*30 wk (n=25)*	*31 wk (n=25)*
Immunoglobulin G	7.8 (6.2-11.9)	10.8 (9-12.8)	9.1 (6.8-11.2)	8.8 (7.2-9.9)	8.8 (6.4-10.9)	7.7 (7-9)
Immunoglobulin M	0.99 (0.5-1.4)	0.92 (0.8-1.1)	1.02 (0.8-1.6)	1.2 (0.9-1.5)	1 (0.5-1.5)	1.1 (0.8-1.3)
Immunoglobulin A	1.5 (1.1-1.8)	1.9 (1.6-2.4)	1.5 (1.2-2.0)	1.7 (1.2-2.1)	1.8 (1.3-2.3)	1.7 (1.2-1.9)

Values in median (IQR). All P >0.05.

Table III Lymphocyte Subsets in Cord Blood of Neonates With Gestational Age of 26-31 Week (*N*=115)

Variables	*26 wk (n=10)*	*27 wk (n=8)*	*28 wk (n=22)*	*29 wk (n=25)*	*30 wk (n=25)*	*31 wk (n=25)*
B cell	8.3 (5.1-13.7)	12.3 (8.9-19.2)	12.2 (8.3-22.2)	12.2 (9.4-19.3)	12.6 (8.5-19.1)	12.5 (8.7-18.1)
T cell	77.9 (73.6-84.3)	74.2 (64.7-78.7)	69.9 (61.6-79.5)	71.3 (58.1-80.1)	70.9 (59.9-79.8)	75.0 (65.6-80.8)
NK cell	7.2 (5.9-9.4)	8.4 (6.4-13.5)	10.2 (6.0-14.6)	9.0 (4.5-15.8)	10.4 (6.3-18.7)	7.4 (4.2-13.2)
NK-T cell	0.9 (0.5-1.7)	0.81 (0.5-2.1)	0.49 (0.4-1.0)	0.79 (0.5-1.2)	0.98 (0.4-1.3)	0.7 (0.6-1.1)

Values presented as percentage of total lymphocytes in median (IQR). All P>0.05. NK cell – natural killer cell.

WHAT THIS STUDY ADDS?

- The normal values of immunoglobulins and lymphocyte subsets for neonates of each gestation are presented.

neonates who developed sepsis and who did not.

The immunoglobulin levels in the study were different from that by Boersma, et al. [4]. This was probably due to differences in the gestation ages of enrolled neonates, with lower gestation in present study compared to other studies. Ahmad, et al. [7] reported IgG levels in preterm in two groups (<34 weeks and >34 weeks). The IgG levels in the present study (5.34 g/L) are lower than Ahmad, et al. [7]. (6.41 g/L), the difference probably due to the differences in gestation in enrolled neonates. The study by Ozdemir, et al. [6] enrolled neonates of <28 weeks, 29-31 weeks, 32-37 weeks and ≥38 weeks. The mean (min-max) IgG levels were 3.7 (1.5-9.6) g/L, 5.4 (3.1-8.7) g/L, 6.7 (3.3-11) g/L and 7.9 (4-20) g/L, respectively. Conway, et al. [13] noted a linear correlation of IgG levels with increasing gestation. Our study also showed similar trend. Sharma, et al. [14] found mean (SD) and range of IgG, IgM and IgA values in 40 preterm infants were 11 (1.5) g/L and 9-14 g/L, 0.34 (0.06) g/L and 0.2 to 0.4 g/L, 0.02 (0.03) g/L and 0-0.12 g/L, respectively, which are higher than our study, probably because they included preterm infants of higher gestations up to 36 weeks. Panayotou, et al. [15] studied serial IgA and IgM in cord blood in healthy preterm neonates of 28-35 weeks of gestation and found that IgA was absent in most cord blood samples. This was in contrast to the presence of IgA in cord blood samples in the present study. As IgM does not cross placenta and hence high cord IgM may reflect underlying intrauterine infection however we had very low value of IgM in our study.

When comparing lymphocyte subsets, there were no studies that had separate values at each gestation. Berrington, et al. [8], observed that preterm had 65% T cells, 23% B cells and 7% NK cells in their blood. These were nearly similar to our study. The T cells and B cells in the study by Quinello, et al. [9] in gestation 30 weeks to 33 weeks were 43.3% and 16.1%, respectively. Our study showed T cells and B cells to be 70.8% and 13.9%, respectively at gestation 30 to 31 weeks. Our study also found no difference in lymphocyte subsets in those who developed sepsis and those who did not. This is in contrast to the study by Bochennek, et al. [12], which showed that neonates who developed sepsis had significantly lower NK cells. The cause for this could not be evaluated.

This study showed that there was no statistically significant difference in the immunoglobulin profile and lymphocyte subsets of the preterm neonates with regards to occurrence of sepsis. However, this study had a small sample size and further studies are needed to establish the normal values of immunoglobulins and lymphocyte subsets at each gestation and their relation to occurrence of sepsis.

Ethics clearance: Approved by the institutional ethics committee no. NK/3996/MD; dated June 28, 2019.
Contributors: KM, RS: conceived the idea of this study; RS, KM, AR, VS, SS: involved in formulating the protocol of this study; RS: collected the samples for this study. The samples were processed in the laboratory under guidance of AR and SS. RS, KM, AR, VS, SS were involved in the writing of this manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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CLIPPINGS

Age adjusted N-Terminal-proBNP (NT-proBNP) to predict major adverse cardiovascular events (MACE) in children *(J Am Coll Cardiol. 2021;78:1890–1900)*

Despite being a valuable prognostic biomarker, NT-proBNP is not established as a prognostic biomarker in pediatric cardiac diseases due to strong age-dependency of its value. In this study, including 910 children with congenital heart disease (CHD), zlog values of NT-proBNP were utilized for age independent evaluation to determine its prognostic power for major adverse cardiovascular events (MACE) (death, resuscitation, mechanical circulatory support, or hospitalization due to cardiac decompensation) in children with CHD. During a median follow up period of 6 months, MACE occurred in 138 children. High zlog NT-proBNP values (>+3.0) were strongly associated with adverse events (adjusted HR 21.1; 95% CI 2.9-154.2, P<0.001). A cut off value of +1.96 achieved a negative predictive value of >96%. Hence, zlog NT-proBNP may play an important role in future management of children with heart disease.

2021 PACES Expert Consensus Statement on the indications and management of cardiovascular implantable electronic devices (cieds) in pediatric patients *(Cardiol Young. 2021;31:1738–69)*

Disease substrates and indications for cardiac implantable devices differ widely among pediatric and adult patients. Therefore, adult guidelines cannot be extended to pediatric population. In 2021, Pediatric and congenital electrophysiology society has released expert consensus statement on the indications and management of cardiovascular implantable electronic devices for appropriate use in pediatric patients. These include indications and management of permanent pacemaker in congenital and acquired heart block; implantable cardioverter defibrillators and insertable cardiac monitors for patients <=21 yr age.

Unification of clinical and administrative nomenclature for pediatric and congenital cardiac care– International Pediatric and Congenital Cardiac Code (IPCCC)-2021 and ICD-11 *(Cardiol Young. 2021;31:1057-1188)*

Development of classification schemes specific for congenitally malformed hearts began with Dr Abott's atlas in 1936. Over the years various attempts have been made to classify the congenital heart diseases and currently International Pediatric and Congenital Cardiac Code (IPCCC) has been incorporated as such in the eleventh revision of International Classification of Diseases (ICD-11). The total number of pediatric and congenital cardiac terms in ICD-11 is 367. This global system of nomenclature for pediatric and congenital cardiac care unifies clinical and administrative nomenclature.

Outcome of COVID-19-positive children with heart disease: A Multi-centric Study from India (*Ann Pediatr Card. 2021;14:269-77)*

From pediatric cardiac centers across India, authors retrospectively studied 94 children and grown-ups with congenital heart disease. One third of patients were symptomatic for COVID-19 and the remaining were incidentally detected positive on screening. Overall mortality in the cohort was 13%. Among the patients who required admission mortality rate was 28%. The risk factors for mortality were disease severity at admission and low socio-economic status.

AHA scientific statement for treatment of myocarditis in children *(Circulation. 2021;144:e123-135)*

Myocarditis in children is a challenging disease and its diagnostic workup, management and follow up are complex with not much evidence. In this scientific statement, authors have defined myocarditis into four strata as biopsy proven, cardiac magnetic resonance (CMR)-confirmed clinically suspected, clinically suspected, and possible myocarditis. The writing group has comprehensively mentioned the current evidence for the role of various investigations and management including medical stabilization and interventions like ECMO, ventricular assist devices and cardiac transplant.

Efficacy and safety of propranolol in infants with heart failure due to moderate-to-large VSD *(Ann Pediatr Card 2021;14:331-40)*

This randomized controlled trial aimed to assess the efficacy and safety of propranolol in 80 infants with heart failure due to moderate to large ventricular septal defect. The primary end-point was the composite all-cause mortality, hospitalization for heart failure, and/or chest infection and referral for surgery. Propranolol in addition to conventional therapy significantly decreased the risk of hospitalization and worsening of Ross heart failure class. There was a trend towards improvement in the primary composite end-point. Therapy was tolerated well without any significant side effects.

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Web Table I Immunoglobulin Levels in Cord Blood of Neonates With Gestational Age of 26-31 Week (*N*=115)

Variables	*26 wk* *n=10*	*27 wk* *n=08*	*28 wk* *n=22*	*29 wk* *n=25*	*30 wk* *n=25*	*31 wk* *n=25*
Immunoglobulin (g/L)[a]	4 (2.7-4.8)	3.7 (3.3-6.7)	4.7 (4-5.6)	5.1 (4.2-6.3)	5.6 (4.8-7.2)	5.3 (4.6-7.2)
Immunoglobulin (g/L)[b]	0.09 (0.04-0.2)	0.07 (0.04-0.08)	0.05 (0.04-0.1)	0.06 (0.04-0.08)	0.06 (0.04-0.08)	0.09 (0.07-0.1)
Immunoglobulin (g/L)[a]	0.03 (0.03-0.05)	0.03 (0.03-0.03)	0.03 (0.03-0.03)	0.03 (0.03-0.05)	0.03 (0.03-0.03)	0.04 (0.03-0.06)

Values in median (IQR). [a]P<0.05; [b]P=0.051.

RESEARCH PAPER

Breastfeeding and Readmission for Hyperbilirubinemia in Late Preterm and Term Infants in Beirut, Lebanon

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Received: December 17, 2020; Initial review: February 15, 2021; Accepted: November 3, 2021.

Objective: To determine whether exclusive breastfeeding is associated with readmission of jaundiced newborns. **Methods**: We retrieved medical records of 51 consecutive neonates >35 weeks with jaundice who were readmitted to the hospital, and compared to 164 controls. Data on gender, gestational age, birth weight, mode of delivery, feeding, bilirubin levels and breastfeeding counseling were analyzed. **Results**: 24% babies were readmitted for hyperbilirubinemia reaching phototherapy level. Early term infants had significantly higher risk for readmission compared to term [OR (95% CI) 2.12 (0.99-4.53); *P*= 0.05]. The risk of readmission was lower amongst subjects receiving mixed/formula feeding [OR (95% CI) 0.51 (0.26-0.98); *P*=0.046] odds of readmission decreased for those feeding >8 times per day (OR (95% CI) 0.46 (0.23-0.91); *P*=0.016], and those who stayed in hospital for more than 2 days after birth [OR (95% CI) 0.95(0.93-0.97); *P*<0.001]. **Conclusions**: Ensuring feeding at least 8 times per day and keeping newborns beyond the first 24 hours decreases the chance of readmission.

Keywords: *Breastfeeding frequency, Breastfeeding initiation, Hospital stay, Management.*

Published online: December 29, 2021; ***PII:*** S097475591600383

Indirect hyperbilirubinemia is a commonly encountered problem leading to hospital readmission in the first week after birth. Reports suggest that 28% of neonates are readmitted within the first 30 days after birth [1]. Major risk factors for hospital readmission for neonatal hyperbilirubinemia are neonatal hemolysis, first time mothers, and early hospital discharge [2, 3]. Exclusive breastfeeding is reported as another identified risk factor for readmission due to hyperbilirubinemia [4]. In a multicenter study from Lebanon, exclusive breastfeeding and discharge at less than 48 hours were found to be associated with readmission for hyperbilirubinemia [5]. Since exclusive breastfeeding has major benefits in decreasing morbidity and mortality [4], therefore, to reinforce the practice of exclusive breastfeeding, the present study was planned with the objective to investigate the incidence of readmitted late preterm and term infants due to hyperbilirubinemia, and to examine the association between exclusive breastfeeding and readmission to hospital for jaundice.

METHODS

This study of hospital records was conducted at three university hospitals for the period between January, 2010 and December, 2019. Medical records at birth as well as at readmission of all infants born at 35 weeks of gestation or more, diagnosed with hyperbilirubinemia and readmitted for phototherapy within the first 28 days were reviewed as cases. Hyper-bilirubinemia cases were those requiring phototherapy based on a total serum bilirubin level at or above the threshold for phototherapy, considering the gestational age, risk factors and chronological age in hours. Control population of non-readmitted infants for each hospital was chosen by gestational age. Those were infants who developed hyperbilirubinemia (defined as total serum bilirubin level above 8mg/dL) but their level stayed below the threshold for phototherapy). Each of the cases was then matched for gestational age to 3 controls. Neonates admitted to the neonatal intensive care unit (NICU) immediately after birth or readmitted for reasons other than hyperbilirubinemia, had liver disease, or congenital abnormalities were excluded from the study.

Data like gestational age, birthweight, gender, length of stay in the hospital at the time of birth, postnatal age, maternal age, maternal education level, parity, mode of delivery, blood group, mother's blood group, ABO incompatibility and percentage of weight loss were

retrieved from the health record. On the basis of gestational age, the infants were divided into three groups, late preterm (34-36 weeks), early term (37-38 weeks) and term (38-42 weeks), as defined by the World Health Organization [6]. Three resident doctors were trained to collect data from the three sites, all medical records were screened and data was filled in pre-defined formats. For the purpose of the study, variables that were reviewed included feeding methods (exclusively breastfed, exclusively formula fed, or mixed feeding), number of feeds per 24 hours, duration of feed, counseling on breast-feeding (number of counseling notes, presence of lactation consultant), bilirubin levels before and after readmission, and duration of phototherapy, if any. The diagnosis and treatment of hyperbilirubinemia as defined above was determined by the treating physician. Consent from the parents was not required because of the retrospective nature of this study. This study was approved by the Institutional Review Board at each study center.

The sample size for this study was calculated by considering a baseline rate of exclusive breast feeding as 50%. Thus, to detect an 18% difference among the readmitted group, alpha error of 0.05 and power of 80%, a sample size of 120 newborns in each group was calculated.

Statistical analysis: Continuous variables were checked for normal distribution using Shapiro-Wilk test. Comparisons were made using the chi-square test for categorical variables and the Student *t* test or Mann Whitney *U* test for continuous variables. Logistic regression models were used to identify risk factors of readmission and Wald test was done to test the significance of the maternal age and gestational age. The goodness of fit of the models were tested using the Hosmer-Lemeshow test. Multivariate conditional logistic regression model was computed and *P* value <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) version 25.0 was used for analysis.

RESULTS

Out of the 215 neonates with neonatal jaundice, 51 (23.7%) were readmitted within 28 days of discharge; their median (IQR) age of readmission was 126 (94-177) hours and the youngest age of readmission was 1.25 days (**Table I**). Among the readmitted subjects, 32 (62.7%) were full term; 14 (27.5%) were early term and 5 out of 51 (9.8%) were late preterm.

Table I Characteristics of Infants Readmitted Within 28 Days (*N*=51)

Variable	*At initial discharge*	*At readmission*
Age (h)[a]	49.0 (41-66)	126 (94-177)
Weight (g)	3118.9 (353.4)	3104 (365.6)
%weight loss[a]	4.8 (1.4-7.3)	4.5 (2.0-6.2)
Bilirubin level[b]	8.55 (2.8)	11.33 (2.1)

Data represent mean (SD) or [a]median (IQR). [b]prior to discharge.

Bivariate analysis showed that the gestational age, mode of feeding, serum bilirubin level at first discharge, and length of stay following birth were all significant risk factors for readmission (**Table II**). Early term infants had significantly higher risk for readmission compared to term infants. More than half of those readmitted were exclusively breastfed compared to controls (56.9% vs 40.9%; *P*=0.04). Almost 80% of the readmitted subjects were reported to have fed less than 8 times per 24 hours (*P*=0.019). Only one center had a formal lactation consultant. Each additional day of stay was associated with a significantly reduced odds for readmission [OR (95% CI) = 0.96 (0.94-0.97); *P*<0.001]. Hospital stay of more than 5 days after birth was protective for readmission for jaundice [OR (95% CI) = 0.09 (0.03-0.21); *P*<0.001].

On multivariate analysis, duration of hospital stay [OR (95% CI) = 0.95 (0.93-0.97); *P*<0.001] and mixed or formula milk feeding were significantly associated with lower risk of readmission compared to breastfeeding [OR (95% CI) = 0.51 (0.26-0.98); *P*=0.046]. A statistically significant association was seen between delivery mode and number of feeds per 24 hours. Each additional feed per 24 hours was associated with a significantly reduced odds for readmission [OR (95% CI) = 0.46 (0.23-0.91); *P*=0.016]; however, this association was only observed for infants born by vaginal delivery.

DISCUSSION

This retrospective multicenter data showed that lower gestational age, exclusive breastfeeding and shorter LOS after birth are all risk factors associated with readmission for jaundice. Protective factors are mixed feeding (formula and breastfeeding) and frequent breastfeeding. We found that infants who fed more than 8 times per day and those whose mothers received breastfeeding support from nurses or lactation consultants were less likely to be readmitted for hyperbilirubinemia. This is in line with the American Academy of Pediatrics (AAP) reports of increased rates of severe hyperbilirubinemia in exclusively breastfed infants [7], and emphasizes the need for providing specific instructions at discharge that encourages frequent breastfeeding to promote weight gain and decrease hyperbilirubinemia and readmission [8]. Similarly, Kankaew, et al. [9] reported that in 116 neonates, breastfeeding for less than 8 times daily was associated with neonatal jaundice, stressing the importance of recommending breastfeeding every 1 to 2 hours in the first 24 hours after birth [10]. This may be challenging for mothers who

Table II Characteristics of Infants With Hyperbilirubinemia at Discharge

Characteristic	*Not re-admitted (n=164)*	*Readmitted (n=51)*	*AOR (95% CI)*
Gestational age (wk)[b]	39.0 (37-40)	38.00 (37-39)	0.79 (0.64-0.96)
Gestation			
Full term	121 (73.8)	32 (62.7)	-
Early term	25 (15.2)	14 (27.5)	2.12 (0.99-4.53)
Late preterm	18 (11.0)	5 (9.8)	1.05 (0.36-3.05)
Birthweight (g)[a]	3155 (442.51)	3241 (490.0)	1.01(1.00-1.01)
Male	87 (53.0)	26 (51.0)	1.09 (0.58-2.04)
Formula and mixed feeding	97 (59.1)	22 (43.1)	0.53 (0.28-0.99)
<8 feeds/24 hr	62 (37.8)	10 (19.6)	2.49 (1.16-5.32)
Bilirubin level at first discharge (mg/dL)[a]	9.84 (3.65)	8.56 (5.30)	0.83 (0.74-0.94)
ABO incompatibility	110 (67.1)	27 (52.9)	1.81 (0.95-3.43)
Length of stay (h)[b,c]	80.0 (55-118.5)	48.0 (43-67)	0.96 (0.94-0.97)
Length of stay following birth (d)			
1-2	26 (16.0)	26 (51.0)	-
3-4	41 (25.3)	17 (33.3)	0.42 (0.19-0.91)
>5	95 (58.6)	8 (15.7)	0.09 (0.03-0.21)

Data present as no. (%), [a]mean (SD), and [b]median (IQR). [c]Coefficient represents crude OR for each additional day in LOS.

undergo cesarian section delivery, as studies reported that women who delivered by planned section were less likely to breastfeed or were less motivated to initiate and continue breastfeeding [11]. We found that each additional feed per 24 hours reduces the risk of readmission among those infants who were born vaginally. This may be explained by the fact that most infants born by cesarean section received frequent mixed feeding in the first 24 hours after birth.

