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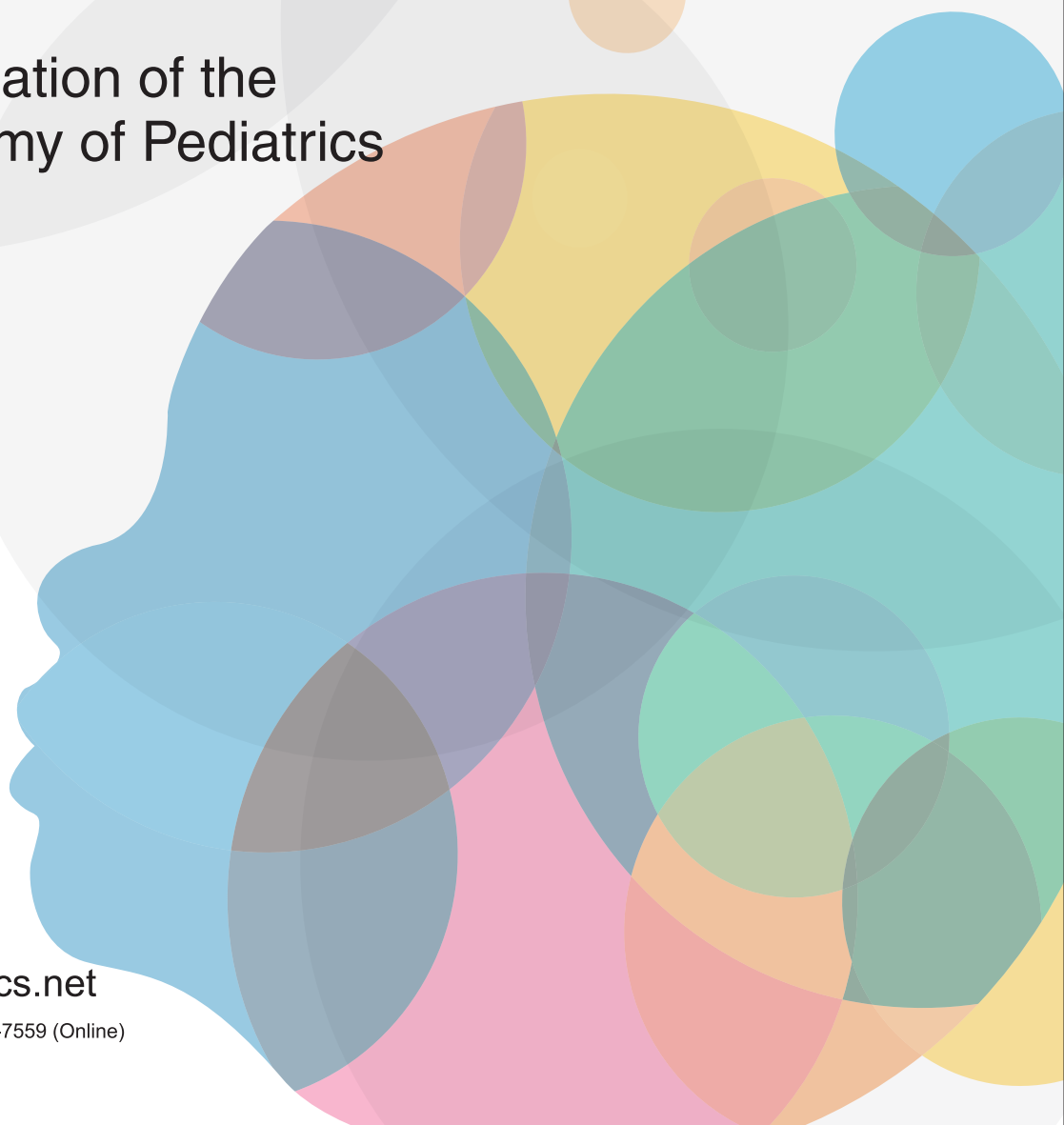
Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 59
NUMBER 11
November 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™

CLINICALLY mildness PROVEN®

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/8Mar2021/05

Indian Pediatrics

November 2022 Volume 59 Number 11

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Impact Factor 2021 of *Indian Pediatrics* is 3.839

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

Address for ordinary letters: **The Editor-in-Chief, Indian Pediatrics, P. Box No. 3889, New Delhi-110 049, India.**
Address for registered/speed post letters: **Dr. Devendra Mishra, Editor-in-Chief, Indian Pediatrics, 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049, India. Tel: (011) 46052593**
E-mail: *jiap@iapindia.org*; Website: *www.indianpediatrics.net*; LinkedIn: *indianpediatrics*
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Safe Roads for Our Children - Miles to Go !

REMESH KUMAR R
President, Indian Academy of Pediatrics 2022
drremesh2006@yahoo.com

Road accidents are the bane of modern civilization. With the invention of the motor vehicle and the increased human dependence on it for transportation, road accidents have become a routine occurrence in day-to-day life. Fatalities arising from road accidents are a common issue of concern and the focus of daily news. While all road accidents may not be fatal, many are responsible for serious injury, loss of limbs or other organs.Children are more vulnerable to road accidents than adults and make up a sizeable proportion of the victims. According to UNICEF, road traffic injuries are a leading killer of school-age children and adolescents globally, and affect developing countries in particular, who account for 90% of all the casualties on the world's roads. Worldwide, it is the number one killer of young people aged 15-29; the leading cause of death for boys aged 5-14; and a top five killer of girls aged 5 and over [1].

AN AVOIDABLE CATASTROPHE

Road safety and associated matters are among the most neglected issues in underdeveloped and developing countries, which are challenged to manage several competing public concerns. Take the following scenarios, for example:

- A family of four is preparing to cross a busy street. As the family is about to cross, the youngest kid – a five-year old – darts across all of a sudden, before the parents can even make a move to grab him. A passing scooterist knocks him down.
- An auto rickshaw with a kid and a parent is approaching the school gate. The child, who is excited to see his friends, suddenly jumps out of the vehicle and falls flat on his face. Fortunately, he suffers only minor bruises.
- A teenage cyclist is zipping down a road when a vehicle hits him, and he is severely injured. The people of the locality rescue him and rush him to a nearby hospital. Unfortunately, the duty doctor is not available, and the hospital also lacks a critical care unit. The boy later dies due to a delay in providing lifesaving treatment.

In each of the above scenarios, tragedy could have been avoided if only there was greater human preparedness. In the first instance, the simple act of one of the parents holding the hand of the child could have prevented the accident. In the second case, an aware parent could have seen through the impulsiveness of the child and averted the mishap. In the third example, the blame falls on the failure of the healthcare system to rise to the situation.

Around 60,000 children die due to road accidents in India every year, according to a study conducted by the National Institute of Mental Health and Neurosciences (NIMHANS) and US-based Underwriters Laboratories, citing figures from 2015 [2]. Losing a child to a road accident is among the worst fears of a parent. Unlike disease or disorder, traffic hazards are man-made and preventable. As stated earlier, casualties arising from road accidents can be greatly reduced with a better response from the healthcare fraternity. Hence, it is high time that we take a deeper interest in the subject and come up with pragmatic solutions.