Lower gestational age as a risk factor corroborates with prior studies [12]. This could be because majority of early-term infants were less likely to be breastfed and mothers less likely to maintain breastfeeding for a long duration [13]. This highlights the need to factor in GA, feeding practices and breastfeeding support when planning discharge and follow up. A combination pre-discharge screening of risk factor scoring and universal screening seems to be the most effective method for identifying infants at risk of hyperbilirubinemia.

Table III Multivariate Logistic Regression Model for Hyperbilirubinemia Readmissions (*N*=215)

Variable	*aOR (95%CI)*	*P value*
Weight (g)[a]	1.0 (1.0-1.0)	0.013
Bilirubin level at first discharge (mg/dL)	0.84 (0.72-0.95)	0.004
Formula and mixed feeding	0.51 (0.26-0.98)	0.046
Feeds/24 h[b]	-	0.02
Vaginal delivery	0.46 (0.23-0.91)	0.016
Length of stay (h)[c]	0.95 (0.93-0.97)	<0.001

Study design adjusts for gestational age, maternal age, and birth hospital. [a]Coefficient represents adjusted OR (aOR) for every increase in 100 g. [b]Interaction between number of feeds per 24 hours and delivery. Coefficient represents aOR for each additional feed per 24 hours. [c]Length of stay following birth.

Prolonged hospital stay after birth was another protective factor found to reduce the risk of readmission. This was similar to previous studies demonstrating decreased readmission risk for those infants who stayed ≥3 days compared to those who were discharged in their first 2 days after birth [10,14]. This is important to address as physiologic jaundice and feeding problems were found to be the leading preventable causes for hospital admission in the neonatal period [15].

Our study has several limitations, covariates in our regression models were purposefully constrained like the contribution of G6PD-deficiency based on the relatively small number of readmissions, which was lower than anticipated and did not reach the needed sample size. Recall bias could not be ruled out due to the retrospective nature of the study. Finally, the results may have limited generalizability as they reflect findings from university hospitals situated in the same city.

To conclude, we found that the readmission risk for neonatal hyperbilirubinemia is independently associated with gestational age, shorter length of stay and inadequate breastfeeding method after vaginal delivery. Identifying infants with these risk factors are crucial first steps in effectively managing infants with or at risk for severe hyperbilirubinemia. Further research is needed to examine

WHAT THIS STUDY ADDS ?

- Insufficient exclusive breastfeeding, along with a shorter hospital stay after vaginal delivery, represent preventable factors of readmission within 28 days after birth for neonates diagnosed with hyperbilirubinemia.

other modifiable determinants of neonatal readmission, and policies are needed to capture admissions to hospitals other than the birth hospital.

Ethics approval: Institutional Review Board at the American University of Beirut; No. PED.LC.12, dated March 14, 2017.
Contributors: HEA, RH: data collection and data curation, writing-original draft preparation; HT: formal data analysis, writing-review and editing; TJ, DAH: data collection, review and editing; LC: conceptualization, methodology, resources, project administration, supervision, validation, writing-review and editing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interest*: None stated.

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NOTES & NEWS

PHOCON 2022

18-20, November, 2022, AIIMS, New Delhi

Annual Conference of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics.

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RESEARCH PAPER

Profile of Neurological Manifestations in Children Presenting With Rickettsial Disease

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Received: April 16, 2021;
Initial review: May 17, 2021;
Accepted: November 03, 2021.

Objective: To study the profile of neurological manifestation of rickettsial disease in children. **Methods**: Review of hospital records was done in a tertiary care hospital for the period from January to December, 2020. Data of all the children fulfilling the inclusion criteria i.e., clinical criteria and serology were retrieved from the hospital records. **Results**: Of the total 7974 children admitted over this period, 178 were diagnosed with rickettsial disease wherein 54 (33.3%) had neurological involvement. Convulsions (59%), altered sensorium (56%), headache (44%), meningeal signs (37%), ataxia, (11%), lateral rectus palsy (7.5%) and stroke (7.5%) were the major neurological manifestations. Cerebrospinal fluid (CSF) analysis done in 30 (55%) children showed pleocytosis [median (IQR) cells 15 (3.75, 50)] with lymphocyte predominance [median (IQR) lymphocytes 11.5 (3, 38.75)] and elevated proteins [median IQR 41.5 (29.75,61)]. Neuroimaging abnormalities noticed were cerebral edema (*n*=7), cerebellar hyperintensities (*n*=5), basal ganglia infarcts (*n*=2) and hippocampal hyperintensities (*n*=1). **Conclusion**: Early recognition of rickettsial infection as a cause of neurological manifestation would facilitate early specific management.

Keywords: *Cranial nerve palsy, Meningoencephalitis, Stroke*.

Published online: January 09, 2022; ***PII:*** S097475591600397

Rickettsial diseases are one among the re-emerging causes of acute undifferentiated febrile illness in several parts of India [1]. Vasculitis is the basic pathogenic mechanism and is responsible for the various manifestations [1,2]. Variable prevalence (28-80%) of neurological manifestations has been reported in rickettsial diseases [3-11]. Early recognition and treatment of rickettsial infection with neurological manifestations is important to prevent the morbidity and mortality associated with the disease.

METHODS

We conducted a review of hospital records of children admitted to a tertiary care hospital in Bangalore between January and December, 2020. 'Rickettsial disease' was the keyword used to search the data in the electronic patient records. Children less than 18 years of age with score more than 14 as per RGA (Rathi Goodman Aghai) scoring system [3], and defervescence of fever within 48 hours of beginning of doxycycline treatment, or positive Weil-Felix test with a single titer above 1:80 or positive IgM/IgG ELISA for scrub typhus (optical density >0.5) with neurological involvement (in the form of headache or irritability or seizures or altered mental status or meningeal signs or focal neurological deficits or cerebrospinal fluid abnor-malities or neuroimaging abnormalities) were included in the study. Children with established alternative etiology of fever were excluded from the study.

A total of 7974 children (<18 year) were admitted in the institution during the study of which 178 had rickettsial disease (RD); 54 of these fulfilled the inclusion criteria. We analyzed the demographic profile, clinical presentations, laboratory investigations, neuroimaging, complications and hospital - outcome in these children. Patients having drowsiness, confusion, stupor, delirium, coma with Glasgow Coma Scale (GCS) score of less than 13 or AVPU scale indicating altered sensorium were treated in the pediatric intensive care unit. A serum sample was sent for Weil-Felix test to the central hospital laboratory (Turnover time 24 hours). Weil felix test was done by Cromatest febrile serodiagnostic (LiNEAR chemicals), Inbios scrub typhus Detect (IgM and IgG ELISA kits).

All children with RD were treated with oral doxycycline 5 mg/kg/day for 5-7 days. Intravenous (IV) doxycycline was used in those for whom oral intake was not possible. Azithromycin 10 mg/kg/day for 7-10 days was used in children who did not respond to oral/IV doxycycline within

4 days of initiation of treatment. All children with neurological involvement were initially treated with IV ceftriaxone, which was stopped if serology was positive for RD. Other symptomatic therapies like antipyretics, anti-cerebral edema measures, intravenous fluids and anti-convulsants were used as per the clinical scenario. Out of 54 children included in our study, CSF analysis was done in only 30 children and neuroimaging (computerized tomography, CT and magnetic resonance imaging (MRI) was done in 22 children only.

Data analysis: Data was collected on a pretested proforma from the hospital patient records and transferred to Microsoft Excel sheet. Mean and standard deviation was tabulated for linear parameters, frequency tables were tabulated for nominal data and analyzed.

RESULTS

Out of 178 children treated as rickettsial disease, 54 (33.3%) had neurological manifestations. Out of 54 children 29 (54%) were males. Mean age of our study population was 7.3 years (SD: 3.62, Median: 7) with youngest child being 1 year and oldest child being 15 years. 51 (94%) children presented between months of August to January, highest incidence being seen in September (*n*=15, 27.85), October (*n*=10, 18.5%) and December (*n*=10, 18.5%).

Fever was present in all the children included in our study with mean duration of 6 days (SD: 3.7 days). Two third (66.7%, *n*=36) of the children presenting with neurological manifestations had fever for 4 days or more. Only 14 (26%) children with neurological manifestation had rashes, out of which two children developed purpura fulminans. Hepatomegaly was noted in 40 (74%) children while hepatosplenomegaly was noted in 9 (17%) children. Edema was present in 30 (55%) children at presentation. Though ophthalmological examination details of all the children could not be retrieved, subconjunctival hemorrhage, petechiae, keratitis, optic disc edema and macular edema were major findings while retinitis with vascular changes were noted in few.

The most common neurological manifestations were convulsions (59%), altered sensorium (56%), headache (44%), irritability and signs of meningeal irritation (37%), ataxia (11%). Lateral rectus palsy was noted in 4 children (7.5%) with three of them showing unilateral right sided involvement while one had bilateral lateral rectus palsy. Right sided hemiparesis was noted in three children while left hemiplegia was noted in one child. Other less common neurological manifestations were titubation, dysdiadokinesia, nystagmus, Slurred speech, dysphagia, dysdiadokinesia and dysmetria suggesting cerebellar involvement. Spectrum of neurological manifestations in rickettsial disease is depicted in **Fig. 1**.

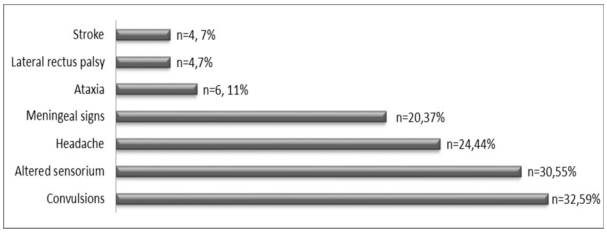

Fig. 1 Neurological features in rickettsial disease.

Anemia, thrombocytopenia and leukocytosis were the major hematological parameters noted while hypoalbuminemia, elevated liver enzymes and elevated C-reactive protein (CRP) were the major biochemical abnormalities (**Table I**). Among the children with elevated liver enzymes, 35 (65%) children had aspartate aminotransferase (AST) elevated more than alanine aminotransferase (ALT), 7 (13%) had ALT elevated more than AST, while 8 (15%) had isolated AST elevation. CSF analysis was done in only 30 children. Elevated protein [median (IQR) 41.5 (29.75) mg/dL], pleocytosis [median (IQR) 15 (3.75,50) cells per high power field] with CSF sugar being normal [median (IQR).53 (46,61) mg/dL] were the notable features in the CSF examination. Cell count was zero in 8 children while lymphocytic predominance [median (IQR) 11.5 (3,38.75)] was noted in 22 children with 17 children showing 100% lymphocytes.

Weil-Felix test was done in all the patients, and 32 (59%) were positive for the test (25 OXK, 6 OX2 and OX19, 1 OX2). Six children tested positive for IgM antibodies while 3 tested positive for IgG antibodies to scrub typhus. Majority (63%) of the children included in our study serologically (positive OXK titers, positive IgM/IgG for scrub typhus) belonged to scrub typhus group. Two children were positive for both OXK by Weil Felix test and IgM for scrub typhus.

Table I Laboratory Profile in Children With Neurological Manifestations (*N*=54)

Parameter	*Value*
Hemoglobin (g/dL)	9.31 (1.26)
Total counts (x10^9/L)	19.56 (2.34)
Neutrophils (%)	65 (16)
Lymphocytes (%)	28 (16)
Platelet count (x10^9/L)[a]	56 (66)
Serum sodium (meq/L)	132 (4)
Serum albumin (g/dL)	2.55 (0.45)
Aspartate aminotransferase (U/L)[a]	152 (107.5)
Alanine aminotransferase (U/L)[a]	114.5 (102.75)
C-reactive protein (U/L)	80.6 (27.24)

All values in mean (SD) or [a] median (IQR).

WHAT THIS STUDY ADDS?

- Association of stroke, cerebellar involvement and lateral rectus palsy in rickettsial disease.

Neuroimaging was done in 22 (41%) children (MRI in 10). Cerebral edema was the most common feature in CT brain which was seen in 7 children, one child showed white mater hypo densities, while CT was normal in 2 children. MRI was normal in 4 children while 5 (4 being positive for IgM scrub typhus) children showed signal changes in cerebellar hemispheres, cerebellar atrophy, two children with stroke showed basal ganglia infarcts and one child showed bilateral hippocampal hyperintensities.

Out of 54 children, 16 children required mechanical ventilation as part of management. Poor sensorium was the most common indication for ventilator support while associated respiratory distress was also noted in 2 children and mean duration of ventilation was 7 days. One child on ventilator support died of refractory septic shock while 15 children recovered from illness. Acute kidney injury was noted among 3 children who eventually recovered. Two children developed purpura fulminants out of which one child had auto amputation of toes bilaterally, while other developed septic shock with ARDS (acute respiratory distress syndrome) with AKI (acute kidney injury) requiring ventilator support but recovered eventually.

DISCUSSION

Neurological involvement in rickettsial diseases occurs typically following bacterial dissemination through the bloodstream and infective vasculitis caused by them. Rickettsia affects small blood vessels, creating central nervous system nodules consisting of glial cells and mononuclear cells around gray matter capillaries. These changes rarely progress to thrombotic occlusion and micro-hemorrhages, thus explaining the rapid reversibility of most neurologic signs [6].

Most common presenting features in our study were seizures and altered sensorium, similar to previous studies from India [7,11]. The clinical manifestations in this study showed higher prevalence of seizures and meningeal signs compared to previous studies [8-10], possibly due to the tertiary-care government healthcare setting of our hospital. Other reasons could be enrolment of only Rocky Mountain spotted fever cases in one study [10], and smaller sample size in the other [8]. CSF findings reported here are also in consonance with the literature [12,15]. MRI in six children with rickettsial disease showed signal changes in bilateral cerebellar hemisphere, which is a new addition to the existing literature [12]. We also report a child with rickettsial encephalitis (Weil-Felix test OXK positive 1:320 titer) with features of raised ICP and isolated 6th cranial nerve involvement. This suggests that cranial nerves can be separately affected by the vasculitis process of RD, as previously suggested by Wai, et al. [14].

As it is a retrospective study, complete data of neurological manifestations, neuroimaging and diagnostic tests of all the children were not available. RD was considered based on Weil Felix test, RGA scoring and response to doxycycline, and only limited children were diagnosed based on confirmatory test.

Rickettsial disease should be considered as etiological agent in acute neurological manifestations, in the appropriate setting, especially in children presenting from endemic areas for these infections.

Contributors: KRA: data collection; SBC: data compilation, statistical and results analysis, discussion writing; MA: introduction and discussion editing; KNV: Discussion and editing of neurological data; KSS: proof reading and editing; GVB: formulation of research methodology, editing of results and proofreading of manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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

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NEWS IN BRIEF

New way to deliver mRNA Vaccines

Needles – Not only children even some adults are also afraid of needle prick. This fear of needle results in low acceptance and adherence with injectable drugs and vaccines. A team of researchers from the Massachusetts institute of technology (MIT) have developed a capsule to deliver injectable drugs directly in the mucosal layer of stomach. In the initial two years, during trials the team had been successful in delivering large molecules like monoclonal antibodies into the stomach mucosa without degradation. Recently they have successfully delivered 150 micrograms of RNA in the stomach of pigs without degradation, which is more than the mRNA present in the COVID-19 vaccines in use at present. Subsequently, the research team documented a successful production of reporter protein by stomach cells. The researchers are now planning to create a systemic immune response in humans, including activation of B- and T-cells, by delivering mRNA vaccines using their capsule. The success of this modality might abolish the need of injection for the delivery of vaccines/drugs in near future, thus helping us to reach our vaccination targets.
(*Matter 31 January, 2022*)

Nano- and Micro-plastics: Danger to our future generations

Recently there are articles on 'Plasticenta' i.e., presence of microplastic particles in human placenta. Plastic, a synthetic material made of polymers, become an integral part of our present day lifestyle due to its features like light weight, durability, chemical and thermal resistance, and low cost. Globally, environmentalists are worried about the impact of plastic and its degradation products on our environment. But what about its effect on our own health? Nano- and micro-plastic particles are <1000 ìm and <1000 nm in size respectively, inside human body these particles can cross through the biological barriers, cause inflammatory reactions in sensitive areas and acts as carriers of various toxic chemicals causing long term effects on human health. As pregnancy, infancy, and childhood are sensitive periods of vulnerability to environmental toxicants exposures. In a recent paper from the Norwegian University of Science and Technology, authors studied the effects of exposure to nano- and microplastics (NMPs) through placental transfer, breastmilk, ingestion, inhalation, and dermal absorption on the health of the newborns and children. Their findings showed that there is a lack of substantial data regarding the effect of NMPs on the health of infants and children, yet they have given recommendations for the policymakers, industry as well as for the families. The important ones includes the appropriate measures to reduce the exposure of the children to NMPs – through steps like removal of the youth involved in plastic waste collection and e-waste burning, reducing the contact of plastic with food items intended for children, regular wet-cleaning of our homes, and careful choice of safer personal care products and building materials etc.
(*Environmental Health Perspectives 26 January, 2022*)

Vaccine against Zika Virus

Since 2015-16, when an outbreak was reported from Brazil, American and African region no treatment is available for Zika virus or its associated disease. It was declared as a public health emergency of international concern by WHO along with the guidelines to prevent its spread. But now a ray of hope has emerged in the form of Zika virus vaccine, which is the result of the collaboration between the Texas Biomedical Research Institute's Southwest National Primate Research Center (SNPRC), Trudeau Institute and Walter Reed Army Institute of Research (WRAIR), where the vaccine is under development. The initial test results of the purified, inactivated Zika vaccine (ZPIV) candidate in non-pregnant animal models, showed its effectiveness in clearing the virus from their blood. While on testing in pregnant mice and marmosets, the vaccine prevented fetal malformations and generated neutralizing antibodies in 80% and 90% cases, respectively. In Phase 1 human trials, it has shown to be safe and able to elicit a protective immune response. Though its, quite early but the results have shown that ZPIV is both potent and durable, and it also has the potential to prevent the harmful consequence of Zika virus infection during pregnancy.
(*npj Vaccines 27 January, 2022*)

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RESEARCH PAPER

Assessment of Causality in Hospitalized Children With Aminoglycoside-Related Nephrotoxicity

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Received: July 21, 2021;
Initial review: August 31, 2021;
Accepted: December 07, 2021.

Objectives: To evaluate the incidence of aminoglycoside-related nephrotoxicity and ascertain drug causality and its risk factors. **Methods:** This prospective study was conducted from January, 2019 to January, 2021, and recruited 110 consecutively admitted children aged 1 month to 12 years, receiving aminoglycosides for ≥4 days. Drug causality was assessed using Liverpool adverse drug reaction causality assessment tool. **Results:** 42 (38.2%) children developed acute kidney injury (AKI), with 71 (64.5%) having composite nephrotoxicity (AKI and/or tubular-dysfunction). Only 17 (15.5%) had AKI definitively attributable to aminoglycosides. Hypotension [OR 0.016 (95% CI 0.01-0.71), *P*=0.03], PRISM-III score 20-29% [OR 55.48 (95% CI 3.66-840.53), *P*=0.004] and post-surgery patients [OR 3.2 (95% CI 1.01-10.1), *P*=0.047] were independent predictors of AKI. **Conclusions:** Only a small proportion of children receiving aminoglycosides had AKI definitively attributable to the drug.

Keywords: *Acute kidney injury, Liverpool assessment tool, Tubular dysfunction.*

Published online: January 05, 2022; ***PII:*** S097475591600390

Aminoglycosides cause acute kidney injury (AKI) due to acute tubular necrosis [1,2]. There is paucity of studies assessing the drug causality of AKI related with use of aminoglycosides. Our study aimed to estimate the proportion of children on aminoglycosides who develop AKI, and to assess the drug causality as well as factors associated with the same.

METHODS

This prospective cohort study was conducted from January, 2019 to January, 2021 at a referral hospital, after approval from the institutional ethics committee. Hospitalized children, 1 month to 12 years old, receiving aminoglycosides for at least 4 days, were enrolled, if estimated glomerular filtration rate (eGFR) (modified Schwartz method) at the time of initiation of aminoglycoside therapy, was ≥30mL/min/1.73 m^2. Exclusion criteria were chronic kidney disease stage 5 or having received aminoglycosides in the previous month.

After obtaining informed consent from the parents, clinical and laboratory details were recorded. Serum creatinine (estimated by enzymatic method, traceable to Isotope dilution mass spectrometry) was measured at enrolment and thereafter, on day 4, 7 and 10 of treatment with aminoglycosides. AKI was defined and classified as per KDIGO guidelines [2,3]. Other biochemical parameters were estimated at admission and at 72-hour intervals, till discharge. Tubular dysfunction was defined as presence of metabolic acidosis (serum bicarbonate <18 mEq/L) with bicarbonaturia (fractional excretion of bicarbonate >10%); or hypophosphatemia (<2 mg/dL) with phosphaturia (low TmP/GFR); or hypokalemia (<3.5 mEq/L) or hypomagnesemia (<1.5 mEq/L) (without an alternative explanation e.g., diarrhea or diuretics); or glycosuria without hyperglycemia. Urine Kidney Injury Molecule-1 (KIM-1) (done on urine samples stored at -40 ^{0}C) was analyzed on day 1, 4 and 7 of aminoglycoside therapy [4] using ELISA kits (ELK biotech).

Aminoglycosides administered included single daily dose of intravenous amikacin at 15 mg/kg/day, or intramuscular streptomycin at 20 mg/kg/day. Dose adjustment was done according to eGFR. Patients were followed-up till discharge/death.

The algorithm of the Liverpool adverse drug reaction causality assessment tool [5] was used to determine whether AKI was due to underlying disease/co-morbidities or the drug per se. The reliability of this tool was assessed by a pilot study in 10 children who developed aminoglycoside-related AKI. Results were judged by consensus within the study group and also by an independent expert. The internal consistency of the tool,

analyzed by using kappa score, was in good level of agreement with the reference study [5].

Statistical analysis: Data were analysed using SPSS-version 20.0. Risk factors associated with amino-glycoside-related nephrotoxicity were assessed by univariate followed by multivariate logistic regression analysis.

RESULTS

Of the 130 children receiving aminoglycosides, 20 were excluded (13 children received aminoglycosides within 1 month; 5 did not give consent; 2 had CKD stage 5). AKI was detected in 42 (38.2%) children. While, at the time of AKI diagnosis, the number of children in AKI stage 1, 2 and 3 were 22 (20%), 10 (9%) and 10 (9%), respectively, the maximum AKI stages developing over the course of hospital stay were seen as 15 (13.7 %) children in AKI stage I, 14 (12.7%) in stage 2, and 13 (11.8%) in stage 3. Only 2 children with AKI were oliguric. The median (IQR) time to develop AKI after aminoglycoside therapy initiation was 7 (4, 7) days.

Tubular dysfunction was noted in 57 (51.8%) children in the form of new-onset hypokalemia in 11 children, hypophosphatemia with phosphaturia in 26, hypomagnesemia in 5, hypocalcemia in 32 and normal anion gap metabolic acidosis with bicarbonaturia in 14 children, the derangements not attributable to concomitant drugs, hypotension or diarrhoea. Thus, composite nephrotoxicity (combination of AKI and/or tubular dysfunction) occurred in 71 (64.5%) children. Urine KIM-1 [median (IQR)] showed significant increase on day 4 [58.82 (35.49, 99.9) pg/mL], as compared to day 1 [1.32 (1.11, 28.96) pg/mL] and day 7 [22.3 (16.72, 36.67) pg/mL] (P<0.001). After a mean (SD) duration of hospital stay of 6.75 (1.6) days, 32 (29%) children had residual renal insufficiency.

Liverpool adverse drug reaction causality assessment tool analysis showed that 17 (15.5%) children had AKI definitively attributable to aminoglycosides, while it was possibly and probably attributable to aminoglyco-sides in another 22 (20%) and 3 children, respectively. Comparison of characteristics between children with AKI and those without, is shown in **Table I.** Children with AKI were older than those without AKI [median (IQR) age 24 (4.75,60) vs 5 (2,24) month; P=0.01] and had greater proportion of hypovolemia, vasopressor requirement and mechanical ventilation.

Multivariate logistic regression showed hypotension [OR 0.016 (95% CI 0.01-0.71), P=0.033], PRISM III score between 20-29% [OR 55.48 (95% CI 3.66-840.53), P=0.004] and requirement of surgical intervention [OR 3.2 (95% CI 1.01-10.1), P=0.047] to be independent predictors of AKI (R^2 34.7%; Goodness of fit P=0.52).

DISCUSSION

We observed AKI in 38.2% of the children receiving aminoglycosides and composite nephrotoxicity in 64.5%. In contrast to previous studies [1,6-9], our patients with aminoglycoside-related AKI were much younger (majority being infants). While more than half of the critically ill children developed AKI in our study, a high incidence of AKI has been reported even in non-critically ill children receiving aminoglycosides [8].

Hypotension, critically ill children, PRISM III score between 20-29% and post-surgery were found to be predictors of aminoglycoside nephrotoxicity. Various risk factors for aminoglycoside-related nephrotoxicity include longer duration of treatment, high initial eGFR, surgery, prior AKI, prolonged hospitalisation [7], vancomycin, high aminoglycoside trough level, heart failure [14], diuretics, hypovolemia, old age [13], initial eGFR <60 mL/min/1.73 m^2, diabetes, iodinated contrast and hypotension [1], most of the studies being in adults. Regional diffe-rences in demography, disease profiles and different AKI definitions could explain differences in these risk factors.

The strength of our study is a reasonably large sample of children studied, using the KDIGO classification for defining aminoglycoside-related AKI. By including tubular markers, we studied nephrotoxicity more compre-hensively. Our study also assessed drug causality of AKI, attributable to aminoglycosides, which has not been studied previously [1,7-9,15]. Our limitations were inability to measure serum creatinine on day 10 in all children. Secondly, as urine KIM-1 values were lower than the limit of quantification, better comparison among children with nephrotoxicity was lacking. We could not perform amino-glycoside drug levels or assess for ototoxicity.

To conclude, the study showed that, though nearly 40% of children receiving aminoglycosides developed AKI, only in 15%, the AKI was definitively attributable to aminoglycosides. The study reinforces the fact that caution must be exercised when using aminoglycoside in hypo-tension as well as in critically ill children.

Ethics clearance: The study was approved by the Institutional Ethics Committee of JIPMER, Puducherry (Approval no. JIP/IEC/2018/447 dated 26.12.2018)

Contributors: MS, SK, NP: managed the patients; MS: collected the data, contributed to protocol preparations and drafted the first version of the manuscript; SK: conceptualized the idea, supervised the data collection and contributed to protocol preparations; NP: supervised the care of the patients in the Pediatric intensive care unit; MR: supervised the laboratory findings. All authors contributed to protocol preparation and approved the final version of the article.

Funding: Intramural grant by JIPMER to SK (JIP/Dean(R)/Intramural/Phs1/2019-20); *Competing interests*: *None stated.*

Table I Characteristics of Children With and Without Acute Kidney Injury (*N* =110)

Characteristics	*AKI (n=42)*	*No AKI (n=68)*	*RR (95% CI)*	*P value*
Age (mo)[a]	24 (4.75-60)	5 (2,24)	-	0.012
Males	27 (64.3)	41 (60.3)	-	0.67
Weight SD score[a]	-1.9 (-3.73, -1.11)	-2.21 (-3.53, -1.19)	-	0.65
Height SD score[a]	-1.46 (-2.48 , -0.41)	-1.44 (-2.88, -0.41)	-	0.85
BMI *z*-score[a]	-1.62 (-4.47,0.11)	-1.87 (-3.93, -0.7)	-	0.97
BMI (m^2)[a]	0.47 (0.28,0.68)	0.32 (0.26,0.47)	-	0.027
Critically ill children	23 (54.8)	17 (25)	3.63 (1.6-8.23)	0.002
PRISM III score 0-19[b]	28 (66.7)	66 (97.1)	16.5 (3.51-77.43)	0.001
Indication for aminoglycoside				
Pneumonia	20 (47.6)	29 (42.6)	1.22(0.56-2.64)	0.61
Urinary tract infection	15 (35.7)	21 (30.9)	1.24(0.55-2.80)	0.6
Meningitis	3 (7.1)	7 (10.3)	0.79 (0.18-3.36)	0.75
Sepsis	2 (4.8)	4 (5.9)	0.8 (0.14-4.5)	0.80
Abscess	1 (2.4)	3 (4.4)	0.53 (0.53-5.25)	0.59
Post cardiac surgery	1 (2.4)	2 (2.9)	2.07(0.81-5.25)	0.12
Aminoglycoside therapy[a]				
Duration	7 (5,7)	7 (5,7)	0.61 (0.2-1.88)	0.42
Dose (mg/kg)	105 (97.5,105)	105 (75,105)	0.61 (0.38-0.98)	0.34
Laboratory parameters[a]				
Initial eGFR (mL/min/1.73m^2)	171.68(135.17,234.32)	115.81 (142,92.81)	0.64 (0.01-62)	0.001
Initial serum urea (mg/dL)	15 (11,21)	17 (12,23.75)	0.7 (0.31-1.54)	0.28
Serum albumin (g/dL)	3.05 (2.47,3.6)	3.5 (3.2,3.875)	0.82 (0.17-3.86)	0.008
KIM-1 (pg/mL) on Day 1	1.29 (1.08,35.98)	1.33 (1.13,1.7)	0.86 (0.39-0.95)	0.65
New metabolic complications				
Metabolic acidosis	7 (16.7)	7 (10.3)	0.62 (0.2-1.88)	0.09
Hypomagnesemia	3 (7.1)	2 (2.9)	0.41 (0.06-2.56)	0.37
Hypokalemia	6 (14.3)	5 (7.4)	0.51 (0.14-1.79)	0.33
Hypocalcemia	15 (35.7)	17 (25)	0.7 (0.31-1.54)	0.23
Hypophosphatemia	14 (33.3)	12 (17.6)	0.59 (0.22-1.25)	0.06
Hypoalbuminemia	12 (28.6)	7 (10.3)	0.36 (0.13-0.98)	0.014
Associated renal disorders[e]				
CAKUT	7 (16.7)	9 (13.2)	1.31 (0.45-3.83)	0.62
Glomerulonephritis	2 (4.8)	0	12.4 (0.17-90.9)	0.25
Shock	14 (33.3)	7 (10.3)	4.35 (1.58-11.98)	0.004
Need for mechanical ventilation	20 (47.6)	14 (20.6)	3.50 (1.5-8.15)	0.004
Need for vasopressors	13 (31)	8 (11.8)	3.36 (1.25-9.01)	0.02
Hypovolemia	14 (33.3)	7 (10.3)	4.35 (1.58-11.98)	0.003
Concomitant nephrotoxic drugs[d]	35 (83.3)	55 (80.9)	1.18 (0.43-3.25)	0.75
Surgical intervention	12 (28.6)	11 (16.2)	2.07 (0.81-5.25)	0.12
Presence of heart disease	4 (9.5)	6 (8.8)	1.09 (0.288-4.11)	0.90
Acute liver failure	3 (7.1)	1 (1.5)	5.15 (0.51-51.3)	0.16
Mortality	7 (16.7)	3 (4.4)	4.33 (1.05-17.8)	0.042

All values are in no. (%) or [a]median (IQR). AKI-acute kidney injury; BMI-body mass index; eGFR-estimated glomerular filtration rate; CAKUT-congenital anomalies of the kidney and urinary tract; PRISM-pediatric risk of mortality score. [b]none had high risk (>29%) PRISM scores; [c]1 child each in both groups had initial eGFR of 35-60 mL/min/1.73m^2; [d]1 child in AKI group had received iodinated contrast; [e]1 child in no AKI group had renal calculi. 2 children in no AKI group had type 1 diabetes mellitus.

WHAT THIS STUDY ADDS?

- Nearly 40% children receiving aminoglycosides develop acute kidney injury, but in only about 15% of them is it definitively attributable to the drug.

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RESEARCH PAPER

Newborn Screening and Clinical Profile of Children With Sickle Cell Disease in a Tribal Area of Gujarat

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Received: August 10, 2021; Initial review: September 21, 2021; Accepted: December 04, 2021.

Objectives: To present the result of newborn sickle cell disease (SCD) screening and clinical profile of SCD newborns in a tribal area of Gujarat. **Methods:** We screened all newborns of sickle cell trait (SCT) and SCD mothers for SCD using high-performance liquid chromatography (HPLC) within two days of birth at a secondary care hospital in a tribal area in Gujarat from 2014 to 2019. Newborns with SCD were registered under an information technology based platform for hospital-based comprehensive care. Neonates were followed prospectively every 3 months. If they missed the clinic visit, a medical counsellor visited them at home to collect the required information. **Results:** Out of 2492 newborns screened, 87 (3.5%) were diagnosed with SCD. Among the 67 newborns screened for alpha-thalassemia deletion, 64 (95.4%) of babies had alpha-thalassemia deletion. We recorded total 554 clinic visits over the period of 221.5 person-years. The rates of acute febrile illness, painful crisis, hospitalization and severe anemia were 42.9, 14.9, 14.9 and 4.5 per 100 person-year, respectively. Two deaths were recorded, and 5 babies (5.7%) had severe SCD. **Conclusion:** We found a high prevalence of alpha thalassemia deletion among newborn SCD cohort in tribal area of Gujarat, and 70% babies had atleast one clinical complication on follow-up.

Keywords: *α-Thalassemia deletion, Follow-up, Mortality, Outcome*.

Published online: January 09, 2022; ***PII:*** S097475591600402

Sickle cell disease (SCD) is most prevalent among indigenous ethnic groups in India. The prevalence of SCD carriers among different tribal groups varies from 1-40% [1-3], with a prevalence of 1-2% among tribal groups in Gujarat [1,4]. Early diagnosis by newborn screening (NBS) followed by comprehensive care, including regular clinical and laboratory check-up and prophylaxis for pneumococcal infection, can reduce the mortality and morbidity among children with SCD [5,6].

Most newborn babies are not screened for SCD in India [7], but the available data suggests that presentation of SCD is varied across regions in India [8-10]. There was a significant loss to follow-up in previous studies, making it difficult to determine the natural history of SCD. The present study was undertaken by systematically following-up a cohort of newborn babies suffering from SCD and receiving comprehensive care.

METHODS

This is a descriptive study of a newborn cohort registered under the comprehensive SCD program in a secondary care hospital managed by SEWA Rural, a non-governmental organization (NGO), in a tribal area in Gujarat. The hospital works as the first referral unit and serves the catchment area of about 1500 villages including 1.5 million population from Narmada and Bharuch districts in southern Gujarat. About 65% of patients are from scheduled tribe population. Inpatient and outpatient care is provided on a highly subsidized basis, or free of cost to the patients [11,12].

A comprehensive care program for SCD was started by SEWA rural in February, 2014 [13,11]. All women visiting the hospital for antenatal care (ANC) were screened for SCD by solubility test and subsequently confirmed by high-performance liquid chromatography (HPLC). The newborn babies born to women with SCD and sickle cell trait (SCT) at the hospital were further screened by HPLC within two days of birth. We used dried spot Guthrie card method or heel prick method to collect the blood sample from the study participants. Hemoglobin analysis was done using automated HPLC on Variant Hb Testing System (Bio-Rad Labs) and Variant NBS (Bio-Rad Labs). Provisional diagnosis of SCD was given by a trained medical doctor based on the HPLC reports. In HPLC reports, if the peak of HbS was higher than HbA,

the baby was marked as SS-phenotype. For all newborns diagnosed with SS-phenotype, the HPLC test was repeated after nine months, and sickle cell status confirmed by DNA analysis.

All the newborns that were diagnosed with homozygous SCD were registered in an electronic registry by a trained counsellor/social worker after informed consent from parents. Parents of each newborn were counselled to visit the clinic once every three months for follow-up care. We followed evidence-based standard protocols for the inpatient and outpatient care of these patients [13]. A trained nurse-counselor collected data and tracked the newborns with SCD. We developed a mobile device application for registration and follow-up. At every visit, the counselor entered the laboratory and clinical data in the application under the guidance of a medical officer.

If any newborn failed to visit the clinic, the device sent an automatic reminder to the counselor, who then telephonically contacted parents of the newborn to remind them to visit the clinic. If the newborn did not visit the clinic for six months, then a trained medical counselor did a home visit of the newborn to collect information. Medical counselors filled the field visit form (which consisted of information about the medical condition of the newborn), collected blood samples and counseled parents to visit the clinic to ensure continuity of care. All information regarding follow-up of field visits (including home visits) were entered in the device by the counselor. The medical officer was responsible for quality assurance. A monthly monitoring meeting of all project staff was scheduled to review the processes.