INTERVENTIONS NEEDED

According to a recent study [3], road traffic injuries (RTIs) result in 1.35 million worldwide deaths, with 90% of them occurring in low- and middle-income countries (LMICs). Although, prevention remains the cornerstone of reducing RTI deaths, improved post-crash care is regarded as a critical intervention that can result in a 35% reduction in trauma mortality. If a complete trauma system were to be implemented in all LMICs with 100% coverage, over 200,000 lives per year would be saved, resulting in a 19% reduction in mortality from RTIs. The more realistic scenario of 50% coverage would result in over 100,000 lives per year saved, or an 8% reduction in mortality. Damage control resuscitation has the highest likelihood of saving lives at 50% coverage; followed by the availability and use of interventional radiology to control bleeding; tranexamic acid for patients with suspected bleeding; and pre-hospital tourniquet [3]. This study; however, covered the overall population and is not child-specific.

It is clear from the above that healthcare response should improve dramatically if we have to achieve better results on par with the developed world, where the casualty figures are significantly lower. Improvement in emergency and trauma care facilities is the need of the hour, and we have a long way to go in this sphere. IAP can take the lead in facilitating the transfer of advanced technologies and protocols from developed countries and modify them for Indian conditions.

On the other hand, prevention continues to be the most desirable goal. Hence, greater thrust should be placed on the prevention of road incidents through awareness and education programs. Such programs can be one of the focus areas for IAP branch units, which can collaborate with schools, traffic police, civic bodies and voluntary organizations to sensitize the public regarding day-to-day measures that can be implemented to enhance road safety.

The following are some of the preventive road safety measures that can be implemented:

- Hold the child's hand while near vehicles or crossing the road. Talk to the child about why it is important to hold hands. Adult supervision is very important in teaching road safety.
- Explain what one is doing when crossing the road together. Involve the child in deciding when it is safe to cross the road. This will teach the child to think in the traffic environment.
- Always be a good role model for the child by wearing a seatbelt, obeying road rules, driving courteously and crossing roads safely.
- Involve children in choosing safe places to play. Separate play areas from driveways and prohibit street play.
- Teach children how to read traffic signals and road signs, about not running on the streets, always using footpaths and zebra crossings.
- Teach children how to cross roads using the 'stop, look, listen and think' process – stop at the kerb, look and listen for traffic, and then decide whether it is safe to cross.
- Make sure children wear bright clothing that can be easily seen by road users.
- Parents often rely on private auto rickshaws, maxi cabs and taxis, which are overloaded beyond their authorized capacity. Parents, schools, and traffic police should address safety issues relating to this.
- Teach children about safe car behavior – such as strapping seatbelts, not trying to open the car door while moving, not sticking one's hand or head out of a moving vehicle; and always getting off from the safer side of the car.
- Teach safe cycling to kids. Get them used to wearing a helmet, knee guards and elbow guards. If they're riding in the night, make sure they wear bright-colored shoes and clothing, not dark hues that put them at risk in the dark.
- Teach children not to cross near blind spots, such as crossing a road between vehicles or any other large object that could endanger them. Children should always cross from a clear area.
- Observe road safety day/week in schools, regularly communicate road safety issues to children.
- Encourage children to take part in interactive programs on road safety conducted by the traffic police department.

Yes, it is quite certain that we can do a lot to prevent road accidents involving children and to save lives in case of casualties. I appeal to IAP branches to launch sustained initiatives to propagate awareness through greater involvement with the community.

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

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INVITED COMMENTARY

Metabolic Bone Disease of Prematurity

JOHN M PETTIFOR,* KEBASHNI THANDRAYEN
Department of Paediatrics, Chris Hani Baragwanath Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
**John.Pettifor@wits.ac.za*

Metabolic bone disease of prematurity (MBDP) is a significant health risk with an incidence of approximately 20% in very low birthweight (VLBW) infants and up to 60% in extremely low birthweight (ELBW) infants in many neonatal units, despite an increasing awareness of its contribution to overall morbidity and protocols to reduce its incidence. The provision of adequate nutrients to very preterm infants in the first weeks of life to prevent increased morbidity (such as poor neurological development, impaired growth, bronchopulmonary dysplasia, retinopathy of prematurity, and metabolic bone disease) is a complex strategy [1]. In this issue of *Indian Pediatrics*, Pournami and colleagues [2] report on a prospective study aimed at reducing the incidence of MBDP in very low birthweight infants with gestational ages of ≤30 weeks by early monitoring of serum phosphorus and supplementation with intravenous and/or oral phosphorus from day 4 of life. Once enteral feeding rates (human milk) of 40 mL/kg/day were achieved, a human milk fortifier was progressively introduced. Overall, the rate of MBDP ranged from 2.8% in those infants with gestational ages between 28-30 weeks to 69.2% in those with gestational ages ≤26 weeks [2]. The overall incidence was considered by the authors to be less than that found in their earlier study in which attention to early phosphorus supplementation was less stringent; the results obtained thus encourage the authors to promote early mandatory use of phosphorus supplements [2].

Although, phosphorus deficiency is recognized as a major player in the pathogenesis of MBDP, perturbations in calcium homeostasis and vitamin D status may also play significant roles, together with serum phosphorus concentrations. Serum phosphorus needs to be monitored carefully during the first few months of life in very preterm infants, especially in those who have respiratory and gastrointestinal complications or who have been on methylxanthines, diuretics or corticosteroids. Researchers have cautioned about the risk of increasing MBDP through stimulating secondary hyper-parathyroidism when low birthweight infants are supplemented with phosphorus supplements alone [3]. In a recent study [4], parathyroid hormone (PTH) concentrations were found to be elevated at a mean of 15 days post-delivery in 40.3% of neonates with gestational ages <32 weeks. Perhaps, not surprisingly, PTH levels did not correlate with MBDP, when the latter was diagnosed using elevated alkaline phosphatase levels and hypophosphatemia, but they were inversely related to gestational age and urinary Ca/Cr ratios. Furthermore, PTH levels were found to be elevated in over 80% of ELBW neonates who were diagnosed with osteopenia on radiographs [5]. These findings indicate that inadequate retention of calcium also plays a major role in MBDP, despite few neonatal units monitoring PTH routinely in very premature infants (in the USA only 1.7% of units monitor PTH routinely).

Even though the role of vitamin D in phosphorus and calcium intestinal absorption in the first few weeks of life is unclear [6], it is important that vitamin D deficiency in the neonate be prevented. Thus, vitamin D supplementation of pregnant mothers should be considered a priority in those countries where maternal vitamin D deficiency is common, so as to ensure neonatal vitamin D sufficiency. Infants born to mothers who are vitamin D deficient, are likely to be vitamin D deficient as neonatal 25-hydroxyvitamin D (25(OH)D) concentrations are generally about 80% of maternal levels. With a half-life of approximately 21 days, 25(OH)D levels in the neonate fall rapidly unless vitamin D supplementation begins as soon as the infant is taking enteral feeds successfully. Although, some neonatologists recommend vitamin D supplementation of premature infants at levels (800-1000 IU/day) greater than those recommended for full-term infants (400 IU/day), there is little evidence to suggest that these higher levels are required unless there is hepatic or intestinal dysfunction. The use of activated vitamin D (calcitriol or alfacalcidol) has not been shown to have advantages over the use of the parent vitamin D, except possibly in situations of severe kidney or liver disease. The

need for close monitoring of vitamin D status with frequent measurements of serum 25(OH)D, which is costly, is unnecessary if there are no contraindications to routine vitamin D supplementation.