The information collected at the time of registration and during follow-up included details of hospitalization, painful events, blood transfusion, acute febrile illness, sepsis, severe anemia (hemoglobin <7g/dL), dactylitis, acute chest syndrome, stroke, sequestration crisis, splenomegaly, hepatomegaly, acute respiratory infection, cough and cold, asthma, foot ulcer, and death. Information about interventions including prescription of required medicines and pneumococcal vaccine status was also recorded during each follow-up visit. We defined severe sickle cell disease when a patient had at least three vaso-occlusive crisis or three hospitalization or three blood transfusions [14].

Statistical analysis: The rate of incidence was calculated in 100 person-years (PY). Descriptive statistics was done using Microsoft Excel 2013.

RESULTS

A total of 2492 newborns born between April, 2014 and June, 2019 were screened for SCD. A total of 87 newborns were diagnosed with SCD and registered in the hospital-based sickle cell registry. Among the 67 newborns screened for alpha-thalassemia deletion, 59 (88%) were homozygous (-α3.7/-α3.7) deletions, 5 (7.4%) were heterozygous (-α3.7/5αα) deletions, and 3 subjects (4.4%) were normal (αα/αα) for alpha gene deletion. Only one baby had HbS-β thalassemia. By October, 2019, none of the 87 newborns were lost to follow-up. A total of 544 follow-up outpatient visits occurred; follow-up period was 221.5 person-years. The number of visits ranged from 1-16 based on age of newborn, which ranged from 51 day to five year.

All newborn babies were from scheduled tribe population and parents of 9.2% of the babies were illiterate and 65.5% had received primary education. Most families were either laborers (41.4%) or doing a formal job (21.8%). 64% of the enrolled babies received amoxicillin prophylaxis and 82 (94.3%) received at least one dose of the 13-valent pneumococcal vaccine. Out of 50 children who completed their second birthday during the study period, 30 (60%) received the 23-valent pneumococcal vaccines. All newborn babies received folic acid treatment during follow-up.

Table I shows the incidence of various complications of SCD – 70 (80.5%) newborn babies had at least one clinical complication during the follow-up period. There was no incidence of acute splenic sequestration crisis or stroke. Splenomegaly (*n*=11) varied from 1 cm to 13 cm from the lower costal margin along the axis of spleen. Hemoglobin levels varied between 6.0-14.5 g/dL (average 9.3 g/dL).

Table I Clinical Events During Follow-up in Newborns With Sickle Cell Disease Enrolled in the Study

Clinical event	*Number of events*	*Event per 100 person-years (95% CI)*
Hospitalization	33	14.9 (9.8-20)
Painful events	33	14.9 (9.8-20)
Blood transfusion	7	3.2
Acute febrile illness	95	42.9 (34.3-51.5)
Sepsis	10	4.5 (1.7-7.3)
Severe anemia	10	4.5 (1.7-7.3)
Dactilytis	1	0.5
Death	2	0.9
Splenomegaly	11	5.0 (2-7.9)
Hepatomegaly	1	0.5
Acute respiratory infection	13	5.9 (2.7-9.1)
Cough and cold	150	67.7 (56.9-78.6)
Foot ulcer	11	5.0 (2-7.9)

Total follow-ups 544; total follow-up period 221.5 person-years. There were no episodes of acute chest syndrome, stroke, sequestration crisis and asthma.

WHAT THIS STUDY ADDS?

- Among newborns with sickle cell disease, 95% of babies had alpha-thalassemia deletion and 70% of babies presented with at least one clinical complication during the follow-up period.

Five babies were diagnosed with severe SCD. Four of these had alpha-thalassemia in homozygous condition. All five children were put on hydroxyurea treatment, with no side effects reported. Two children died during the follow-up; a 2-year-old baby was hospitalized with fever, convulsion/unconsciousness, severe pallor, splenomegaly and died within few hours of hospitalization, and another 5-month-old baby died at home after fever, cough, and shortness of breath for two days.

DISCUSSION

In India, very few reports are available on the health-seeking behavior, follow-up visits and coverage of proven interventions among children with SCD. In our targeted screening, 3.5% of the newborns were diagnosed with HbS and started on preventive treatment. Another study from Central India with a similar methodology had 4.5% newborns diagnosed with SCD [10], and the prevalence of HbS-α thalassemia was found 28% among newborn SCD babies in a previous study from Gujarat [9].

Uyoga, et al. [15] reported that in Kenya, the mortality rate for children under five years with SCD was 5.8 per 100 PY. While in a Jamaican sickle cell cohort, 14% of SCD children died before the age of two years when effective intervention strategies were not implemented. We found mortality of <1% in SCD children, when effective intervention strategies were implemented. A study from Gujarat reported that 21.8% children with SCD aged <5 years presented with severe clinical complications [9]. Another study from central India showed that 85% of children with SCD had some clinical symptoms by the age of 5 years and the mortality rate was 3.65 per 100 PY [10]. In our cohort, the mortality was similar to results of the Cooperative Study of Sickle Cell Disease (CSSCD) (1.1 per 100 PY) [22] and Dallas cohorts (0.6 per 100 PY) [16], both studies from developed countries. The lower death rate in Dallas cohort might be due to longer period of follow-up. In the Dallas cohort, if we consider only first six years of life, the mortality rate was 0.81per 100 PY, which is comparable to our cohort.

Infection was a leading cause of death among SCD children and acute febrile event (42.6 per 100 PY) was one of the vital features in our cohort. The similarity between painful events (14.8 per 100 PY) and hospitalization (14.8 per 100 PY) shows the improved care seeking behavior among the parents of the children with SCD. In the Jamaican study, a total of 8% of the children (age range 15 months-14 years) were diagnosed with a stroke. In the Nagpur study, the incidence of stroke was 3.0 per 100 PY [10] while in our cohort, none of the SCD babies had stroke. This lower stroke incidence could be due to the lower age-range of our cohort.

Our study is the first to systematically evaluate a newborn cohort of SCD patients for 3-4 years without any loss to follow-up. It has certain limitations. Firstly, we developed the IT-based technology in December, 2015, which ensured high-quality data entry. Chances of missing data may have been higher and the quality of data may have been affected during manual registrations. Second, as newborn babies were followed up in outpatient clinics and through home visits every three months, this may have increased chances of recall bias.

Our study presents a different genotypic picture of SCD compared to other parts of India. Although, a high prevalence of alpha-thalassemia deletion was seen, majority of SCD newborns presented with at least one clinical complication of SCD.

Acknowledgements: Mr Jitendra Joshi towards his contribution in the development and maintenance of the IT system. Aditi Desai for proof reading for English grammar.

Availability of data: The data that support the findings of this study are available at *https://doi.org/10.6084m9.figshare.14095627*

Ethics clearance: SEWA Rural institutional ethics committee; No. SR/IEC/2017/05/04, dated May 31, 2017.

Contributors: KD: performed experiment, analysis of data and drafted the manuscript; GD, SD: conceptualized the study, finalized the study design, performed experiement and critically reviewed and revised the manuscript; YI, MBM, PM: involved in data collection, interpretation of findings, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding: Anupam Rasayan India Limited. *Competing interests*: None stated.

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Indian Academy of Pediatrics Guidelines on Screen Time and Digital Wellness in Infants, Children and Adolescents

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Justification: Screen-based media have become an important part of human lifestyle. In view of their easy availability and increasing use in Indian children, and their excessive use being linked to physical, developmental and emotional problems, there is a need to develop guidelines related to ensure digital wellness and regulate screen time in infants, children, and adolescents. **Objectives**: To review the evidence related to effects of screen-based media and excessive screen time on children's health; and to formulate recommendations for limiting screen time and ensuring digital wellness in Indian infants, children and adolescents. **Process**: An Expert Committee constituted by the Indian Academy of Pediatrics (IAP), consisting of various stakeholders in private and public sector, reviewed the literature and existing guidelines. A detailed review document was circulated to the members, and the National consultative meet was held online on 26th March 2021 for a day-long deliberation on framing the guidelines. The consensus review and recommendations formulated by the Group were circulated to the participants and the guidelines were finalized. **Conclusions**: Very early exposure to screen-based media and excessive screen time (>1-2h/d) seems to be widely prevalent in Indian children. The Group recommends that children below 2 years age should not be exposed to any type of screen, whereas exposure should be limited to a maximum of one hour of supervised screen time per day for children 24-59 months age, and less than two hours per day for children 5-10 years age. Screen time must not replace other activities such as outdoor physical activities, sleep, family and peer interaction, studies, and skill development, which are necessary for overall health and development of the children and adolescents. Families should ensure a warm, nurturing, supportive, fun filled and secure environment at home, and monitor their children's screen use to ensure that the content being watched is educational, age-appropriate and non-violent. Families, schools and pediatricians should be educated regarding the importance of recording screen exposure and digital wellness as a part of routine child health assessment, and detect any signs of cyberbullying or media addiction; and tackle it timely with expert consultation if needed.

Keywords: *Cyberbullying, Digital technology, Harmful effects, Management, Media addiction, Prevention, Screen-based media*.

Published online: December 29, 2021; ***PII***: S097475591600384

Screen time and digital technology have become an inevitable part of childhood, with shift of learning and socialization to virtual environments [1]. However, concerns on ill-effects of excessive exposure to screen and digital media have emerged. Several professional organizations and World Health Organization (WHO) have issued recommendations on digital wellness and screen-time for children [1-6]. As the scope of digital awareness and content may differ according to cultural and socio-demographic background, guidelines need to be developed in regional context.

PROCESS

In August 2020, the Executive Board of the Indian Academy of Pediatrics (IAP) constituted a task force to formulate guidelines and recommendations on screen time and digital wellness in children. (**Annexure 1**: List of

participants). Nine sub-committees were constituted to conduct detailed search of literature and prepare narrative review of evidence on the following topics: *i*) Definitions and types of digital media; *ii*) Extent of problem of digital media/screen time use by children; *iii*) Importance of digital media; Harmful effects of screen time on *iv*) health, *v*) development and psychology, and *vi*) child safety and security; *vii*) Effective interventions to address screen time and digital wellness; *viii*) Family and societal perceptions; and *ix*) Existing guidelines and legislation related to use of digital media and screen-time.

These sub-committees prepared the first draft of their respective reviews by December, 2020. These were then internally discussed and refined on e-mail with small group meetings of the sub-committees. The second draft was prepared, based on all inputs, and re-circulated to all members. A National Consultative meeting was held on 26 March 2021 on digital platform (Zoom) where all the reviews were discussed, and the deliberations among experts provided the direction to frame the draft of recommendations. The final document was prepared by the Writing Committee after several rounds of revisions and was approved by the IAP Executive Board.

EXTENT OF PROBLEM

Screen exposure is reported as early as infancy in almost all countries. The nomenclature used for defining screen time and types of media is summarized in **Box I** [7-13]. Among under five children, excess screen time prevalence varies from 10% to 93.7% across the high-income countries, and 21% to 98% in the middle-income countries [14]. However, there is inhomogeneity in criteria used to define excess screen time, varying from more than one hour in some studies [15-17] to more than two hours in others [18,19]. Overall screen time ranged from 0.9 to 3.5 hours/day among under five children; 1.0 to 3.1 hours/day among school-aged children; and 1.3 to 7.1 hours/day among adolescents across different studies.

Western Literature

Earlier studies done on screen time reported television as the most preferred and commonly watched screen over other digital-media devices [20,21]. The American Academy of Pediatrics (AAP) statement on media use in school-aged children and adolescents, reported average daily TV time over 2 hours per day in children above 8 years of age. Approximately three-fourths of teenagers owned a smartphone and 25 percent of teenagers were found to be "constantly connected" to the Internet. Social media sites, mainly Facebook, Twitter, and Instagram were being used by 75% of teenagers. Approximately 80% households owned a device used to play video games, boys being the most avid video game players [1,2].

Indian Scenario

Indian studies demonstrate shows a similar trend as western world with initial exposure to screen-based media as early as 2 months of age; and median age of first exposure to screen at 10 months. Most children are exposed to screen-based media by 18 months of age; with greater usage of smartphones (96%) than television viewing (89%). Nearly 65% families keep their television on while having dinner [22]. In another Indian study (2019), four out of five preschool children reported using smartphone devices, primarily for games and videos [23].

In a study among Indian adolescents, three-fourth (76.4%) of them viewed television during mealtime, and only 22.9% had family rules for watching television. Screen time for the vacation and holidays was more than school days (3.9 (2.8) and 3.2 (2.8) hours/day respec-tively). Most used devices were television (96.5%) and mobile phones (56.7%) [24]. A systematic review of Indian studies depicted smartphone addiction among adolescents, ranged from 39% to 44%. [25].

Factors Affecting Screen Time

Many studies have observed and assessed different factors

Box I Definitions of Common Terms Used in Digital Media

- *Screen time/digital engagement time*: Total time spent in watching screens like computers, laptops, tablets, smartphones, television, and handheld video games in a day [7-10].
- *Digital wellbeing/wellness*: Maintaining health of the individual user and the community, in all spheres while using digital media and tools for personal, professional, educational, or recreational purposes. It includes safe and responsible behavior and conduct in digital environments, so as not to harm any living ones or the environment [11].
- *Media*: It refers to different types of mass communication for example print, broadcast, and internet media [12]. These can be divided into traditional (print and broadcast) and newer media.
- *Digital media:* These are defined as a group of media or applications that operate with the use of encoded numeric data formats and allow the creation and exchange of user generated content [13]. It includes blogs, social networking sites, collaborative projects, virtual game worlds, apps, and virtual social worlds. Smart-phones, computers, laptops, and tablets are the devices used to access the digital media [1,2].

associated with increased or decreased screen time in children. Various systematic reviews have identified more than 30 correlates across various age groups [26,27]. Factors influencing screen time can be related to children (age of introduction of screen device, duration of sleep, sedentary preferences, eating in front of screen, fast food consumption); parents and caregivers (parental screen-time and perceptions, working hours, education); and demographics and environment (easier access to digital media, high background television time, number of screen devices at home, socioeconomic status, working of parents from home, lockdown).

HARMFUL EFFECTS OF SCREEN TIME

Parents, pediatricians, and policymakers need to be cognizant of the harmful effects of screen use in children. Television exposure is the most studied electronic media; mobile dependence, internet access, gaming addiction, and social media addiction are some of the other areas of concern.

Obesity

Various longitudinal cohort studies and randomized controlled trials (RCTs) have demonstrated a cause and effect relationship between screen media use and obesity [28]. Watching television for more than 2 hours per day has been shown to cause obesity among preschool children as well [29]. Food advertisement is an important link connecting media time with unhealthy food consumption and subsequent obesity [30]. Other proposed mechanisms of screen exposure and obesity include decreased physical activity, increased intake of high-calorie, low-energy food, and decreased sleep [31]. Sleep deprivation leads to changes in ghrelin and leptin, causing increased hunger and decreased satiety. Short sleep duration leads to increased snacking and eating outside of normal mealtimes, especially at night thereby leading to consumption of more unhealthy calories [31].

Sleep Disturbance

Blue light emitted by electronic media suppresses and disrupts melatonin secretion. Use of light emitting media prior to sleep is associated with decreased subjective sleepiness and suppresses late evening rise of pineal melatonin [32]. Violent or sexual content portrayed in the media can cause excitement, fear or stress in children, leading to delayed onset of sleep. Violent daytime media exposure has also been associated with sleep problems, nightmares and night awakenings, again affecting sleep quality adversely [33]. Social media use and internet surfing was seen to cause maximum sleep onset latency and mid-sleep awakenings [34]. Use of media as sleeping aids was found to be associated with higher fatigue, later time to bed, lesser hours of sleep per week and poorer sleep quality [32-34].

Postural Effects and Visual Disturbances

Most children using a cell phone or laptop tend to have poor posture, with head tilted forward and shoulders stooping forward to look at the screen. This can lead to increased stress around the cervical spine with early wear and tear, and degeneration. According to the American Optometric Association, computer vision syndrome is a complex of eye and vision problems, experienced during or related to computer work. Refractive errors, astigmatism and ocular discomfort are some of the commonest eye problems. Reduced blink rate and amplitude have been consistently reported with screen use, leading to headaches [35].

Cognitive Development

Exposure to adult-directed television content early in life, as well as high background television exposure has negative association with the child's executive functioning and cognitive development [36]. Background television has been shown to impair the quality and quantity of parent-child interaction and disrupt sustained toy play in this age group [37]. A systematic review concluded that children with excess screen time are at a higher risk of delayed language development, learning problems (lang-uage and mathematics), and reading problems [28]. Children older than 6 years are more likely to watch adult-directed media, which can influence anti-social and aggressive behavior, due to exposure to violent content. Changes in aggression can be long-lasting and shape the child's personality. Adolescents who are exposed to violent video games reported increased hostility, physical fights and poorer school performance [38].

Body Image Perception and Emotional Disorders

Negative social comparisons (e.g. getting fewer 'likes' on a social media picture) can lead to worsening body image perceptions and harmful psychological impacts in a vulnerable mind [39]. Early exposure to television at age 1 and 3 years has been associated with attention problems at age of 7 years [40]. Systematic reviews and meta-analyses have demonstrated small but significant associations between social media use and depressive symptoms [41-43].

Drug and Substance Abuse

Exposure to media violence may result in subsequent aggressive behavior and ideas, anger, and arousal [44]. Exposure to smoking in movies is identified as a risk factor for taking up smoking among children [45]. Viewing alcohol advertisements is found to increase immediate alcohol consumption relative to non-alcohol advertisements [46]. Cyberbullying can have strong psychological impact, and seems more strongly linked with substance abuse and

depression as compared to traditional bullying [47]. Sexting is receiving, sending, or forwarding sexually explicit messages or photographs. Teen sexting can lead to unhealthy sexual practices, and perpetration of sexual harassment. It has also been linked to negative outcomes such as depression and low self-esteem [48].

BENEFICIAL EFFECTS OF SCREEN MEDIA

Learning and Social Interaction

For children above 2 years of age, shared use of media between children and parents may help enhance learning interactions. Adolescents find social media useful to develop and nurture friendships [49]. Digital media can promote healthy behaviors and counter undesired effects among children and adolescents [50]. Social marketing campaigns are effective means to promote behavior change, like prevention and control of substance abuse, encouraging physical activities, maintaining healthy diet and prevention of sexually transmitted diseases [51]. According to a systematic review, tailored audio or text messages on cell phones can enable adolescents improve their health-related knowledge, increase compliance to medications and disease monitoring, setting reminders for regular appointments [52].

Other Benefits

Children and adolescents can experience positive emotions and learn moral values through digital media. Digital technologies (watching TV, playing videogames, using computers and smartphones) when used in moderation (<2 to 4 hours/day) may promote psycho-logical and emotional well-being. Preschoolers and early elementary school graders can identify and feel basic emotions like happiness, sadness, anger, and fear port-rayed in digital media. Playing on computer-based games may have additional benefits of enhancing abstract thinking, analyzing information and improve planning, problem-solving skills, scientific reasoning, artistic and creative skills of children and adolescents [53,54].

EFFECTIVE INTERVENTIONS

Interventions have been conducted in the community, school, home/family, and clinics. Mode of intervention varied from providing knowledge, aiming at behavioral change, environmental, or regulatory interventions, or their combinations. Most of the interventions were based on behavior change theories. Most studies were from western world; Indian data is meager. The most effective interventions included those which specifically targeted and set goals for reduced TV viewing or screen-media use, used electronic monitoring devices, contingent feedback systems or clinic-based counseling, had high levels of parental involvement, and/or recruited participants who were already overweight or obese at baseline, had restricted access to the television or computer, or by providing opportunities for physical activity [55,56]. In a systematic review [57] of 21 studies in children between 3 to 11 years, 'TV turnoff week' strategy was documented beneficial to reduce screen time. A recent review of 17 studies [58] suggested that the most effective factors resulting in effective reduction in screen time included long duration of intervention (≥6 months); and conduct in a community-based or preschool/childcare setting.

EXISTING GUIDELINES: GLOBAL AND INDIAN SCENARIO

Global Guidelines

Guidelines and recommendation on screen time have been advocated by various professional societies as well as by World Health Organization [1-6]. Guidelines on screen time were issued by American Academy of Pediatrics (AAP) in 2001 [59] and further modified in 2013 and 2016 so as involve all age groups, from infancy to adolescents [1,2]. Canadian Paediatric Society released similar guidelines in 2017, which were updated in 2019 for older children and adolescents [60]. In 2019, WHO, in its global action plan on ending childhood obesity and promoting physical activity, advocated no sedentary screen time for 1-year-olds and screen exposure of less than 1 hour/day in 2-5 years old; lesser the better [61].

Indian Guidelines

Indian Psychiatry Association in 2020-2021 issued recommendations for media use in children and adole-scents up to 18 years of age [62]. These guidelines advised zero screen time in children <2 years. Between 2 to 5 years viewing for specific purposes like educational games or teaching aid for a limited period (not longer than 30 minutes per session, and not more than two sessions per day, under supervision - a shared media use), rather than for entertainment was advocated. Adult interaction with the child during media use was stressed upon.

During COVID pandemic when screen time became a necessity for online education, PRAGYATA guidelines were issued by the Ministry of Information and Broad-casting in association with National Council for Education, Research and Training (NCERT). Pre-primary children should not be made to sit in front of screens for over 30 minutes while children of Classes 1 to 8 should limit online classes to two sessions (30-45 min duration each) and four sessions (30-45 min duration each) for classes 9-12 [63].

Indian Academy of Pediatrics (IAP) released its parental guidelines for screen time in 2021, which cautioned about the harms of excess screen time and also provided guidelines to parents on the permissible screen viewing time, digital

hygiene, healthy use and the right age for use of various platforms of social media [64].

IAP GUIDELINES AND RECOMMENDATIONS

Based on the review of evidence and existing guidelines from other agencies, and the deliberations during, before and after the meeting, the group arrived at the following consensus guidelines:

A. Guidelines for Children and Families

1. *Infants and children aged 0-23 month*

- Children below 2 years age should not be exposed to any type of screen.
- Screen media (e.g., smartphones, tablets, television) should not be used to facilitate feeding.
- Screen media should not be considered as an easy option to calm a crying/distressed child.
- Families should avoid incidental exposure of child to screen media by not leaving the devices on, and should avoid watching the screen while engaging with the child, or with the child in the same room.
- Parents should look out for and prevent screen exposure in their absence e.g., when the child is being looked after by a domestic help or in a crèche or daycare center.
- Parents should involve child in physical play activities, storytelling, music, movement (dance), and age-appropriate toys to promote early childhood development.
- Minimal and occasional screen time may be allowed for social interaction with close family members staying at distant places.

2. *Children aged 24-59 month*

- Limit screen time to a maximum of 1 hour per day (with each session not more than 20-30 min); the lesser, the better.
- Use only one screen at a time. Do not start a habit of media multitasking.
- Screen time needs to be always supervised by the caregivers. Promote shared use of screen media between child and families to ensure interaction and quality exposure.
- Caregivers should ensure that the content being watched is educational, age-appropriate, non-violent, healthy, and preferably interactive.
- Do not use screen media during meals, within one hour before sleep, or during surface travel.
- Children should have at least 3 hours of physical activities of any intensity (including at least one hour of physical activity of moderate-to-vigorous inten-sity), and 10-14 hours of good quality sleep daily (younger the child, more the sleep duration).

3. *Children aged 5-10 year*

- Limit screen time to less than 2 hours per day; the lesser, the better. This includes recreational screen time, and time spent on screen at home to complete educational and extra-curricular assignments.
- Screen media exposure should be mainly for the purpose of education, learning, and social interaction. Recreational screen time should be kept to a minimal.
- Parents should monitor when children are using screens for education so that children are not straying away from lessons to play games, view online content, or communicate with others online.
- Screens should not be used to overcome boredom. Boredom is an emotion, and should be celebrated and encouraged as the cauldron of imagination and creativity.
- The device used by child should belong to one of the parents, and child should not get an independent phone/tablet/laptop. Modify the home environment by restricting access to the television or computer using a digital control device.
- Co-view and monitor use of digital media by children to ensure appropriateness of content, and children's safety and security.
- Encourage and reward appropriate use of screens. Discuss with them strategies and reasons to reduce screen time. Teach children to record their own screen time and ask them to inform parents and adults in the family, immediately, about any inappropriate or disturbing material/messages viewed online. Do not permit the use of social media by the child except to catch up with educational, sports and extra-curricular assignments. Children and young adolescents are not mentally ready to handle social platforms such as Facebook, Twitter, WhatsApp, Instagram etc.
- Screen time must not replace study time, play time, sleep time, family time or 'me' time. Children of this age should have 9-12 hours of sleep, and at least one hour per day of physical activity of moderate-to-vigorous intensity.

4. *Adolescents (10-18 years age)*

- Balance screen time with other activities that are required for overall development. These activities include at least one hour of outdoor physical activity

(playtime), 8-9 hours of night-time sleep, and time for schoolwork, meals, hobbies, peer interaction and family time. If any of the above activities is compro-mised due to screen time, then screen time needs to be appropriately reduced to accommodate the same.

- Educate adolescents about safe and healthy use of screen devices. Most of the screen time should be related to education, communication, skill develop-ment and promoting healthy lifestyle and safety.
- Monitor media use by adolescents and ensure that they are not using/downloading any violent or undesirable content. Discuss the content with them and use this opportunity to instill media literacy (promote critical thinking to interpret media messages), values, healthy and safe lifestyle, and knowledge of cyberlaws and strategies to detect fake news and messages.
- Monitor social media use by adolescents to ensure data privacy, cybersecurity, and detect any signs of cyber-bullying or media addiction. Most apps and media are linked to email account, especially the offensive or adult content. All the content can be monitored and seen by checking what a child is doing by monitoring the email.
- Ensure that screen use is not interfering with their academic performance, mental health, talent develop-ment, and acquisition of values. If it is, regulate the screen use appropriately. If that does not work, consult the pediatrician for guidance.
- Parents should update themselves regarding new technology so that they could effectively monitor the media use by adolescents and can detect any inappro-priate activity. They should have passwords and ability to access all online accounts at any time to protect and teach youngsters about their digital footprint.
- Before allowing adolescents to use a social media platform/video game, parents should familiarize them-selves with it and allow only if they think it is appro-priate for age.
- Parents should act as a role model to promote digital wellness in the whole family. They need to limit their screen time and be a role model for children and adolescents.

5. Guidelines for healthy use of media

Parents should talk to children regarding healthy use of media before permitting them to use gadgets and make them responsible digital citizens. They must formulate clear rules about the online content that is apps, social media sites and games that they are allowed to access.

Children feel secure and are able to self-regulate better when boundaries and rules are laid down for behavior. Parents should formulate 'digital rules' to encourage healthy media usage when their child begins to use a digital device. These should be age appropriate and new rules could be added as the child becomes older. This needs to be monitored and reviewed with the child regularly. A few more rules for maintaining 'digital hygiene' are:

- Ensure a warm, nurturing, supportive, fun filled and secure environment at home. Children follow rules if they are guided in a respectful and empathetic manner.
- Screens should be switched off 1 hour before bedtime as blue light emitted from devices suppresses melatonin secretion necessary for healthy sleep.
- Adopt the correct posture while sitting in front of the computer and the mobile phone [64]. To reduce eye strain and dryness of eyes, it is important to follow 20-20-20 rule (see screen for 20 min, take a break for 20 sec, and look at an object 20 feet away).
- Avoid multitasking. While doing offline homework, all screen devices should be switched off.
- Avoid programs and games with violent content. Ensure proper privacy settings on the computer, safe search engines on browsers and apps, and anti-virus software, but do not depend on them as children can easily hack around them. For young children, install protective software to restrict access to inappropriate websites.
- Use 'teachable moments' on the media to convey family values, healthy lifestyle and interpret media messages. For example, irresponsible sexual behavior leading to unwanted pregnancy can be talked about while or immediately after co-viewing programs showing casual sexual encounters between teens.
- Mark digital free zones like bedroom, dining table, kitchen, bathroom, and motorized vehicles where no family member uses a gadget.
- Decide upon a digital fasting time when no family member uses any device and utilizes that time for family bonding. The schedule for such digital fasting (short daily breaks or/and longer weekend breaks) can be deci-ded through mutual convenience of family members.

Parents should role model healthy media use, formulate a family media usage plan and teach online etiquette. These are listed in **Box II.**

B. Guidelines for Pediatricians

- Screen media should not be used to distract the child to facilitate examination and procedures.
- During routine well child and adolescent visits and

immunization visits, pediatricians should ask/observe the parents and adolescents about their screen exposure practices and impart anticipatory guidance to follow age-appropriate digital wellness guidelines.

- Provide written/printed material to families for appropriate use of screens and promote digital wellness. Display IEC material (preferably non-screen) in the clinics to educate families about digital wellness.
- Encourage non-judgmental communication with parents, children, and adolescents. Involve them in decision making regarding how best to reduce screentime and mitigate ill effects of unhealthy media usage that may be already occurring in the children and/or families.
- Involve both parents during educational/counseling sessions while discussing the strategies to reduce screen time for their children.
- Children above the age of 5 years and adolescents should be interviewed in private and with confidentiality regarding details of screen usage, duration, frequency, and content of programs viewed and its effects on their activities of daily living and development. They should be screened for cyberbullying, online sexual harassment and media addiction. They should be motivated to follow healthy media usage.
- All children failing the maximum permitted limits of viewing screens should be followed up subsequently during next visit or telephonically. Those detected with media addiction should be referred to a mental health professional.
- Educate other community members about impact of screen media on child's health and development and promote digital wellness and role modeling in the society.

C. Guidelines for Schools

- Ensure that screen-based devices (e.g., smartboards, LED screens) are not the only tools used for teaching-learning activities. Use a mix of conventional instructional media (e.g. chalk and board, whiteboard, flipcharts) and digital tools for education. Do not promote screen-based devices as the primary or best mode of teaching-learning.
- Ensure that online educational content, only

Box II Online Etiquette and Safety

Children and Adolescents

- Follow the golden rule of interpersonal relationships; treat others as you want yourself to be treated. Never post hurtful messages. Disagree politely.
- Use the right language for communication. Avoid the use of swear words. Do not use all caps while typing as it implies that you are screaming.
- Do not post private information like home address, passwords, personal photograph, and family and school details.
- Respect the copyright laws and do not download or copy without permission.
- Think before you type, post, and share to check if it is true, kind and legal. Before posting a picture, discuss with a parent. Do not post inappropriate material. Anything posted online cannot be erased completely as it leaves a digital footprint.
- Never meet a digital friend in person alone whom you have never met before.
- Make internet a safe place by reporting online misbehavior to trustworthy adults.
- During online schooling, maintain the decorum of the class, wear proper attire and follow the instructions of the teachers.

Parents

- Teach, monitor and role-model good online manners as above.
- Whenever an incident of cyberbullying or online misbehavior is detected.
  - o Reassure your child that you love him/her and will help.
  - o Ask the child to take a break from the online world.
  - o Block the sender.
  - o Do not respond to the hurtful message.
  - o Save the message to enable reporting.
  - o If you know the bully, try talking to the parents.
  - o Contact the school teacher to inquire about bullying in school. Most schools have anti-bullying policies.
  - o Try contacting the digital platform provider to block and report the bully. If bullying does not stop, report to the cyber police.[a]

[a]*Cyberbullying, sexting and online sexual solicitation are cybercrimes and can be reported at cybercrime portal of Government of India (https://www.cybercrime.gov.in).*

supplements and does not replace the routine teaching-learning and physical activities in the schools, except during disasters and calamities when school attendance is not possible. In case online education is the only option, schools should follow PRAGYATA guidelines issued by Department of School Education and Literacy. Ministry of Human Resource Develop-ment, Government of India (*https://www.education. gov.in/sites/upload_files/mhrd/files/pragyata-guidelines_0.pdf*).

- Minimize assignments, homework, and evaluations that need use of screen, especially for children up to 10 years of age. Avoid screens wherever possible.
- Actively build an environment and have a school policy for limiting the importance and use of digital screens. Educate children about digital wellness by conducting exhibitions, competitions, and debates. Educate children using pictures and stories of families that model healthy media usage.
- Educate parents about digital wellness and cyber safety during interaction with parents.
- Do not allow children to bring/carry digital devices to school.
- Do not allow school activities to be posted on mass social media, like making pages for picnics or other school activities.
- Teachers should not be allowed to use phones during the class and should not be expected to read or respond to emails during school hours.

D. Role of Indian Academy of Pediatrics (IAP)

- Indian Academy of Pediatrics should ensure promotion of and dissemination of these guidelines to children, adolescents, schools, pediatricians and com-munity through IEC material, campaigns, conference deliberations and workshops.
- The Academy should advocate and appeal to the government for including digital literacy and wellness issues in the school curriculum and ensure provision of services and help for avoiding and mitigating safety and security issues associated with use of internet.
- Children, parents, and public should be advocated about using the media to promote learning, skill deve-lopment, social communication, health and wellness. They should also be educated about the associated ill health effects of the excessive use of screen-based digital media.
- Encourage member pediatricians to hold meetings, discussions with each other as well as other stake-holders like parents, teachers, and leaders in the community. Members should report and point out offensive and misleading content and advertisements to the concerned authorities.
- Encourage families and schools to develop and follow screen policy.
- Promote research related to screen use and family perceptions in different settings.

Funding: None; *Competing interest*: None stated. RM is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the World Health Organization.

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ANNEXURE 1

IAP Guideline Committee on Digital Wellness and Screen Time in Infants, Children, and Adolescents

Chairpersons: Bakul Parekh, Piyush Gupta; *Convener*: Dheeraj Shah; *Co-conveners*: G V Basavaraja, Purna Kurkure, Harish Pemde; *National Coordinators*: Samir Dalwai, Preeti Galagali; *Members*: Nigam Prakash Narain, Anand Vasudev, G Sudhakar, Shekhar Dabhadkar, Ananda Kesavan, Raj Kumar Gupta, Sanjeev Goel, Atanu Bhadra, Geeta Patil, Sudhir Mishra, Prashant Jadhav, Remesh Kumar; *Members (Literature search and review team)*: Padmasani Venkat Ramanan, Nidhi Bedi, Sanwar Agrawal, Jijo Joseph John, S Narmada, Vidushi Mahajan, Pinky Meena, Chabungbam Smilie, Hema G Mittal; *Invited Experts:* Manoj Sharma (Clinical psychologist), VC Mehta (Ophthalmologist), Rajesh Mehta (WHO-SEARO), Deepti Agrawal (WHO-INDIA), Gopal Krishnan (Media Expert), Afridah Rehman Ali (Media personality–TV Anchor); *International media experts*: Michael Rich, Yolanda N Evans.

Referencing Made Easy: Reference Management Softwares

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Reference management softwares are a powerful tool in the researchers' armamentarium. They primarily help in re-sequencing, re-styling and reformatting of the citation content in the research manuscripts. They also enable multi-user collaboration on research and allow the researcher to manage database searches and digital libraries. Using these softwares allows synchronization of cloud based digital libraries on multiple electronic devices enabling remote access, and also allows for management of online portfolios. We, herein, describe the basic principles, functions, and limitations of various reference management softwares.

Keywords: *Bibliography, Citation, Metadata, Research.*

Published online: September 4, 2021; ***PII:*** S097475591600363

Researchers often use existing medical literature as books, journal articles, monographs and internet sites as a base for new research articles. The researcher should duly acknowledge and give credit to the previous researcher for their contribution by citing the referenced literature sources at the end of one's article. Referencing enables the research work to be compared in the light of existing evidence base to generate more constructive and generalizable data. Correctly cited, valid and easily accessible references allow the readers to cross-verify and interpret existing literature base to further their understanding. Appropriately referenced articles enable the journal editors to identify potential researchers who could review the manuscript or write an editorial for the research, for their journal. It also helps the reviewers and editors run appropriate plagiarism checks in keeping with journal policies [1].

The task of repeated re-sequencing of hundreds of references for thesis and literature review necessitated by multiple revisions is an ordeal. All such data and articles needs to be stored, cross referenced and sequentially cited in a proper target journal format and style. Fortunately, citation management has evolved and has never been as easy as it is today. Reference management softwares (RMS) (alter-natively called citation management software, or biblio-graphic management software) allow authors to search, record, manage, write, and utilize bibliographic citations/references in an appropriate format to meet the publishing requirements of various journals and publishers.

Over the last 30 years, RMS have evolved beyond their basic functions to allow the user to create their databases, create in-text citations and share databases, enabling collaboration with fellow researchers [2-6]. Popular RMS available today include Zotero, EndNote, Mendeley, F1000 Workspace, JabRef, Citavi, Bibsonomy, WizFolio, Docear, Qiqqa, ReadCube Papers, Colwiz, Paperpile, and Microsoft word [7].

Reference management system

Though there exist multiple RMS in the market, few popular ones include Zotero, Mendeley and EndNote (**Table I**) [8-10]. EndNote was first released in 1988 (Thomson Reuters). It is one of the most popular software, and allows users to store files on remote server (via EndNote Web) [8-10]. Its manuscript matcher allows matching of the research manuscript to relevant journals. Its latest version (EndNote 20) allows de-duplication of references by digital object identifier (DOI) and/or PubMed Central Identifier (PMCID) and allows for annotation in a portable document format (PDF) [9,11]. Zotero is a free citation manager which was developed at George Mason University in 2006 and has since evolved into a stand-alone software [9]. Mendeley was released in 2008 and has evolved into both online (Mendeley web) and desktop components (Mendeley Desktop) [12]. Microsoft Word (Windows) also offers a built-in feature for creating bibliographies. One can select the citation style, insert citations, add new sources and insert bibliographies in its references tab [9].