In order to assess the efficacy of early phosphate supplementation (within 4 days of life) in the prevention and management of MBDP and in reducing the other complications such as growth retardation in VLBW and ELBW infants, there is a need for more formal assessments through randomized controlled trials, monitoring not only serum phosphorus, but also other disturbances in bone mineral homeostasis.

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

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INVITED COMMENTARY

To Supplement or Not to Supplement With the Sunshine Vitamin in Sunny Countries?

SUMA UDAY,[1,2] WOLFGANG HÖGLER[2,3]*

[1]*Department of Endocrinology and Diabetes, Birmingham Women's and Children's Hospital, Steelhouse lane, Birmingham, UK;*
[2]*Institute of Metabolism and Systems Research, University of Birmingham, Edgbaston, Birmingham, UK;*
[3]*Department of Paediatrics and Adolescent Medicine, Johannes Kepler University Linz, 4020 Linz, Austria.*
**Wolfgang.Hoegler@kepleruniklinikum.at*

Vitamin D, also known as the sunshine vitamin, is readily synthesized by the skin on exposure to Ultraviolet B (UVB) radiation in sunlight. However, there are multiple factors which prevent humans from effectively synthesizing adequate vitamin D such as dark skin pigmentation, use of culturally covered clothing, unavailable or unreliable sunlight exposure. Classifying vitamin D as a vitamin is a misnomer given that it is derived from cholesterol and structurally resembles other steroid hormones such as the adrenal and sex hormones. Moreover, active vitamin D or 1,25-dihydroxyvitamin D is in fact a potent hormone that increases intestinal absorption of calcium and phosphate. Lack of vitamin D leads not only to bone hypomineralization, causing rickets in children and osteomalacia in children and adults, but can also lead to life-threatening complications of hypocalcemia in infants such as seizures, hypocalcemic dilated cardiomyopathy and rarely death [1]. Consequently, ensuring adequate vitamin D status in infants is undisputable [2].

Goyal and colleagues [3] demonstrate, in an open label randomized controlled trail in infants that daily supplementation with 400 IU vitamin D is more effective than 30 minutes per week sunlight exposure in improving serum 25 hydroxyvitamin D levels and preventing rickets in infants at six months. Given that the risk of sun burns and later skin cancer in individuals of South Asian skin type are very rare, perhaps longer periods of sunlight exposure could have been explored since sun exposure duration is known to correlate positively with serum 25-hydroxyvitamin D levels [4].

Unsurprisingly, the response to intervention was directly correlated to compliance in both sunlight and supplementation groups in the study by Goyal, et al. [3], and parents were more compliant with supplement use than sunlight exposure. Further exploration of factors that led to non-compliance with the seemingly more natural and cheaper public health measure, sunlight exposure, would have been valued. Whilst it has been highlighted that supplements are more effective than sunlight exposure in improving serum vitamin D levels, the question is whether compliance can be ensured over prolonged periods of time in the real world without frequent monitoring which is offered in the research setting? The authors acknowledge the issues with adherence and cost attached to supplement use [3].

A longitudinal study from Ireland of 364 infants demonstrated that daily supplement initiation at birth was 92%, falling to 30% at 12 months of age in a well-educated and well informed population [5]. We have previously demonstrated the variation in adherence to infant supplementation across various European countries where infant vitamin D supplementation policies are frequently in place [6]. Improved adherence was noted with robust policies incorporating national monitoring of supplement uptake and parental education [6]. Having robust policies in place and ensuring their effective implementation is a multi-task operation and involves various stakeholders from policy makers to politicians to healthcare professionals and families to name a few [7]. Whilst sunshine deplete countries which already have vitamin D supplementation policies in place, such as the United Kingdom, are struggling to effectively implement these policies and exploring alternative strategies [7]; sunshine replete countries such as India are appreciating that supplementation is more effective than sunlight exposure. Achieving vitamin D sufficiency through sunlight exposure in sun rich countries is dependent on multiple factors including season, pollution, desire for fair skin, increase in time spent indoors, and not to mention, the cautions imposed by dermatologists [8]. So how do we best, and cost-effectively, tackle the global public health concern of vitamin D deficiency? The answer is mandatory food

fortification with additional supplementation of specific risk groups.

The lifelong cycle of vitamin D deficiency begins in utero with the deficient mother passing on the deficiency to her newborn. Therefore, recognizing the need for supplementation in the pregnant mother is the first step towards eliminating deficiency in the newborn followed by supplementation of the infant. Several studies have highlighted the high prevalence of vitamin D deficiency in adolescents and women of childbearing age groups. However, reaching every individual at risk through supplementation is impossible. Much more elegant is food fortification with vitamin D, which is a feasible and cost-effective endeavor for willing nations [9]. With supplementation approaches, caution should be exercised in countries where pharmaceutical marketing regulations are less vigorous and no monitoring policies are in place, i.e., lending to the free availability of active vitamin D analogues (such as calcitriol and alfacalcidol), over the counter [10]. Less informed healthcare professionals, chemists or members of the public may not appreciate the difference between chole/ergocalciferol preparations and active vitamin D analogues [11].

In conclusion, supplementation of infants with vitamin D is indicated globally and certainly should be implemented in India, even more so since traditional diets are low in calcium, putting all infants at risk. Sunshine is not an option that can be properly dosed or adhered to. Ultimately, achieving vitamin D sufficiency at a population level requires multi-prong policies tailored to the local environment and population, specifically to the most vulnerable groups i.e., ethnic risk groups, and particularly their infants and pregnant women.

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

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PERSPECTIVE

Childhood and Adolescent Anemia Burden in India: The Way Forward

ANURA VISWANATH KURPAD,[1] HARSHPAL SINGH SACHDEV[2]

From [1]Department of Physiology, St John's Medical College, Bengaluru, Karnataka; [2]Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi.

Correspondence to: Prof Harshpal Singh Sachdev, Senior Consultant Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, B-16 Qutab Institutional Area, New Delhi 110 016. hpssachdev@gmail.com

The burden of anemia in Indian children, based on capillary blood sampling, is believed to be profound and worsening (67.1%) according to the successive National Family Health Surveys (NFHS). This might be an overestimate. The recent Comprehensive National Nutrition Survey of Indian children, that used venous blood sampling, found only less than half (30.7%) the NFHS prevalence, of which only one third was due to iron deficiency (ID). Unfortunately, the apparently worsening NFHS anemia burden estimate has been interpreted as an inadequacy of the present iron supplementation policy. This has led to additional iron supply through mandatory rice fortification. However, the lack of efficacy of iron supplementation appears inevitable, if the true prevalence of iron deficiency anemia is only about 10%. Thus, etiology is a critical consideration when devising appropriate and effective prevention policies. Future policies must focus on precision, thoughtfulness, restraint, and community engagement.

Keywords: *Fortification, Hemoglobin, Prevalence, Iron deficiency*.

Published online: Aug 26, 2022; ***PII****: S097475591600447*

THE PRESENT

Current Prevalence and Causes of Anemia in India

The most influential surveys to describe the state of anemia in Indian women of reproductive age (WRA) and children (6-59 months) have been the different rounds of the National Family Health Survey (NFHS), conducted every 5-10 years. In the most recent of these surveys, from NFHS-4 in 2015-2016 [1], to NFHS-5 in 2019-2021 [2], the prevalence of anemia has been high, but changing in an apparently adverse manner from 53.2% to 57.2% in WRA and 58.6% to 67.1% in children. This has been a matter of concern and debate. These NFHS surveys, though conducted with a granularity that could quantify anemia at the district level, were nevertheless limited methodologically (see below for uncertainties) and did not investigate the specific etiologies of anemia. Without this knowledge, it has been erroneously assumed that the predominant or sole cause of anemia in India is dietary iron deficiency (ID). Thus, most policy initiatives focus on iron, without any specific knowledge of national prevalence of ID.