A recent survey on graduate students showed that Mendeley (39%), EndNote (20%), Zotero (16%) and

Table I Comparison of Various Reference Management Softwares

Parameter	*EndNote*	*Mendeley*	*Zotero*
Cost	Paid	Basic version free, with paid additional storage	Basic version free, with additional paid storage
Storage	Basic: 2 GB Paid version: unlimited	Free plan 2 GB Various paid plans	300 MB Free Various paid plans
Work without internet	Yes[a]	Yes	Yes
Organize records into folders	Yes	Yes	Yes
Customizable display	Yes[a]	No	no
Offline availability	References files stored locally[a]	References files stored locally	References files stored locally
Duplicate checking	Yes	Yes	yes
Direct export from databases	Yes	Yes	yes
Reference sharing	Yes, via email (also pdf)	Yes, via email ; Sharing folders: in public groups only references	No
Creates formatted bibliographies in text citation	Yes[a]	Yes	Yes
Store PDFs	Yes[a]	Yes	Yes
Extract data from PDF	Yes[a]	Yes	Yes

[a]*EndNote basic does not have these features. PDF: portable document format.*

RefWorks (10%) were the most common RMS used. While other surveys have shown that faculty were more likely to use EndNote (48%) than graduate students (31%) [9]. Among those undertaking systematic reviews, 80% were found to use an Endnote RMS [10]. Cross-sectional surveys of different specialities reveal popularity of Endnote and Mendeley, amongst health sciences, while Zotero was more popular in social science disciplines [8]. There are several factors that determine the choice of RMS among various researchers (**Box I**).

Functions of RMS

Creating bibliographies: RMS provides a platform where we can save the article explored in the web browser can be saved. This creates a list of bibliography for that searched topic. It allows for batch of references accessed from PubMed to be saved. Writing a research paper or research project report can require deletion and inclusion of more data leading to frequent alteration of reference sequence. RMS are best known for their ability to help researchers generate properly sequenced bibliographies towards research papers, in any desired format as per target journal policies (e.g., AMA style, Vancouver style). They enable in-text reference insertion, addition or deletion, and automatic resequencing of the citation order in the manuscript [13]. Among few studies which compared RMS in terms of bibliographic accuracy, one review concluded that Zotero generated most accurate bibliographies [3].

Many RMS offer options to search external databases (Endnote, Mendeley, Paperpile, Sciwheel, Refworks), but few (Sciwheel, EndNote desktop) recommend articles of interest on the basis of what's already in the user's library [14]. Few RMS e.g., EndNote (desktop version) help the researcher find full text options for the citations imported from search alerts. This tool is especially a boon for teams undertaking systematic reviews [15].

Storing and managing references and full text content: RMS allows for storage of articles in an appropriate retrievable format, for ease of referencing and sequencing, right from the stage of protocol preparation until the final manuscript submission. It also allows the researcher to undertake simultaneous projects by creation of parallel folders in the software. These digital libraries of stored references can be backed up on cloud storage (web based versions), allowing access from multiple computers. It is important to note that as one's digital library grows, it may necessitate purchase of additional storage space.

RMS may offer single station software (desktop based) interfaces or web-based programs. Both have their own advantages. While desktop based softwares are not limited by website time lags and offer offline accessibility, web based versions offer cloud storage, accessibility across multiple computers and enhanced networking [10,13,16-18]. Fortunately, most RMSs such as EndNote, Zotero and Mendeley offer both web-based and single station platforms [7].

Box I Factors to be Considered While Choosing a Reference Management Software (RMS)

- Should allow import of citations from bibliographic databases and websites and allow organisation of citations into groups within the RMS.
- Should allow annotation of citations.
- Should have appropriate writing styles, pertinent to field of interest .and construction of unavailable writing styles.
- Cost of the program should be affordable, including cost for upgrading storage (Free or paid by university).
- Should be able to interface with available word processing software e.g., Microsoft word, LibreOffice, google docs, to facilitate in-text citation with appropriate plugins 6. Should have ability to process PDF(Portable Document Format), annotate and retrieve metadata when using drag and drop feature.
- Should allow interchange of data with other reference managers through standard metadata formats (e.g., RIS, BibTeX)
- Should be compatible across available operating systems Mac, Windows.
- Should have ability to screen electronic libraries and transfer appropriate references into the program.
- Training resources and technical support should be easily available.
- Should allow portability of references through cloud storage with syncing of data files and attachments , allowing access across multiple electronic devices.
- Should have a user friendly, customisable interface and occupy less disk space.
- Compatible with smart phones : availability of mobile apps.
- Should allow sharing of data (RMS database or portions of it) with other collaborators.
- Should have offline accessibility.
- Should have web and desktop based versions
- Should have other features as removing duplicate references etc.

Drag and drop feature: Often the researchers store PDF formats of the references at the time of literature review. Some RMS allow appropriate citation to be generated by just a drag and drop of the PDFs into the RMS. This is accomplished by identification of metadata as DOI or international standard book number (ISBN) in the PDF [5,13,19]. These identifiers also enable RMS to obtain citation information and avoid duplication [20]. Researchers can use annotations as sticky notes and text marking in their PDFs stored in the RMS for clarity. This feature is supported by Endnote, Mendeley and Citavi, but not by other RMS, which need external editors as adobe acrobat reader [7].

Sharing the data with other collaborators: Most RMSs (web based) permit enhanced networking functionality, allowing users to share references and PDFs enabling collaboration on research. But it can get tricky to share across different RMS as one is prompted to do so in various formats like Bib LaTeX, BiBTeX (.,bib), CSL JSON (JavaScript Object Notation), RIS (Research Information Systems) (.ris) , Endnote XML (.xml)(Extensible Markup Language) among others. Amongst these, RIS (.ris) is a standard citation format across EndNote, Mendeley, and Zotero. On downloading the database, PDFs and other attachments are not directly exported and links to word processor plugins maybe lost [21,22].

When doing collaborative researches, references maybe shared and edited with other researchers in Endnote, Mendeley, Papers (enterprise version), Bibsonomy and Citavi [7]. However, desktop and web-based user interfaces may differ towards group management as addition of people in groups, and permission for selective record viewing.

Researchers often utilize social networking, to publicize their research work and communicate with like-minded researchers. But only few RMS like Bibsonomy, Mendeley and Zotero support this function, by allowing publication of a personal profile/curriculum vitae, following of other researchers, and communication in similar interest groups [7].

Password protection: It is available in software as EndNote, Zotero, Mendeley but is absent in others like KBibTeX, JabRef and Bebop [6,23].

Word processor integration: Most researchers prefer to work and create their articles in Microsoft word (windows), LibreOffice and Google docs. It is therefore essential for these RMSs to have plugins to interact with these softwares, enabling incorporation and auto sequencing of citations. Most software such as EndNote, Mendeley, Citavi, Zotero, Sente have this compatibility unlike Refbase and RefDB. Very few RMSs are compatible with google docs (e.g., Zotero, Papers and RefWorks). Similarly, LibreOffice is compatible with systems such as Mendeley and Zotero [6,23].

Searching and retrieving references from online

KEY MESSAGES

- Reference management software can help create and store the research article databases, create in-text citations, and enable collaboration with fellow researchers.
- Bibliography created by RMS needs to be checked for possible errors as per the requirement of the journal or the assignment.

databases: Some RMS import literature from online external databases. They offer in-app searching of databases with web browser plugins to allow identification of reference data from journal websites. This automatic entry of references minimises typographical errors with all essential citation related information (as title, author, journal, date of publication etc.) being downloaded directly into the RMS library [13]. Searching online databases via RMS may miss some citations as compared to searching native databases (as PubMed , Ovid) [24].

Maintaining portfolios: Many programs require students to maintain academic portfolios, where documentation of competencies and documents can be undertaken. Few RMS such as Papers allow for creation of such portfolios [25].

Exportation to Excel: It is important to share the citation searches between collaborators, in various formats as Excel, especially when undertaking systematic reviews. This functionality is offered by managers like Zotero and Endnote where appropriate formats (RIS, Research information systems format and CSV, comma-separated values format) maybe exported in external files (Excel) [26,27]

Tool for summative assessment: Some RMS such as EndNote, offer unique features that allow for their use towards summative assessment. Herein, each examination details may be stored as a citation with multiple files attached in any format as needed. Similar examinations maybe integ-rated as group sets, data backed up on cloud servers or offline on hard-drives, and confidential documents pass-word protected. But certain features expected in exami-nation management systems as certificate authentication and multilayer authentication are not available in RMSs [28].

Mobile applications: Some referencing software have their own mobile apps as Mendeley and EndNote. Others as Zotero, have third party apps for iOS and android. There are short YouTube videos available guiding their use.

PROBLEMS WITH RMS USE

The use of citation management software does not guarantee the absence of referencing errors within a manuscript. The author should verify each citation as per journal specific author guidelines. Studies have shown citation errors in RMS output, when compared to journal requirements, particularly in author names, capitalization, punctuation, journal title and dates [4,29]. References often get duplicated when they are stored in different group sets, which may result in duplication of inserted citation in the bibliography [30].

Every researcher needs to meet the specific citation requirements (APA, Chicago, Vancouver etc.) of target journal to submit an article. An open XML (extensible markup language) based citation style language (CSL) enables the formatting of citations and bibliographies. If the required format is missing in the RMS, the researcher may need to learn the use of the style editor function of the RMS to create bibliography in the missing format [20].

Various file formats are available for storing bibliographic data which include Research information systems (RIS), BibTeX, Endnote XML and Citeproc JSON. Often RMS do not recognise all these formats. This hinders migration from one RMS to another and of multiple RMS simultaneously [19,20].

Although, there exist many unique identification numbers and schematics for journal articles, as DOI, Pub-Med identifier (PMID), ISBN, PMCID, or the ArXiV ID [19,20]. There are no uniformly acceptable article identifiers that are acceptable across databases and libraries. This complicates de-duplication and metadata retrieval by RMS [31].

IMPLICATIONS FOR PRACTICE

Users often find RMSs challenging. Researchers often neither have knowledge about various RMS, nor have time to learn them [8,32]. For ease of self-taught researchers, step-by-step usage guides are available on the net, as either YouTube videos or RMS specific webpages and blogs. Researchers may post their specific queries on these blogs, which may then be answered by technical staff or their co-researchers. Self-help options such as online tutorials and webpages, are favored by graduate students in learning RMS [8]. This self-taught mode can be

complemented by library services in large institutions. A core group of librarians of an academic library can act as an invaluable resource. A webpage with resources can be created in institutions with links to RMS vendor webpages and online support forums. Since different users have varied needs and resources, tools as workshops, one-to-one consultations, online tutorials, creation of webpages with resources, email and online chat assistance, can be utilized to enable training of students and faculty in the use of RMSs [8]. Workshops customized to basic and advanced training serve an important role in RMS adoption by researchers [32].

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

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Pattern and Profile of Co-Sleeping in School-Aged Children

This cross-sectional study was conducted among parents of children aged 5-12 years to determine the prevalence and pattern of co-sleeping among children,and sleep problems associated with it. Out of 275 children, 269 (97.8%) co-slept. Among co-sleepers, bed-sharers were 131 (48.7%) and room-sharers 138 (51.3%). Factors associated with bed-sharing were child's age and socioeconomic status. Wake-up resistance and night terrors were more in bed-sharing children.

Keywords: *Bed sharing, Sleep hygiene, Sleep pattern, Sleep problem*.

Published online: February 2, 2022: ***PII:*** S09747405

Co-sleeping is defined as a child sleeping along with parents/siblings/other family members and includes 'bed-sharing' (sharing the same sleeping surface) and 'room-sharing' (sharing the same room). Co-sleeping in infants has been shown to promote mother-infant bonding and breastfeeding, and to promote a sense of security and well-being in older children [1]. Prevalence of co-sleeping in school age children has been reported by studies in India but there is not much data on pattern of co-sleeping viz., bed-sharing and room-sharing [1]. Although, co-sleeping is reported as beneficial, some studies report sleep problems associated with co-sleeping in older children [2,3]. This study was conducted to study the prevalence and pattern of co-sleeping, and sleep problems associated with it in children aged 5-12 years.

This survey was conducted from March-June, 2019, after Institute ethical clearance, in the pediatric inpatient and outpatient unit among willing parents of stable children aged 5-12 years. We excluded critically ill, those with chronic or debilitating illness, and children with disability. Using the prevalence of co-sleeping as 79.7% from previous study [4], 5% allowable error, CI of 95, and 10% drop out rate, sample size was calculated as 275.

By systemic random sampling, parents of every third child were interviewed by an investigator using a pretested semi-structured questionnaire, validated for face validity, and pretesting and back translation. The Cronbach alpha for sleep items was 0.761. Sleep history pertaining to the one week prior to their hospital visit was obtained from the participants, after written consent, and when children were interviewed, assent was obtained from them. The questionnaire included demographic particulars, bedtime, wake-up time, night sleep duration, co-sleeping pattern and common sleep problems.

Data were analyzed using SPSS software version 21. Chi-square test was used for categorical variable and *t*–test for continuous variables. Participants were classified as bed-sharers and room-sharers. Multivariate logistic regression was used to find factors influencing bed-sharing. *P* value <0.05 was considered significant.

The mean (SD) age of the 275 children was 8.7 (2.3) years. Out of these 269 co-slept (97.8%). Among the co-sleepers, 131 (48.7%) were bed-sharers and 138 (51.3%) were room-sharers. Preference of children and parents with respect to sleep arrangement and reasons for the same are given in **WebTable I**. The sleep habits and sleep problems of bed-sharers and room-sharers are shown in **Table I**. The weekend sleep duration was significantly longer in bed-sharers than room-sharers [10.4 (1.4) vs 10.0 (1.4) hours, *P*=0.03]. Similarly wake-up resistance (*P*=0.03) and night terrors (*P*=0.04) were significantly higher in bed-sharers than room-sharers (**Table I**). There was no statistical difference in other sleep habits and other reported sleep problems. With respect to parents, sleep problems in the form of altered sleep schedule, frequent night awakening, reduced sleep duration, or marital distress were reported by 63 overall (22.9%), out of which 36 (57.1%) were bed-sharers and 27 (42.9%) room-sharers (*P*=0.12). On multivariate analysis, only younger age [aOR (95% CI) 2.4 (1.45-3.97); *P*=0.001] and upper socioeconomic class [aOR 995% CI) 2.14 (1.15-3.98); *P*=00.017] were found to be significantly associated with bed sharing.

Prevalence of co-sleeping was 97.8% in the present study. Other studies in India have shown rates between 67-80% [1,4].

Table I Sleep Characteristics of Bed sharers and Room sharers

Variable (n, %)	*Bed-sharers (n=131)*	*Room-sharers (n=138)*
Weekday sleep duration[a]	9.4 (1.0)	9.3 (1.0)
Weekend sleep duration[a,b]	10.4 (1.4)	10.0 (1.4)
Late bedtime[c]	48 (36.6)	60 (43.5)
Late wake up time 7 AM	26 (19.8)	16 (11.6)
Reduced sleep duration[c]	29 (22.1)	39 (28.3)
Bedtime TV	85 (64.9)	101 (73.2)
TV time >2 h	13 (9.9)	25 (18.1)
Screen time duration[a]	1.3 (0.9)	1.4 (1.1)
No. of sleep problems[a]	1.4 (1.4)	1.2 (1.2)
Wake up resistance[b]	52 (39.7)	38 (27.5)
Snoring	16 (12.2)	23 (16.7)
Nightmares	17 (13.0)	24 (17.4)
Night terrors[b]	20 (15.3)	10 (7.2)
Sleep talking	31 (23.7)	22 (15.9)
Day time sleepiness	23 (17.6)	18 (13.0)
Bedwetting	23 (17.6)	26 (18.8)

Data expressed as no. (%) or [a]mean (SD).[b]P<0.05. [c]as per reference 5.

Li, et al. [6] in their study among Chinese children with mean age of 8.5 years reported higher solitary sleeping (47.7%), while a co-sleeping prevalence of 12-50% were observed in other studies [6-8]. In our study the prevalence of bed-sharing was 48.7% and room-sharing was 51.3%, much higher than that reported by Li, et al. [2]. Gupta, et al. [4] reported higher bed-sharing, nearly in 3/4th of the study subjects in another study from India [4].

Wake-up resistance shown to be higher in bed-sharers may be due to the good duration of sleep associated with bed-sharers. In the study by Li, et al. [2], bed-sharing was associated with later bedtime, later wake-up time, and shorter sleep duration. Jiang, et al. [9], reported bed-sharing was associated with bedtime resistance, daytime sleepiness and sleep anxiety [9]. Generally, bed-sharing is reported to alleviate night terrors but in our study it was observed more in bed-sharers. It could be related to anxiety and overprotection and this may be a contributory factor to bed-sharing. Mishra, et al. [1] observed that co-sleeping was protective in that it increased the quality and duration of sleep and showed lesser incidence of nightmares due to the increased sense of security [1]. Andre, et al. [10] observed that perceived sleep quality was better in bed-sharing. A previous study [8] showed that co-sleeping was associated with higher couple distress, unlike ours where marital stress consequent to co-sleeping was reportedly low. Under-reporting could be one factor but it could be related to parental perception also as co-sleeping is culturally acceptable and preferred practice. Kim, et al. [3] reported 52% of co-sleeping mothers had sleep problems and reported lower self-efficacy.

Socio-economic status and younger age in children were significantly associated with bed-sharing in our study, similar to previous observations [3,6]. Jiang, et al. [9] reported positive parental attitude as the most important determining factor for bed-sharing. In the present study, co-sleeping was not only the norm but was also highly acceptable and preferred by both parents.

Limitations of the study were single-center hospital-based sample with parental reporting of children's sleep problems, and using non-validated questionnaire.

Ethics clearance: Institutional ethics committee; No. IEC/PP/2018/12/132 dated June 5, 2018.

Contributors: BC: concept, design, data acquisition, analysis, interpretation, drafting, reviewing for intellectual content; DK: data analysis, interpretation, intellectual content; SA: data interpretation, drafting, reviewing for intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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

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Web Table I Reasons for Co-sleeping/Solitary sleeping Among the Study Participants (*N*=275)

Variables	
Parental preference	
Co-sleeping	251 (91.3)
Solitary sleeping	24 (8.7)
Child's preference	
Co-sleeping	256 (93.1)
Solitary sleeping	19 (6.9)
Parents' reasons for co-sleeping (n=251) [a]	
Emotional bonding	98 (39)
Security of children	97 (38.6)
Tradition norm	29 (11.6)
Economic use of available space	20 (8.0)
Child fears sleeping alone	4 (1.6)
Perceived comfort and wellbeing of the children	2 (0.8)
Parents' reasons for solitary sleeping (n=24) [b]	
To develop a sense of independence in the child	17 (70.8)
For privacy	3 (12.5)
Difference in bedtime due to academic schedule	2 (8.3)

[a]*Allows for timely sleep in one family;* [b]*One family each reported differences in lighting preferences and mother had a surgery.*

Are Parents Informed Well Enough About Their Child's Long-term Risks Related to Undescended Testis?

Worldwide, recommendations for timely surgical repair of undescended testis (UDT) are not well translated into clinical practice, potentially due to suboptimal patient/parent education. We evaluated the frequency and content of information provided to affected parents of 310 consecutive cases of UDT undergoing orchidopexy. Parents were enquired regarding details of education provided by the attending clinician. 18% of parents were not provided with detailed information regarding any long-term consequences of untreated UDT. In the 79% who were educated, information about impaired fertility was frequent, while malignant degeneration, hypogonadism and testicular atrophy were poorly communicated. 49% of all parents searched for further information on the internet or through a second medical opinion. The frequency and level of detail of information regarding long-term complications provided to parents of children with UDT is suboptimal and needs to be improved.

Key words: *Cryptorchidism, Infertility, Testicular cancer.*

Trial registration: German Clinical Trials Register, DRKS00015903.

Undescended testis (UDT) is among the most common reasons for pediatric surgery worldwide. Untreated, UDT features a risk for various long-term sequelae, including testicular cancer of UDT and impaired testicular growth and functionality, atrophy and even infertility. Additionally, there is evidence for UDT-associated hypogonadism.

To avoid these complications, international clinical guide-lines recommend early surgical orchidopexy, usually at 12 to 18 months of age. However, this goal is currently only achieved in a small proportion of affected patients [1]. Late orchidopexy in children with UDT seems to have several underlying causes viz., suboptimal knowledge regarding clinical guidelines, secondary UDT (which mostly occurs later in childhood), referral delay, parental reservations, and others [2]. The aim of this study was to analyze the frequency and quality of medical information regarding long-term risks of UDT provided to affected parents by their physicians.

This study was performed at six urology/pediatric surgery departments in Germany between April, 2016 and June, 2018. We prospectively analyzed 310 consecutive cases of boys with UDT undergoing orchidopexy. All children had initially been diagnosed and referred by the treating primary care pediatrician.

Parents were interviewed anonymously using a question-naire prior to the surgical intervention of the children. A significant language barrier was an exclusion criteria for the study. Specifically, we inquired details of UDT-specific medical education and informed consent provided to the parents by the attending clinicians, and also asked whether and how parents tend to search for further information on UDT-related medical risks. The inclusion and exclusion criteria have been previously described in detail [2]. Statistical analyses were performed using SPSS version 23 (IBM Inc.). The *P*-value was calculated using the Chi-square test.

We enrolled 310 boys with a median (IQR) age of 27 month (14-60) (**Table I**); 18% (*n*=56) of the patients' parents were not provided with detailed information regarding any long-term consequences of untreated UDT. In the 79% (*n*=244) who were educated, information about impaired fertility was frequent (95%, *n*=230), while malignant degeneration (64%, *n*=156), hypogonadism (40%, *n*=96) and testicular atrophy (2%, *n*=4) were poorly communicated. The median time lag between the pediatricians' initial diagnosis and surgical treatment was 2 month.

Forty-nine percent of all parents (*n*=153) searched for further information after their consultation, mostly on the internet (76%; *n*=117) or through a second medical opinion (17%; *n*=26). Specifically, primarily provided information about UDT-related risks led to a significantly increased interest in obtaining further information after the consultation (*P*=0.03). Interestingly, delayed surgery (>12 months) did not lead to more frequent risk information (*P*=0.45) or to a higher motivation to search for further information (*P*=0.35) as well as a diagnose-treatment-delta of more than two months (*P*=0.22 and *P*=0.35, respectively). Of all utilized internet resources, Google was used much more frequently than social networks, and mobile devices were more popular than desktop computers (**Web Fig. 1)**. When assessing the quality of the acquired additional information, the most commonly used source (internet) was rated the worst (score 2.2), while medical journals were rated most helpful (score 1.7), on a scale from 1-5 by the parents (**Fig. 1**).

The degree of suboptimal education reported in this study at 19% was surprisingly high. Further, parents who were edu-cated about UDT risks mostly received incomplete information, which is concerning as the risks of UDT are serious [3-7]. Niyogi and Clarke have demonstrated distinct differences in opinion between patients and surgeons about the information to be provided before surgery [8]. These included the level of expertise of the surgeon as well as the risk of complications. Several studies have shown that parents' experience of information flow regarding their child's surgery may vary. Similarly, when obtaining informed consent for clinical

Table I Characteristics of Children With Undescended Testis (*N*=310)

Characteristics	*Value*
Preterm birth	129 (43)
Pre-existing conditions	76 (25)
Regular medication	46 (15)
Malformation	35 (18)
Primary undescended testis (pUDT)	103 (33)
pUDT one-sided	58 (56)
pUDT both sides	35 (34)
pUDT side unknown	10 (10)
Acquired undescended testis	104 (34)
Unknown testicular position	103 (33)
Surgery in time (≤12 mo)	53 (18)
Age at UDT diagnosis (mo)[a]	24 (11-48)
Age at surgery (mo)[a]	27 (14-60
Time from diagnosis to therapy (mo)[a]	3 (1-7)
Conservative treatment prior to surgery	17 (51)

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

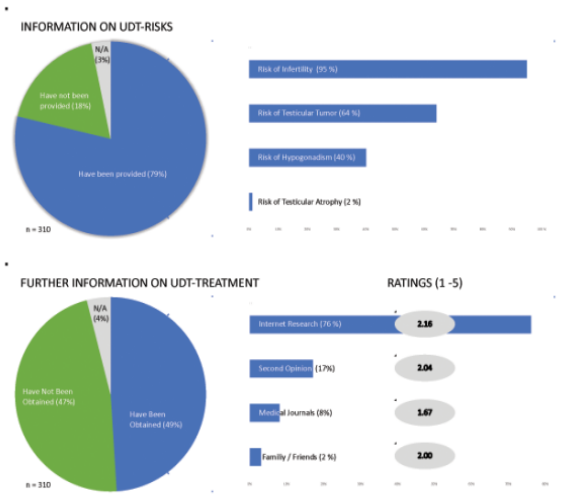

Fig. 1 Frequency and content of provided Information regarding UDT risks (top); Further information-seeking behavior of parents of boys with undescended testis undergoing orchidopexy (bottom). This illustration shows how frequently And where further UDT information was obtained by the parents and how the Information quality was rated (range 1 [very good] - 5 [very poor]).

research in children, there is a discrepancy between parents' evaluation of the adequacy when being educated and evaluation of specific understanding or even memorization [9]. In this sense, the main limitation of this study is the fact that parents were asked whether and to what degree they were informed about UDT risks by their physicians. Hence, some uncertainty about miscommunication or even forgetting of discussed matters may have occurred. On the other hand, this study well reflects the degree of information that was finally retained by the affected parents, and demonstrates the need for improvement regarding patient/parent communication. As a modern way to improve patient/family education, the use of internet and social media campaigns e.g., for children with UDT, has proven to be a promising strategy [10].

Importantly, the assessed cohort was sampled at the point of registering their child for orchidopexy in urology/pediatric surgery departments. Hence, the decision to go ahead with surgery had already been made. In other words, if parents who agree to surgery are improperly informed, it is not far-fetched to reason that parents of boys with UDT who are not planning for surgery will at least be equally informed, if not even less. Consequently, clearer communication of long-term UDT risks and tailoring the flow of information to the specific needs of affected families may help to overcome the dilemma of late orchidopexy in boys with UDT.

Further information was sought by parents who received at least some initial information regarding UDT risks by their physician, demonstrating the positive effects of informing families to empower them towards taking control of their own health rather than being steered purely by their doctors.

Medical professionals treating children with UDT should make an effort to thoroughly inform affected parents about long-term complications of UDT. This may be an important step towards minimizing the widespread UDT treatment delay and towards earlier diagnosis and treatment of long-term sequelae.

Acknowledgements: Dr Philip Boehme, Dr Karin Lawrenz, Prof Ralf-Bodo Troebs, Prof Peter Schmittenbecher, Dr Jan Beume, Dr Simone Poetzsch, and Dr Beate Schwarz for assistance in planning and conduct of the study.
Ethics clearance: Witten/Herdecke University Ethics Committee; No. 162/2015, dated Nov 26, 2015.
Contributors: SD, SW, KH: study conception, study design; SD, MD, SR: data acquisition; SD, MD, KH: data analysis; SD, KH: Manuscript draft; SR, SW: supervision/revision. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interest*: None stated.

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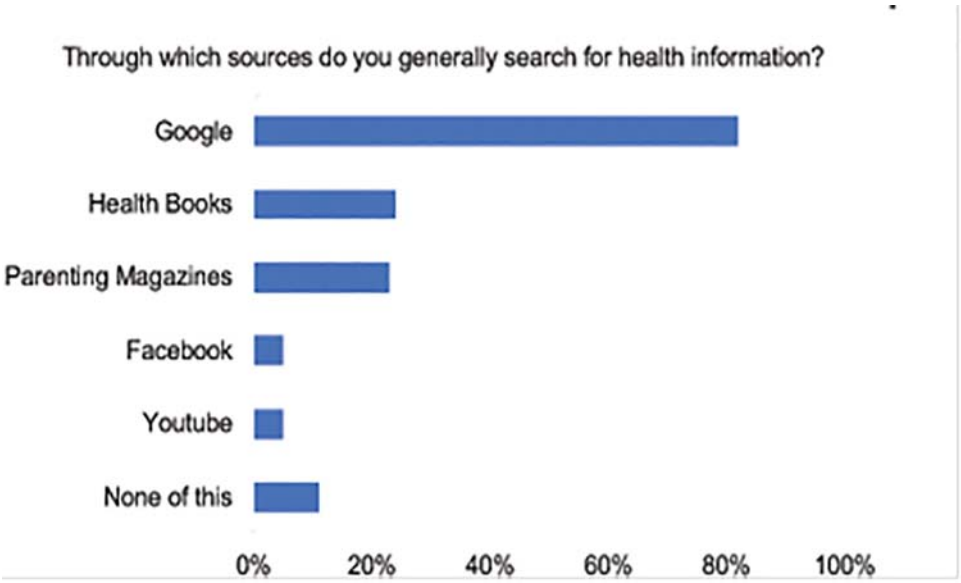

Web Fig. 2 Information-seeking strategies of involved parents regarding medical context.

Bicycle Handlebar Injuries in Children During the COVID -19 Pandemic

Consequences of the ongoing coronavirus disease 2019 (COVID-19) pandemic include nationwide school closure. In countries with limited access to the internet and remote learning, 90% of enrolled students are being confined at home. With children resorting to recreational activities, we have seen an increasing trend of sports-related abdominal trauma in our region.

Bicycle handlebar injury (BHI) accounts for 5-14% of motor vehicle injuries that result in abdominal trauma in children [1]. Although, it is a low-impact injury, it can lead to severe internal organ damage. The initial signs are minimal and the symptoms develop hours after the injury, resulting in delay in seeking medical attention. We report four consecutive children who had serious internal organ damage secondary to BHI with one child with life-threatening abdominal compartment syndrome (ACS).

These four children (3 girls) were admitted with BHI to the pediatric intensive care unit of our tertiary teaching hospital between April, 2020 and May, 2021. The median age was 12 years and there was a significant delay in presenting to hospital. (median time to reach hospital; 14 hours). Clinical symptoms were varied with abdominal pain and distension, hematuria and handle bar-tattooing. Radiological imaging showed liver and renal laceration. All children required blood transfusion and the median hospital stay was 13 days. The children were managed conservatively with no mortality.

One child among the four had life-threatening ACS with a stormy clinical course. She was a 15-year-old female who sustained minor bruises over the abdomen after a fall from a bicycle, and arrived 16 hours after trauma at our center. On arrival, she was in hemorrhagic shock with handlebar tattooing on the abdomen (**Fig. 1**). The Focused assessment with sonography for trauma (FAST) and radiological imaging showed hemo-peritoneum and liver laceration. In spite of fluid resuscitation and massive blood transfusion, the shock did not resolve, with persisting oliguria. There was a progressive increase in abdominal distension and respiratory distress worsened requiring mechanical ventilation. With the suspicion of ACS, the intra-abdominal pressure (IAP) was serially monitored. An IAP of >26 mm Hg along with organ dysfunction was diagnostic of ACS [5], thus decompression was done with a peritoneal drain, which resolved the shock. She was later extubated and discharged after 10 days of hospital stay.

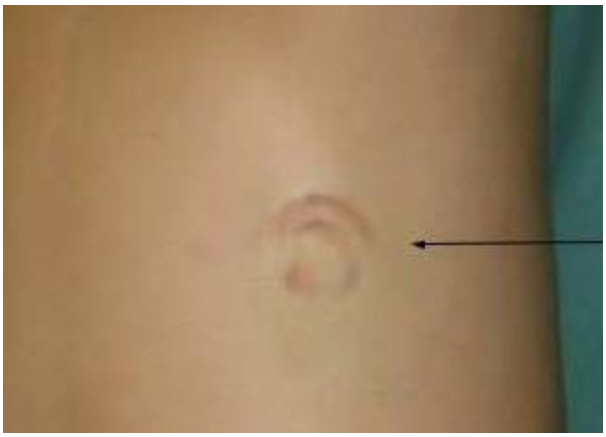

Fig. 1 Handlebar tattooing over the abdomen (black arrow).

With the closure of schools in the pandemic era, we have witnessed an increase in the frequency of BHI from 2% (1/50) to 15% (4/26) of all the trauma admissions before and after the onset of the pandemic, respectively. The median age of our group of children was similar to other reports, with the abdomen being the most common site of injury [2]. As with our report, other authors have reported an increase in odds of having a serious intra-abdominal injury whenever there is a handlebar imprint [4]. Delayed presentation is a major risk factor for increased morbidity [4].

In all the children, FAST identified major injuries which was later confirmed by CT. We found that FAST had high sensitivity in detecting serious intraabdominal trauma similar to previous reports. Management of BHI is challenging, especially when the presentation is late. When compared to other modes of abdominal trauma, the requirement of surgical intervention is more in BHIs [2]. We managed to treat the children conservatively, especially the one with ACS with timely abdominal catheter decompression thereby avoiding emergency laparotomy. There is a relative paucity of literature on ACS in children compared to adults. There are no reported cases of ACS secondary to BHI in the literature. Intraperitoneal bleed and requirement of massive resuscitation are responsible for 8% of the ACS associated with high (50%) mortality, which was also present in our child [3]. Serial IAP monitoring is recommended if two or more risk factors for ACS are present [5].

BHIs are frequently underestimated and the occurrence of ACS can be overlooked. Serial physical examination and IAP monitoring are recommended in children with BHI for early recognition and management of ACS. Non-invasive measures to reduce IAP, if performed in time, reduce the requirement of decompressive laparotomy, which is associated with high mortality rates.

Ethics clearance: Institutional ethics committee, KS Hegde Medical Academy; No.INST.EC/EC/53/2017-18, dated September 11, 2020.

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Langerhans Cell Histiocytosis and Osteosarcoma in Children: A Radiological Mimic

Osteosarcoma presents in adolescent age with radiologically aggressive bone tumor, while Langerhans cell histiocytosis (LCH) commonly presents with radiological features of a less aggressive bone lesion [1,2]. We report here two cases of osteosarcoma and LCH with an unusual radiological presentation.

***Case* 1**: A 30-month-old boy presented with swelling over proximal left leg and limping of one-month duration without history of trauma. A 2×2 cm hard swelling, fixed to bone, with mild tenderness was present without any systemic abnormalities. *X*-ray showed a well-defined expansile lytic lesion with narrow zone of transition in meta-diaphyseal region without cortical breaks or significant periosteal reaction (**Web Fig. 1A**). Magnetic resonance imaging (MRI) showed multiseptated peripherally enhancing eccentric lesion without significant periosteal reaction, soft tissue component (**Web Fig. 1B** and **C**). Age and radiological findings were suggestive of LCH. Biopsy showed malignant spindle cells with osteoid formation, typical of osteoblastic osteosarcoma. Immunohistochemistry (IHC) for analplastic large cell lymphoma (ALCL) (CD30) and LCH (Langerin) were negative and CD99 was cytoplasmic positive but without crisp membrane positivity, which ruled out Ewing sarcoma. Thus, diagnosis of osteosarcoma was confirmed. Metastatic work-up was negative. He received six cycles (29 weeks) of methotrexate, adriamycin, cisplatin (MAP) chemotherapy. After 10 weeks (2 cycles) of chemotherapy, MRI post contrast T1 image showed interval regression of adjacent marrow changes and periosteal reaction with reduction in thickness and enhancement of internal septations suggesting treatment response (**Web Fig. 2A and B**). As the child was only 30-months-old, wide-excision and endoprosthetic implant was not a feasible option. Parents were unwilling for above-knee amputation. Hence, we proceeded with wide excision, extracorporeal radiotherapy, and internal fixation. At end-of-treatment, disease was in complete remission (**Web Fig. 2C**). Presently, the child is on follow-up without any evidence of disease, 3-year post-treatment.

***Case* 2**: An 11-year-old girl presented with right thigh pain and limping of one-and-half-month duration without history of trauma. Diffuse swelling and tenderness were present with normal overlying skin at the proximal left thigh without any systemic abnormalities. Blood investigations were normal. *X*-ray showed an irregular lytic lesion involving the upper meta-diaphyseal region with periosteal reaction and cortical-break (**Web Fig. 1D**). MRI showed expansile heterogeneously enhancing lesion involving femoral neck with cortical-break and soft tissue component, which was suggestive of an aggressive bone tumor (osteosarcoma or Ewing sarcoma) (**Web Fig.1E** and **F**). Another lytic lesion was noted in right posterior acetabulum. Biopsy showed sheets of cells having moderate cytoplasm with convoluted vesicular nuclei admixed with eosinophils, diagnostic of LCH. There was no evidence of small round blue cells (for Ewings sarcoma or non-Hodgkin lymphoma) or malignant cells with oseoid formation (for osteosarcoma). IHC for CD1a was diffusely strongly positive. Skeletal survey did not reveal any other bone involvement. She was diagnosed to have multifocal bone LCH without risk-organ involvement. She was started on LCH III protocol. Re-evaluation after 12 weeks induction with vinblastin and prednisolone showed residual lytic area, area of mineralization with regression of periosteal reaction and cortical break (**Web Fig. 2D**). End-of-treatment skeletal survey showed areas of remineralization with cortical thickening without any periosteal reaction, soft tissue component or cortical break (**Web Fig. 2E**). Currently, at 18-month post-treatment, she has no evidence of disease, and can walk without support.

Osteosarcoma presents radiologically with features of aggressive bone lesions like periosteal reaction, periosteal elevation, osteoid formation in soft tissue, wide-zone of transition, cortical break, and pathological fracture [3]. Only 2% of patients present before 5 years of age [1]. In LCH, early lesions appear lytic, expansile, with irregular margin, cortical thickening, and smooth periosteal reaction. As lesions become chronic, they may resolve or appear as punched-out well-defined lesion with sclerotic margins [2]. LCH usually presents at a median age of 3 years and multisystem involvement is more common [4].

Rarely osteosarcoma can radiologically mimic a variety of conditions [5]. In a series of 52 patients (adults and children), six cases of high grade osteosarcoma diagnosed by cytology had atypical radiological appearance and one case of radiological osteosarcoma had histopathological diagnosis of soft tissue sarcoma [5]. In a series by Sundaram, et al. [6] two children with well demarcated osteolytic lesions in tibia diagnosed radiologically as aneurysmal bone cyst, later on were diagnosed as osteosarcoma on open biopsy.