This knowledge lacuna was filled by a recent national survey of Indian children aged 1-19 years, called the Comprehensive National Nutrition Survey (CNNS), conducted between 2016 and 2018 [3]. This unique survey investigated not only the prevalence of anemia, which on average was about half (30.7%) of that estimated by the NFHS, but also its specific causes, by assessing venous blood biomarkers that reflected the body status of different erythropoietic nutrients. Examples of these measured markers are serum ferritin for iron status, C-reactive protein for inflammation (which affects ferritin concentrations and allows for filtering out children who had infections or inflammation), serum folate, vitamin B_{12} and vitamin A concentrations for their respective status [3]. All these have diagnostic cut-offs that indicate deficiency (or the presence of inflammation for CRP).

In an analysis of the CNNS anemia etiology [4], it was shown that in children aged 1-4 years, only 36% of anemia was due to ID, while 19% was due to folate and vitamin B_{12} deficiency, and the rest was due to other causes. In older primary school children, only 16% of anemia was due to ID, while 24% was due to folate and vitamin B_{12} deficiency, and the rest was due to other causes. In adolescent children, only 21% of anemia was due to ID, while 25% was due to folate and vitamin B_{12} deficiency, while the rest was due to other causes. In effect, the CNNS has shown us that a lack of dietary iron is not the major cause of anemia in India, especially in older children, and that other causes, including inflammation, may be more important, and should be considered when going forward.

THE UNCERTAINTIES

Is the Prevalence of Anemia Really High, and Is Micronutrient Deficiency Really Profound and Pervasive in India?

With these extraordinarily high and persistent NFHS

anemia rates, there are uncertainties. Is anemia prevalence really that high? Is it possible that such a high baseline prevalence could have stubbornly resisted the effects of iron supplementation for decades? One possibility for a lack of response to supplementation is false-positive anemia diagnosis, or that ID prevalence was wrongly presumed to be overly high, from the very beginning.

Therefore, it is important to consider if the estimates of anemia or ID prevalence are inflated in India. There are at least two reasons to believe this is correct:

Blood Sample

The first reason is the way in which blood is sampled for Hb estimation. In the influential NFHS surveys, capillary blood from a finger prick is used to measure its Hb concentration [1,2]. An important study from Uttar Pradesh, on almost 1000 women who agreed to simultaneous sampling of capillary and venous (antecubital vein) blood, with immediate measurement of both blood samples on the same point-of-care instrument, showed that capillary blood had a lower hemoglobin (Hb) concentration than venous blood, by about 1 g/dL [5]. This meant that the anemia prevalence, measured by venous blood was 35.2%, about half that measured by the capillary blood sample (59.2%) in the same women. This is the best evidence available for a direct comparison between capillary and venous blood, since issues like different instrumentation for different blood samples, and long and differential wait times for analysis, plague other comparative studies.

Hemoglobin Cut-off

The second reason to think that anemia prevalence might be overestimated, is that the diagnostic Hb cut-off may be wrong, or too high. A higher cut-off will result in more anemia being diagnosed, as the average Hb value in the Indian WRA population [6] is close to the current Hb cut-off that is suggested by the WHO [7]. The problem is that the WHO Hb cut-off is based on a statistical examination of the Hb distribution in Western healthy populations (the cut-off is taken as the 5th percentile of this normal distribution). However, even within the USA, there are differences in Hb distributions in healthy black and white populations surveyed in the National Health and Nutrition Examination Survey [8]. Therefore, there is good reason to believe that the Hb distribution might be left-shifted in healthy Asian populations, for example. If so, this would result in a lower Hb cut-off. In a rigorous examination of healthy children from the CNNS, based on a very large number of filters for socio-economic status and biomarkers for adequate nutritional status among others, the 5^{th} percentile of the Hb distribution for boys and girls aged 1-19 years, was 1-2 g/dL lower than the WHO prescribed cut-off [9]. A similar phenomenon has been observed in an analysis on preschool children and WRA involving 25 low-middle income countries [10]. Using the India-specific cut-offs for children [9] in the original CNNS sample, would lower the national anemia prevalence substantially, by two-thirds.

Effectively, the correction of both these problems (the type of blood sampling and the Hb cut-off used) might reduce the anemia prevalence to less than 20% but confirming this will need prospective national surveys with venous blood, as well as consensus on the need for population-specific Hb cut-offs, with the implicit recognition that one-size-does-not-fit-all.

Iron Requirement

Finally, iron deficiency in India has been overestimated in terms of the daily requirement metric. In part, this was due to the substantially higher iron requirements that were previously suggested for Indian WRA, of 20-30 mg/day [11,12]. This requirement, when conflated with the Indian vegetarian diet containing 8.5 mg iron/1000 Kcal of energy, suggested that most Indians would have inadequate iron intake, and therefore, high prevalence of iron deficiency (ID). However, this is an overestimate, and the present correct daily iron requirement for WRA, defined in 2020, is 15 mg/day [13], met in a diet of 1750 Kcal/day, and easily attainable from normal diverse diets. The final proof of a lower-than-expected ID prevalence lies in empirical data, which are available from the CNNS [14]. ID prevalence was about 30% in children, and even lower (11-15%) in primary school children and adolescent boys [14]. The patterning of ID (measured as CRP adjusted serum ferritin) was also counterintuitive, in that it was higher in urban children, and in the higher wealth quintiles, despite adjustment for relevant confounders. The utilization of iron to form Hb was therefore relatively ineffective in the poorer children, possibly due to residual biological effects of earlier infections and deficiencies of additional hematopoietic nutrients [14]. This provides credence to the need for multiple nutrients (diverse food) rather than single chemical nutrient initiatives and simultaneous attention to combating inflammation, including through improved water supply and sanitation.

THE FUTURE: THE WAY FORWARD

Delink nutrient supplementation policies to simple anemia prevalence

The prevalence of anemia (however high or low that may be) cannot be attributed to a single nutrient deficiency and should not be translated into a supplementation policy for that alone. Anemia is multifactorial in etiology, and single

nutrient supplementation policies must be delinked from simple anemia prevalence estimates. For example, it is now well known that iron deficiency is not the common cause for deficiency anemia in India; it is only one cause. Other erythropoietic nutrients like vitamin B_{12}, folate and protein are also important. Hereditary anemias like thalassemia or sickle cell anemia are prevalent in certain parts of India. Hygiene and the environment [15], including air pollution with PM2.5 [16], may be other contributing factors. A holistic approach is required, instead of fragmentary initiatives. Thus, policy initiatives that target specific nutrients like iron in response to a general survey of anemia, without any knowledge of cause, or any knowledge of whether dietary iron is inadequate, is a knee-jerk reaction. Given that nutrients in excess can be dangerous, this is unjustified, and there is a need for precision. A careful and measured consideration of all the facts at hand is required, and if the facts are unavailable, then relevant surveys are required.

Stop Unbalanced Policy Initiatives

Even if a single nutrient policy is initiated, over-enthusiastic and muscular implementation, instead of measured and precise steps, is an unbalanced approach that is unlikely to yield any dividends. It is important to recognize that single policy approaches, including the layering of identical interventions [17], also have their own dangers. For example, universal and mandatory iron supplementation and/or fortification, which could result in excess iron intake and body stores, can increase the risk of diabetes or dyslipidemia [18], or oxidative risk to those with hereditary anemias, even with heterozygous traits [19,20], or the risk of an adverse composition of the micro-biome in children who eat iron fortified food [21]. There will be severe penalties that will be paid by those subjected to these unbalanced policies. A simpler way to filter out ineffective (and potentially unbalanced) approaches, is to simply examine systematic reviews of the efficacy of the intended policy initiative. An example is with rice fortification, where a systematic review of all trials performed with fortified rice on humans, concluded that it is unlikely to prevent anemia in the population [22]. That should have given some pause.

Give Food a Chance: It is the Most Pragmatic Way Forward

A case in point for food, is the recent finding that cessation of the mid-day-meal during the one-year COVID lockdown, in 2020-2021, resulted in an increase in anemia prevalence in South Indian school children; yet the prevalence of iron deficiency did not increase during this period in these children. This demonstrates the importance of a mixed diet supplying multiple erythropoietic micronutrients [23]. Thus, whole food approaches will be better and safer for children. However, it is often stated that the only way forward is to supplement or fortify food staples with chemical nutrients, rather than the more difficult but logical food-based approach. These chemical approaches are touted as 'practical and pragmatic', 'short-term' and eventually, 'complementary to diverse diets'. Nothing is further from the truth: these are slogans for technological solutions that do not benefit the real stakeholders, or the children, who only need simple but diverse diets, delivered with precision. Indeed, the fortification of staple foods with chemicals might be antithetical to dietary diversity, as populations are educated to eat only that fortified staple.

Do Not Forget the Environment

Going back to the analysis of anemia in the CNNS data [4], the largest proportion of its prevalence in primary school children (almost half), and pre-school children and adolescents (about one third) was of 'other' unknown causes, including inflammation. That is, these causes were other than nutrient deficiency. Subclinical inflammation is an important cause of anemia, due to many reasons, including reduced erythropoiesis due to cytokine effects on the bone marrow, reduced iron absorption, and reduced erythrocyte survival time [24]. While it is difficult to unequivocally prove the efficacy of specific sanitation measures, for a variety of reasons, negative associations between anemia and improved sanitation have been observed [25], suggesting that poverty alleviation, with improvement of hygiene, pollution [15,16] and adequate prevention and treatment of childhood infections, is a critical part of reducing childhood anemia prevalence.

CONCLUSIONS

The future for anemia prevention policies is one of thoughtfulness, precision, restraint, and community engagement through education. Thoughtfulness and restraint go together, through rigorous review of the evidence available. They lead to the inevitable conclusion that it is time to implement precision in public health, since the etiology of anemia is multi-factorial and varies geographically and temporally. Initiatives to implement precision in public health are underway in India, for example, with the Screen and Test approach for prevention and treatment of anemia [26].

Precision will avoid the universal and mandatory one-size-fits-all interventional approach, with its risk of many harms, including economic and ethical dimensions [27]. Multi-sectoral involvements and actions are required, instead of the popular and ever-present lament and focus on iron, as if a single nutrient could offer a silver bullet. In the near future, point-of-care devices must be developed

to enable specific etiological diagnoses of anemia, to define appropriate interventions at the individual level. This individual approach to public health, will have a positive, multiplicative effect on anemia. At all costs, current methods and metrics must be improved, and thoughtful restraint applied, such that unnecessary panic, and reactionary knee-jerk policies do not occur.

Acknowledgements: AVK and HSS are recipients of the Wellcome Trust/Department of Biotechnology India Alliance Clinical/Public Health Research Centre Grant (IA/CRC/19/1/610006). AVK is also supported by the India Alliance through their Margdarshi Fellowship.

Contributors: Conceptualized, drafted and finalized by both authors, who will be equally accountable for the content.

Funding: None; *Competing interests*: HSS is a member of the WHO Guideline Development Group on Anemia: Use and interpretation of haemoglobin concentrations for assessing anemia status in individuals and populations. AVK and HSS are members of the National Technical Board on Nutrition and of Task Forces and Expert Groups on anemia constituted by the Department of Biotechnology, Ministry of Health and Family Welfare and the Indian Council of Medical Research.

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RESEARCH PAPER

Incidence of Metabolic Bone Disease After Implementation of Bone Protective Nutritional Strategies: *A Prospective Cohort Study*

ARIF ABDULSALAM KOLISAMBEEVI, FEMITHA POURNAMI, AJAI KUMAR PRITHVI, ANAND NANDAKUMAR, JYOTHI PRABHAKAR, NAVEEN JAIN

From Department of Neonatology, Kerala Institute of Medical Sciences, Trivandrum, Kerala.

Correspondence to: Dr Femitha Pournami, Consultant and Academic Coordinator, Department of Neonatology, Kerala Institute of Medical Sciences, Trivandrum 695 029, Kerala. femi_shifas@yahoo.com

Received: April 20, 2022; Initial review: June 04, 2022; Accepted: September 07, 2022.

Background: Metabolic bone disease (MBD) is a morbidity of multifactorial etiology with a high incidence in very preterm infants. We planned to study the incidence of MBD after implementation of bone health focussed nutritional strategy (BNS) in those <30 weeks gestation at birth.

Methods: This prospective cohort study including preterm newborns (<30 weeks) who received nutrition that incorporated (*a*) Early initiation of intravenous potassium phosphate; (*b*) Early enteral supplementation with multicomponent human milk fortifier at enteral feed tolerance of 40 mL/kg/day feeds itself; and (*c*) Weekly phosphorus measurements with optimization of enteral intakes. Incidence of MBD at 4 weeks of postnatal age and beyond were analyzed. Other relevant safety and clinical outcomes were measured.

Results: Of the 67 included neonates receiving BNS, 20.9% were classified as MBD. There was a low rate of hyperphosphatemia (4.5%) and hyperkalemia (2.9%). Full enteral feeds were achieved by median (IQR) of 6 (5,7) postnatal days.

Conclusion: In preterm newborns (24-30 weeks) MBD incidence was 20.9% after BNS was implemented. Intravenous potassium salt of phosphorus and early use of HMF were safe and feasible.

Keywords: *Bone health*, *Intravenous phosphorus, Outcome, Preterm nutrition*.

Trial Registration: CTRI/2020/12/029576 ***Published online*:** September 09, 2022; ***PII:*** S097475591600453

Optimizing nutition in very preterm infants, right at the outset, constitutes a pivotal part of neonatal intensive care. Adequate quantities of early mineral intakes would ensure maintenance of physiological serum levels and aid in establishing normal postnatal growth [1]. Metabolic bone disease (MBD) in preterm infants result from many reasons: inadequate stores and postnatal deficiency of phosphorus, calcium, magnesium, vitamin D; use of drugs like caffeine, steroids; and lack of movement [2]. Reporting of MBD is largely inadequate with non-uniform definitions and unclear descriptions of strategies to prevent the disorder [3,4]. Diagnosis of MBD is challenging due to its indolent nature, manifesting only when severe demineralisation sets in, with clinical features like craniotabes, overt rickets, growth failure and even fractures [5].