In case 2, child presented at an older age, which is a common age of presentation for aggressive bone tumors. Radiological

features were also favoring clinical diagnosis, but there was another lesion in the acetabulum, which was not a typical feature of bone sarcomas. There was no other bone involvement or systemic involvement characteristic of LCH. LCH most commonly involves flat bones. Potepan, et al. [7] reported a series of seven children of LCH, where initial *X*-ray findings were suggestive of malignancy (large lytic lesion, purely destructive in nature). Lesion sites were pelvis, tibia, femur, clavicle, jaw and scapula. All children were treated with chemotherapy for LCH or curettage and long-term follow-up showed complete remission. Apart from this series, there are rare reports of LCH mimicking osteomyelitis [8].

We reported these two cases to highlight the difficulties in radiological diagnosis of bone lesions in children and the manner in which they can behave like radiological mimics. A limitation of our report is that for the child in case 1, we could not process additional IHC for Ewing sarcoma and ALCL. Radiologically, bone lesions in children can sometimes be confusing and histopathology will help us to reach a final diagnosis.

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

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Spontaneous Neonatal Arterial Thrombosis of Axillary Artery

Neonatal arterial thromboembolism is uncommon [1], and most commonly it is related to arterial catheterization or another iatrogenic injury. Currently only few case reports describe spontaneous arterial thrombosis, manifesting immediately after birth, failure to identify can have serious consequences [2-4]. We describe a neonate with spontaneous upper limb artery thrombosis manifesting immediately after birth leading to massive limb ischemia.

A male infant of a diabetic mother was born at 36 week gestation by cesarean section due to cephalopelvic disproportion (birthweight 3650 g), with an Apgar score of 10/10/10. At birth, the physical examination detected cyanosis of the right upper limb from the middle of the shoulder to the acral parts. The upper limb was livid and paretic. The formation of bullae in the forearm was observed after a few hours of life.

After transport and admission of the patient to the neonatal intensive care unit (NICU), Doppler ultrasound and computed tomography angiography (CTA) was urgently performed. Scans revealed a complete thrombotic occlusion in the distal 3 cm of axillary artery (**Fig. 1**). Due to the age of the child and the location, interventional catheter-directed thrombolysis (CDT) could not be technically performed. Systemic thrombolysis was contraindicated because of imminent surgery. Therefore, anticoagulant therapy was started. A bolus of unfractionated heparin (UFH) was administrated, followed by continuous heparinization with concomitant antithrombin III (AT III) substitution. Conservative treatment had no effect on the extent of ischemia, so surgical thrombectomy with a Fogarty catheter was done on the first day of life. Despite attempts at revascularization and continuous hematological treatment, irreversible changes of right forearm (mummified fingers, extensive necrosis of the forearm and distal part of the shoulder) persisted.

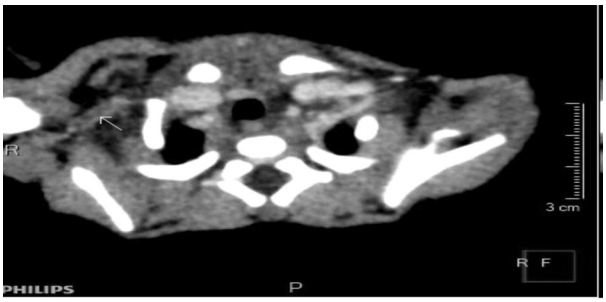

Fig. 1 Computer tomograph angiography scan of complete thrombotic occlusion in the distal 3 cm of axillary artery (white arrow).

On the sixth day of life, the amputation of the devitalized part of arm was done with negative pressure wound therapy. Concomitantly, hematological therapy continued and was later changed to low molecular weight heparin (LMWH). A diagnosis of prothrombotic thrombocytopathy platelet aggregation (sticky platelet syndrome type 1, SPS I) was confirmed, with exclusion of other thrombophilic condition such as AT deficiency, factor II mutation G20210A, factor V Leiden, *MTHFR* gene mutation, and homocysteine deficiency. Growth and development of child at 12 months is age-appropriate.

The actual incidence of spontaneous arterial thrombo-embolism in newborn is unknown and varies depending on the method used for assessment. It is assumed that arterial thromboses represent 50% from all thrombotic events in neonatal period. Identified risk factors can be categorized into four subgroups maternal (e.g., gestational diabetes), congenital (e.g., placental pathology), acquired (e.g., sepsis) and inherited prothrombotic abnormalities [3,7]. Prematurity, maternal gestational diabetes and presence of SPS I associated with platelet hyper-agreeability were identified as predisposing factors. Although SPS usually occurs in the third and fourth decade of life, cases in childhood are also reported [8].

Management of spontaneous arterial thrombosis can be challenging. Therapeutic approaches and drug dosage are not standardized. The goal of treatment is interrupting thrombus propagation, enhancing tissue perfusion with complete recovery of the affected area, while minimizing risk of bleeding [6]. The most commonly used therapeutic modalities in the literature are heparin, LMWH, tissue plasminogen activator (tPA), urokinase and streptokinase. Microsurgical techniques appear to improve outcome and should be reserved for severe cases [3,5]. Metabolism of the discussed medications is different in the neonate. Heparin is used in a higher dose compared to adults, but there is still a lack of consensus on the ideal dose. The use of thrombo-lytic agents is promising but has never been proven in randomized controlled trials [3,7]. Interventional radiological management of acute ischemia can be difficult, although catheter-directed thrombolysis has been reported to be bene-ficial in selected patients [5].

The most important lesson from this case is the need of prompt recognition of symptomatic thromboembolism with urgent treatment. Despite the lack of data on effectiveness of specific treatments, we feel that an early aggressive approach to treatment can improve outcome.

Funding: This work was supported by Ministry of Health of the Slovak Republic under the project registration number 2019/44-UKMT-7.

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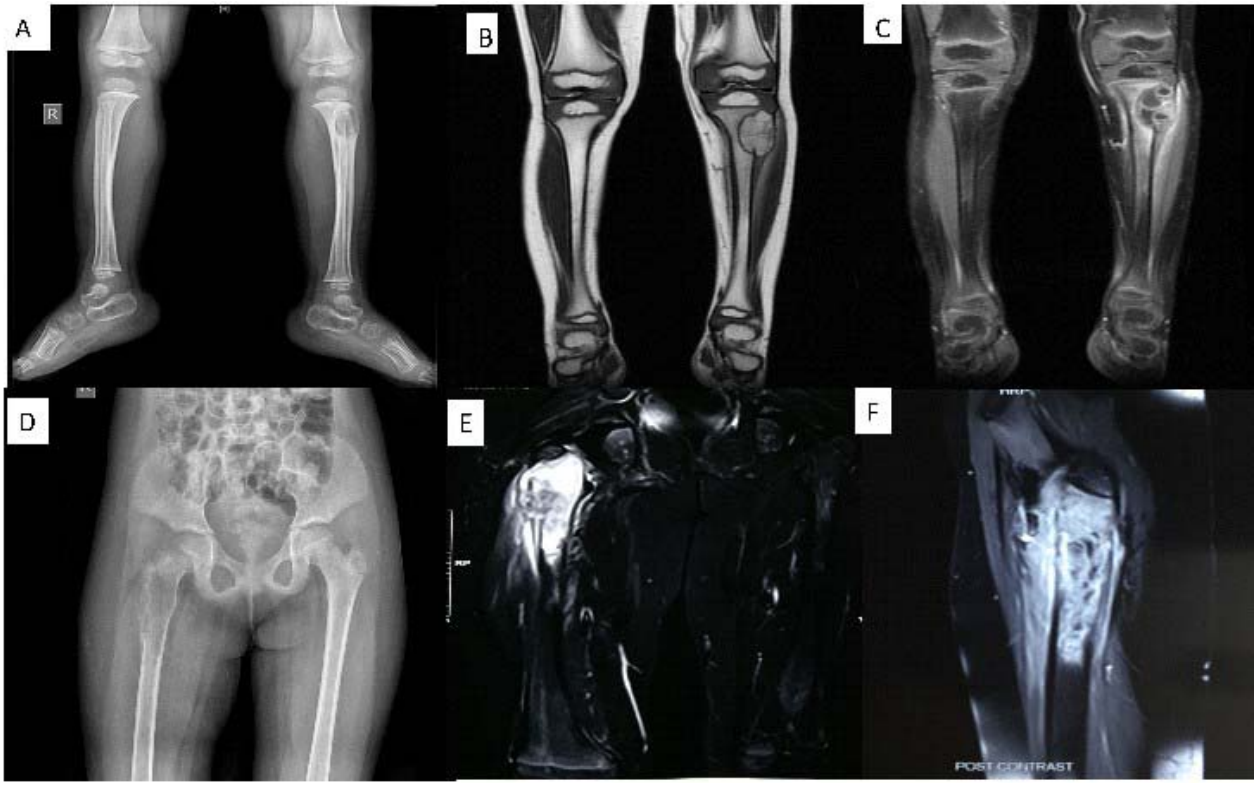
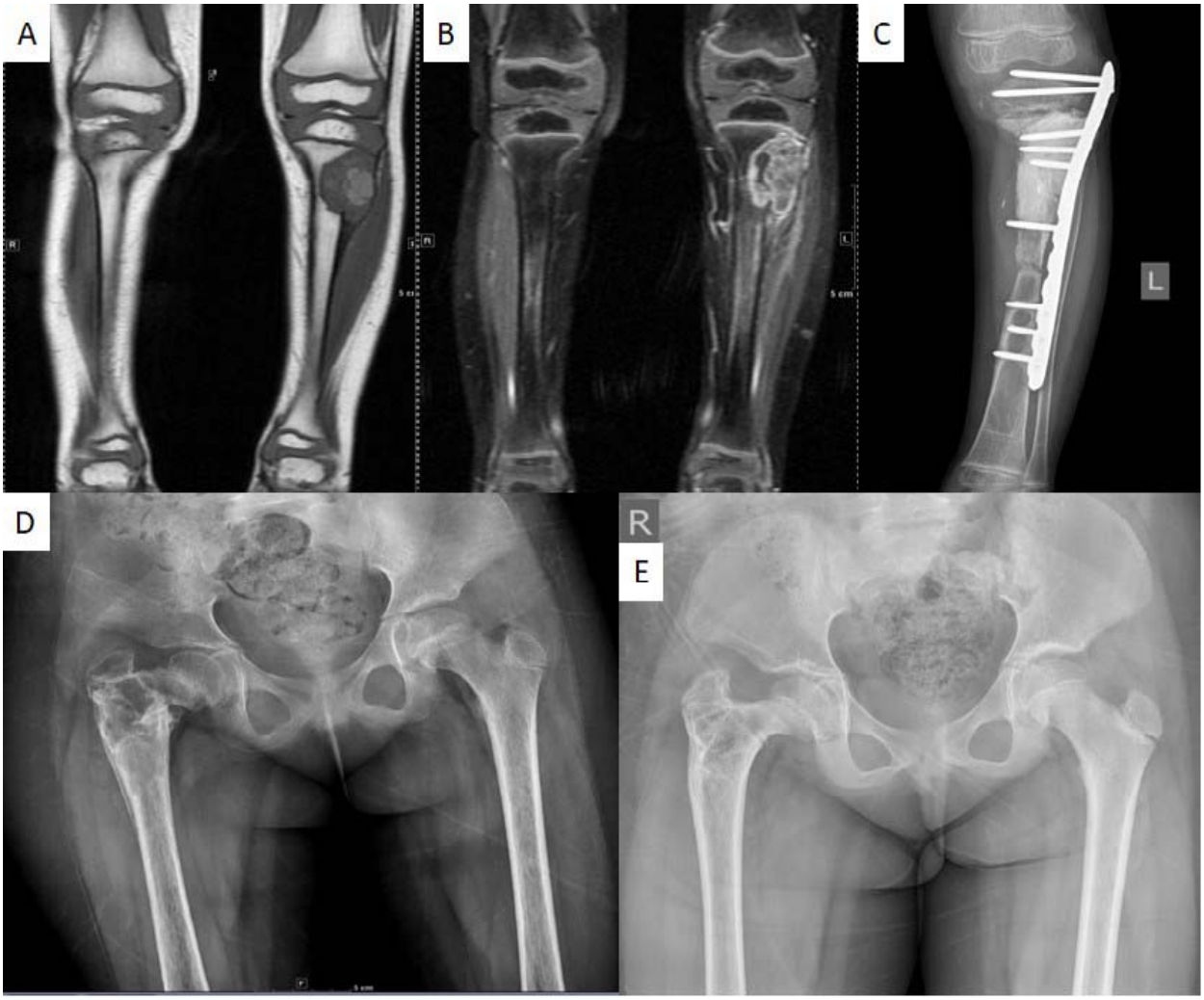


Web Fig. 1 (**A)** X-ray of case 1 showing well defined eccentrically located lytic expansile lesion involving proximal metadiaphyseal region of left tibia with a narrow zone of transition without periosteal reaction **(B)** T2 coronal section MRI of left tibia showing well corticated hyperintense eccentrically located mildly expansile lesion with fluid-fluid levels without periosteal reaction or cortical break **(C)** post-contrast coronal section MRI of left tibia showing heterogenous enhancing lesion with predominantly peripheral enhancement and enhancement of internal septa without any obvious solid enhancing area **(D)** X-ray of case 2 showing poorly defined lytic bone lesion with the significant periosteal reaction 'Codman's triangle' and cortical break in the proximal femur. (**E)** Coronal STIR image of the right femur showing hyperintense heterogeneous lesion with soft tissue hyperintensity(**F)** Post-contrast MRI of the right femur showing heterogeneously enhancing lesion with marrow involvement, cortical break, and soft tissue component.



Web Fig.2 (A) Case 1 MRI T1 coronal section of left tibia showing residual well corticated eccentric lesion with interval appearance of irregular T1 hyperintense area suggestive of intratumoral bleed **(B)** Case 1 Post-contrast MRI coronal section of left tibia showing interval regression of adjacent marrow changes and periosteal reaction with reduction in thickness and enhancement of internal septations**(C)** Case 1 post treatment X ray AP view knee joint post extracorporeal radiotherapy and reimplantation with internal fixation **(D and E)** Case 2 – serial X rays (post week 12 chemotherapy and end-of-treatment X ray) showing progressive mineralization of bone with regression of cortical destruction, periosteal reaction and soft tissue component.

Evaluation of Children With Hematuria: Deveil Lies in the Details!

We read with interest the paper by Mishra, et al. [1], and would like to compliment the authors on their work highlighting the importance of gross hematuria in children with various renal disorders. We have the following queries related to the paper:

The authors have noted infection-related glomerulonephritis (IRGN) to be the commonest cause of hematuria in their study; however, there is no clarity from methodology how IRGN was diagnosed. It is also not clear whether these children recovered completely on follow-up or if any of these children met the criteria for kidney biopsy [2] due to delayed or non-resolution, and reclassified as C3GN, which is known to present similarly [3].

In non-glomerular hematuria, the children labeled to have unknown cause could possibly have nutcracker syndrome, which is an important, and not so rare, cause of painless hematuria in children [4].

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AUTHORS' REPLY

We thank the authors for their interest in our study [1]. We herein provide detailed responses to the issues raised:

For the study purpose, all diagnoses, including IRGN, were made based on standard diagnostic criteria [2], and it was not possible to define them individually in the article, due to constraints of word limit. Most of the children diagnosed as IRGN were post-streptococcal glomerulonephritis. Others were those having similar presentation with self-limited course, quick recovery and normalization of kidney functions and C3, though, without raised ASO titres (other serological tests for evidence of streptococcal infection are not available in our hospital), but clinically and history-wise best explained as having an IRGN. Regarding kidney biopsy, as well as all further evaluations, standard indications were followed [3], as also mentioned in methods section of the paper. Recovery and follow-up details are already available in the Results section [1]. The diagnosis of IRGN was established with certainty only after following up C3 levels and ASO titers, if raised, till resolution.

In this study, four children with non-glomerular hematuria were labelled to have unknown cause. Nutcracker syndrome is one of the known causes of unexplained gross hematuria, which commonly presents with specific clinical features like pelvic or flank pain, varicocele, recurrent episodes, with an overall incidence of less than 2% of all children with hematuria [4]. However, this was not diagnosed in the four children after ultrasound, Doppler and cystoscopy, which are part of our department's work-up protocol in a child with non-glomerular hematuria. Moreover, the treatment for nutcracker syndrome is conservative till the age of 18 years as symptoms are known to resolve in many. All these patients with unexplained hematuria are under regular follow-up.

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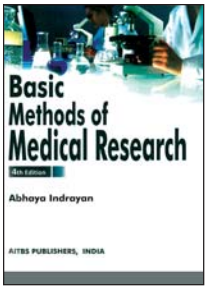
BOOK REVIEWS



Basic Methods of Medical Research

ABHAYA INDRAYAN
AITBS Publishers, India
J-5/6, Krishan Nagar, Delhi.
Pages: 394; Price: Rs. 499/-

An in-depth understanding of research methods necessitates reducing bias and uncertainty. A systematically designed study helps the researcher in finding sound scientific results.

This book provides a coherent approach to explain the intricacies of applied medical research from the conception of problem to reporting of the results. The concepts are presented with real-life examples and no prior special background knowledge is needed. Three chapters are devoted to medical uncertainties that help a researcher to understand the sources of bias and how to control these biases in designing as well as in the analysis stages. Important concepts of each chapter are highlighted in boxes, and a rich comprehensive glossary of methodological terms is provided at the end.

The book will be extremely useful for the postgraduate students of Medicine, Nursing, Pharmacy, and allied subjects, as well as for young medical faculties in preparing project protocols, thesis, dissertations, and papers for publication in medical journals.

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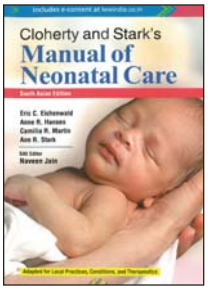

Manual of Neonatal Care

ERIC C EICHENWALD, ANNE R HANSEN, CAMILIA R MARTIN, ANN R STAR
SAE Editor: **NAVEEN JAIN**
Wolters Kluwer (India) Pvt . Ltd., New Delhi.
Pages: 1112; Price:Rs.1350/-.

India has made significant progress in maternal and neonatal care in the last decade. Neonatology contributes a significant proportion of pediatric practice, and there has always been a felt need for a neonatal care book that caters to the problems specific to South Asian countries. Choherty and Stark's Manual of Neonatal Care (South Asian Edition) covers the current knowledge of various perinatal condition, and at the same time fulfils the gap to a great extent, and is going to help students and healthcare providers practicing neonatal care.

The manual has 18 sections covering over 70 chapters, written by experienced authors from India and abroad. It has covered the Asian problem/issues very well. Chapters such as developmentally supportive care, discharge planning, decision-making, and ethical dilemmas are important additions.

I congratulate the editors and contributors for presenting this difficult subject in a simple, practical format, while maintaining an evidence-based approach.

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

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