Although phosphorus administration is recommended prophylactically from the very first hours after birth, this is standard practice only in those parts of the world where suitable formulations are available [6]. The lack thereof of literature pertaining to early phosphorus use in this part of the world is probably proof of suboptimal use [7]. We are restricted by non-availability of intravenous phosphorus formulations that can be used in immediate postnatal life. Moreover, most units across the country use enteral supplementation as multicomponent human milk fortifier (HMF) after at least 100 mL/kg/day milk feeds are safely established and tolerated [8]. In a previous study published from our own unit, we reported a high incidence of MBD (30%) in infants born between 27-32 weeks gestation despite implementing what we considered a practical and optimal nutrition policy [9]. This revelation led us to revise

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our protocols to: *i*) Supplement phosphorus early with the only available potassium salt of phosphorus as soon as safely possible; *ii*) Strict adherence to standard feed regimens (SFR) along with use of human milk and earlier initiation of oral phosphorus as HMF (when infant tolerated 40 mL/kg/day feeds); and *iii*) Weekly monitoring of serum phosphorus levels to optimize intakes as intravenous (IV) or oral formulation based on the infants' parenteral/enteral nutritional status. This study aimed to prospectively assess the incidence of MBD in those born at ≤30 weeks gestation after implemen-tation of a bone health focussed nutritional strategy (BNS).

METHODS

This prospective observational study was conducted between January, 2020 and April, 2021, in our Level IIIB teaching unit. The institute has written policies for commencing aggressive parenteral nutrition soon after birth, minimal enteral nutrition and standard feed regimens, use of mother's own milk (MOM) and pasteurized donor human milk (PDHM) [9,10].

All in-born and out-born neonates, ≤30 weeks gestation, admitted within 24 hours of age, were included. Those with congenital or acquired renal diseases, whose parents refused consent, and who did not survive or did not complete care in the unit till discharge were excluded. Written informed consent was taken from parents for data collection. Institutional ethics committee and scientific research committee approval was obtained before initiation of the study. The study protocol was registered with the Clinical Trials Registry of India.

All eligible neonates were managed as per the BNS, constituting supplementation of intraveneous potassium phosphorous, enteral phosphorous as HMF introduced earlier than conventional practice and optimisation of phosphorous supplementation by weekly monitoring of serum levels. Supplementation of intraveneous phosphorus, as a potassium phosphate salt, was initiated usually by day 2 or 3 of life, if urine output >1mL/kg/day and serum potassium <5.5 meq/dL. The amount of intraveneous phosphorus (Potphos) in parenteral nutrition was calculated to target potassium requirements (1-2 meq/kg/day) and phosphorus requirements (25-50 mg/kg/day). Intraveneous phosphorus was continued till the neonate was on parenteral nutrition (which was stopped when feeds reached atleast 100 mL/kg/day feeds). Daily serum potassium and phosphorus levels were measured while on IV supplementation. If potassium levels was noted ≥6.5 mEq/L, or phosphorus >8 mg/dL, IV phosphate was withheld till values were normal. Enteral phosphorus as HMF was initiated early once enteral feeds of 40 ml/kg/day was tolerated (at half strength, i.e., half of 1 g sachet in 25 mL expressed breast milk or PDHM) [11]. HMF was changed to the standard, full strength (1 g in 25 mL MOM/PDHM) once the neonate was on 100 mL/kg enteral feeds. Target enteral phosphorus intake targeted was 100 mg/kg/day of phosphorus, once full enteral feeds were achieved. If serum phosphorus remained <5.5 mg/dL, additional phos-phorus was supplemented as oral calcium phosphorus (syrup Ossopan D). If phosphorus levels still remained low despite optimum supplementation, vitamin D intake was optimized and phosphorus was supplemented separately using sodium-acid-phosphate granules (Addphos, Steadfast Medishield) to optimize enteral absorption [12]. We assessed the side effects in terms of proportion of neonates having hyperkalemia, hyperphosphatemia while on IV phosphorus, days to full feeds (as a measure of feed intolerance, given that early HMF was used), invasive ventilation days, bronchopulmonary dysplasia and extrauterine growth restriction (EUGR) [13,14].

Metabolic bone disease was defined as the nadir of serum phosphorous <5.5 mg/dL or the peak serum alkaline phosphatase (ALP) >800 IU/L, as measured from 4 weeks postnatal age till discharge [15]. Any clinical signs of MBD were noted. Radiological investigations were done, if indicated.

Sample size was calculated for an estimated true proportion of MBD as 0.3, with precision level of ±0.12 and a Confidence level of 0.95, to be 57 [9]. Allowing a loss of 10% (due to death or transfer out before completion of treatment), final sample size was planned to be 62. Statistical analysis was conducted using STATA version 16.

Statistical analysis: Fisher exact test was done for comparison of proportions. A value of $P<0.05$ was considered statistically significant.

RESULTS

Of 71 infants born at ≤30 weeks gestation, 67 were included (2 infants were transferred out before completion of care, 1 died and 1 had a major surgical condition). The baseline characteristics are depicted in **Table I**. The different parameters related to BNS are described in **Table II**. Half strength HMF was added when infants reached median (IQR) enteral feed tolerance of 60 (60,60) mL/kg/day.

Table I Baseline Characteristics of Preterm Newborns (< 30 weeks) Enrolled for Bone Nutritional Strategy (*N*=67)

Characteristics	*No.* (%)
Gestational age[a]	29 (27,30)
Birth weight (g) [b]	1071 (268)
Small for gestational age	20 (29)
Male sex	34 (51)
Inborn babies	65 (97)
Cesarean section	65 (97)
Antenatal steroids	
Complete coverage	35 (52)
Incomplete coverage	32 (48)
Chorioamnionitis	4 (6)
Pregnancy-induced hypertension	10 (15)
Abnormal doppler	19 (28)
PPROM	6 (9)

All values are in frequency (%), except [a]median (IQR) or [b]mean (SD). PPROM–preterm premature rupture of membrane.

Table II Parameters of Phosphorus Supplementation in Enrolled Preterm Newborns (*N*=67)

Bone protective strategy	*Median (IQR)*
Duration of parenteral nutrition (d)	5 (3,7)
Duration of IV potassium phosphate (d)	3 (2,4)
Day of life at which HMF was supplemented as full strength (at 100 mL/kg feed volume)	5 (4,6)
Total duration of HMF supplementation (d)	25 (14,28)
Duration of PDHM with HMF (d)	7 (5,8)
Cumulative IV phosphorus intake (mg/kg)	111.6 (74.4,148.8)
Cumulative phosphorus intake from HMF (mg/kg)	1019.1 (521.4,1185)
Cumulative phosphorus intakes as sum of IV and HMF (mg/kg)	1110.4 (668.5,1332.2)

HMF:Human milk fortifier, PDHM:Pasteurized donor human milk. IV-intravenous.

Parenteral nutrition was commenced within hours of birth. IV phosphorus was started after day 2, once urine output was established and serum potassium was <5.5 meq/dL. Daily serum perturbations of phosphorus levels are represented in **Web Table I**. The median (IQR) weekly serum phosphorus levels are depicted in **Fig. 1**.

Some included neonates did not have a daily monitoring of serum phosphorous levels as they were not started on parenteral nutrition based on birth weight criteria in which case they did not receive IV Potphos (*n*=12). This was according to the predefined nutrition protocol. In some neonates, potassium values were high on day 2 (>5.5 meq/dL), hence IV Potphos was delayed until safety criteria were met. IV Potphos was administered only till PN was indicated, hence the number of days of IV Potphos and daily phosphorous monitoring varied.

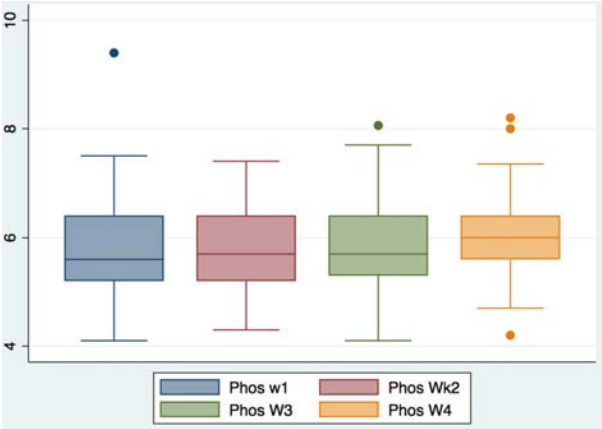

Fig. 1 Box Whisker plot showing serum phosphorus values from week 1 to week 4 of neonatal intensive care unit stay.

Not all neonates had weekly serum phosphorous sampling, it was deferred if they were on direct breast milk feeding and not receiving HMF, not warranting monitoring and optimisation as a part of BNS. In such neonates only fourth week sample was done. In some cases there were inadvertent misses of weekly sampling.

Of all included neonates with ≤30 week gestation, 14 (20.9%) developed MBD. The proportion was higher at lower gestation ages at birth: 9 (69.2%) among all those ≤26 weeks, 4 (22.2%) between 27-28 weeks and 1 (2.8%) at 28-30 weeks.

Among those diagnosed to have MBD, five babies required more than the conventional calcium phosphate supplementation: sodium acid phosphate salt in one, and activated vitamin D supplementation in four infants.

Hyperkalemia (serum level >6.5 meq/L) was noted in 3 out of 152 total samples taken for monitoring. Hyperphosphatemia was noted in 4.5%; none of them were associated with ECG changes or clinical manifestations that required therapy. Feed plan modification from standard regimens were required in 16 (23.8%), but the median (IQR) time to reach full enteral feeds was 6 (5,7) days. Other clinical outcomes are showed in **Table III**.

DISCUSSION

Our prospective observational cohort study analyzed the incidence of MBD after implementation of bone focussed nutritional strategies with best utilization of available resources.

Published literature describes the risk factors for MBD as prematurity, preeclampsia, chorioamnionitis, male gender, low birth weight and postnatally parenteral nutri-

Table III Clinically Relevant Secondary Outcomes in Preterm Neonates (≤ 30 weeks) Receiving Bone Focussed Nutritional Strategies (*N*=61)

Parameter	*No. (%)*
Weight-based EUGR	38 (56.7)
Length-based EUGR	25 (37.3)
Occipito frontal circumference (OFC) - based EUGR	1 (1.4)
Invasive ventilation (d)[a]	8 (5,15)
BPD	8 (11.9)
ROP requiring laser therapy	7 (10)
Sepsis	3 (4.4)
NEC Stage 2 or more	1 (1.7)

All values are in no. (%) or [a]median (IQR). EUGR: Extrauterine growth restriction, BPD: Bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, ROP: Retinopathy of prematurity. EUGR: >1 z-score difference between birth z-score and discharge z-score.

tion, glucocorticoids, drugs like methylxanthines, NEC and BPD [2,16]. We chose a population of preterm babies born ≤30 weeks gestation, most of whom were extremely low birth weight (ELBW), as they are physiologically more vulnerable for MBD [2,16].

Studies from other units have reported high incidence of MBD among ELBW babies. While Lyon, et al. [3] described incidence of MBD as high as 50% among ELBW babies in 1987, later in 2009, Mitchell, et al. [17] described a decreased incidence to 15% among ELBW babies [3,17]. Rustico, et al. [4] described birthweight specific incidence between 16-40% among very ELBW and very low birth weight (VLBW) neonates [4]. The incidence of metabolic bone disease of prematurity in our study was less than what we published in 2019 (before BNS) [9]. We expected a higher incidence in the present study as we enrolled a cohort of smaller preterm neonates (25-30 weeks) than our previous report (27-32 weeks). The precise incidence remains elusive, partly due to lack of agreement on the definition of MBD. The biochemical criteria for identifying MBD have become more stringent in the recent times. Recent recommendations propose serum phosphorus levels of <5.5 mg/dL as most sensitive criterion for diagnosis of MBD. Serum alkaline phos-phatase levels >800-900 U/L have been used as cut off values for diagnosis of MBD. Further, the authors have questioned the utility of specific ALP in diagnostic utility, as compared to total ALP activity [18].

High amino acids protein intake without adequate phosphorus supply leads to significant tissue deficit and hypophosphatemia, due to the increased transport of phosphorus (also potassium) into the cells. This condition is named as refeeding-like syndrome in preterm neonates. This is overcome by optimizing the parenteral nutrition with optimal phosphorous supplementations [19]. Organic phosphate solutions (sodium glycerophosphate, glucose-l-phosphate) are now available in other parts of the world and substantially improved co-solubility of these compounds with calcium salts allows maintenance of in-utero accretion even postnatally [20]. Pereira-da-Silva, et al. [6], showed that high early calcium and phosphate intake by PN within first hours after birth can prevent bone strength impairment in preterm neonates. They studied neonates with a mean gestational age of 29.6 weeks and birth weight of 1262 g. Salts that are available in the country are potassium compounds that are not advised for use in the first few postnatal days when urine formation is less due to reduced glomerular filtration rates. Each mL of this formulation (Potphos, Neon pharmaceuticals) contains 4.4 meq of potassium and 93 mg of phosphorus. Phosphorus containing fluids cannot be reconstituted to supply calcium salts as it results in precipitation of calcium phosphate [21]. These issues are less often addressed during planning of parenteral nutrition in most resource restricted settings [7].

The best source of nutrition in the short and long-term is undoubtedly MOM, but unfortified human milk does not provide sufficient minerals to VLBW neonates [22]. Although use of Multicomponent HMF is practiced in NICUs all over the world, there is variability in practice. Most centres initiate fortification after the preterm neonate is on 100-150 mL/kg/day of enteral nutrition. Recent literature suggests use of HMF earlier [11]. We tried to initiate HMF once 40 mL/kg/day enteral feeds were tolerated, however in practice this ranged from 40 to 100 mL/kg/day during the study period; median being 60. Since we started HMF early, we were cautious; initially HMF was administered at half strength as described in the methodology. Earlier use of HMF was not associated with increase in feed intolerance, measured as time required to achieve full enteral feeds, as compared to our previous experience (when HMF was started at the conventional 100 mL/kg enteral feeds) [9,10]. The median (range) total duration of HMF supplementation was 25 (3-40) days.

There was a clear trend of decreasing incidence of hypophosphatemia across week one to week four with increase in median serum phosphorous values increased with ensuing postnatal age in weeks. This probably reflects the serial decrease in phosphorus loss through maturing renal tubules.

Hyperphosphatemia (>8 mg/dL) was uncommon in our study, endorsing the safety of the enteral phosphorus doses. A study published by Katharine, et al. [22] analyzed for the incidence of hyperphosphatemia among premature babies receiving the fortified human milk, they used human milk-based fortifier. In that study they concluded that incidence of hyperphosphatemia was mild and transient. We found hyperkalaemia in 2/67 (2.9%) neonates leading to withdrawal of intravenous phosphorus, although their hemodynamic status and ECG were normal and restarted after potassium values were normal. Farida, et al. [23] described the incidence of hyperkalaemia among ELBW and VLBW as 3% as compared to 2.9 % in our study .

In our study with pre-defined standard feed regimens, we could achieve 100 mL/kg/day enteral feeds on the day 6 (5,7) median (IQR). This indicates that there was no significant feed intolerance, despite early use of HMF. We attribute the success of early enteral feeding to the strict adherence to SFR and pro-active promotion of MOM. The time to full enteral feeds is comparable to other published studies. Dutta, et al. [8] published guidelines for feeding of low-birth-weight babies. The authors reported that for preterm babies <1000g, two weeks may be required to

WHAT IS ALREADY KNOWN?

- Intravenous phosphorus is recommended from day 1 of life in international guidelines, but no potassium-free salt of intravenous phosphorus is available in India.

WHAT THIS STUDY ADDS?

- Strategies with focus on phosphorus and nutrition can lead to decreased incidence of metabolic bone disease in preterm neonates.
- Intravenous potassium phosphate is safe for use in preterm neonates as part of a bone health focussed nutritional strategy.

achieve full feeds (150-180 mL/kg), while for babies 1000-1500g birth weight, one week may be enough. In an RCT published in 2010 [24], babies achieved full feeds within one week. We observed an EUGR rate of 38 (56.7%). In the study by Kim, et al. [25] including babies born <28 wks with mean (SD) birth weight of 899 (189) g, the authors observed EUGR prevalence, using the same measure of *z*-scores as definition, at about 70%. These babies were much smaller at the start.

Neonates at the thresholds of viability (22-23 wks), who would be most affected by MBD, were not included in this study as survival at this gestation in the unit is negligible. We did not plan a comparative cohort for ethical reasons. A before- and after study that compared our previous cohort might have added value, but we felt that significant differences in patient characteristics and nutrition protocols during the time epochs made the contrast less meaningful [9]. The actual days of intravenous phosphorous administration was small; hence utility cannot be determined. We did not include use of Dual energy *X*-ray absorptiometry (DEXA) as it involves exposure to ionizing radiation, not available at the bedside and entails additional costs. Measuring bone speed of sound (SOS) by quantitative ultrasound was also not planned in order to give priority to pragmatism and generalisability [5]. Still, our study had some noteworthy strengths. The population included preterm babies (≤30 weeks gestation) who are known to be at high risk for MBD. Through our prospective (BNS) nutrition study, we could demonstrate that stringent implementation of nutrition protocols is possible and beneficial. We explored the alternatives to intravenous phosphorus preparations and evaluated safety of the same; Larger studies will be required to recommend routine use. The earlier use of HMF was found to be safe. Our nutrition policies were pragmatic and applicable to units with facilities for parenteral nutrition.

Incidence of MBD in preterm neonates (≤30 wks) was 20.9% after implementation of nutritional strategies (BNS) targeted at improving bone health. Early intravenous potassium phosphate could be initiated and safely administered. Hyperkalaemia and hyperphosphatemia were uncommon. Early initiation of enteral phosphorous as HMF (after 40 mL/kg/day feed volume) and optimisation of phosphorous supplementation by weekly monitoring was possible.

Contributors: NJ,FP: conceived the study; AAK: collected data. All authors contributed to clinical care of the included neonates. AAK,FP,NJ: conducted statistical analysis; AAK,FP: wrote the manuscript and all authors approved the final draft.
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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Web Table I Serum Phosphorous Levels in Neonates Who Received Intravenous Potassium Phosphate

Day of IVPotassium phosphate[a]	*Hypophosphatemia events (< 5.5 mg/dL)* (*n*=80)	*Normal phosphorus (5.5– 8 mg/dL)* (*n*=75)	*High phosphorus events (> 8 mg/dL)* (*n*=5)
Day 1, *n*=54	29 (53.7)	24 (44.4)	1 (1.8)
Day 2, *n*=39	20 (51.2)	17 (43.6)	2 (5.1)
Day 3, *n*=40	17 (42.5)	22 (55)	1 (2.5)
Day 4, *n*=16	8 (50)	7 (43.8)	1 (6.2)
Day 5, *n*=11	6 (54.5)	5 (45.4)	0

All values are expressed as no. (%). n in row heading indicates total numbers of samples done. IV – intravenous.

RESEARCH PAPER

Simulation Based vs Conventional Training for Initial Steps in Delivery Room Care of Preterm Neonates: *An Open Label Randomized Trial*

DILIP NEUPANE, AKASH SHARMA, ANU THUKRAL, M JEEVA SANKAR, RAMESH AGARWAL, ASHOK K DEORARI
From Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi.

Correspondence to: *Dr Anu Thukral, Associate Professor, Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029.*
dranuthukral@gmail.com
Received: March 05, 2022;
Initial review: April 07, 2022;
Accepted: August 01, 2022.

Objective: To assess whether simulation based education (SBE) improves the practices and knowledge of junior residents for stabilization of a preterm neonate in delivery room as compared to conventional education (CE). **Methods:** This trial randomized 24 pediatric residents to either SBE (*n*=12) or CE (*n*=12) groups. One-time SBE was imparted to the SBE group. Both the groups had similar facilitator participant ratio and equally timed sessions. The individual skills scores and performance by preterm stabilization performance evaluation (PSPE) score in real time were recorded using a validated tool within 8 weeks of the training. Knowledge gain was evaluated using pre and post-test scores. **Results:** The mean (SD) skill and PSPE scores were comparable between the two groups (skill score 51.1 (8.1), 46.5 (7.8), respectively mean difference 4.6; 95% CI -2.1 to 11.3; PSPE-score 80.2 (14.2) vs. 82.9 (10.3); mean difference -2.68; 95% CI -8.35 to 13.71). The mean (SD) knowledge gain was similar in the groups [4.4 (1.9), 5.3 (4.1); mean difference 0.91; 95% CI, -1.81 to 3.64. **Conclusion:** In junior residents, a one-time SBE session, when compared to conventional task training, did not lead to improvement in the performance of the initial steps of neonatal resuscitation.

Keywords: *Formative assessment, Newborn, Resuscitation, Simulation, Skills.*

Trial registration: CTRI/2018/03/012436 ***Published online*:** August 26, 2022; ***PII:*** S097475591600446

Simulation based education (SBE) offers greater opportunity than real-life scenarios to improve skills, sharpen clinical decision making, increase confidence to work as a team and improve the overall team performance [1]. However, some studies suggest no difference in skills acquisition [2]. Evidence on the utility of simulation is limited by longer time spent during SBE as compared to conventional education (CE) [3], and lack of studies on utility of SBE for initial stabilization of preterm neonates. The PRONTO initiative incorporated simulation training as a part of a broader package of interventions [4], while the Helping Babies Breathe initiative has tested the effect of SBE on perinatal mortality in low resource settings [5].

Given the dearth of evidence in the above-listed domains and simulation being recommended by many internal bodies as the training tool [6], we hypothesized that immersive learning from SBE would result in better acquisition of skills as well as better performance in real time in the delivery room for initial stabilization of preterm neonates as compared to the conventional task training among first and second year pediatric residents [7,8].

METHODS

This randomized trial was conducted in a level-3 neonatal intensive care unit (NICU) of a teaching institution from January, 2018 to July, 2019. The first- and second-year pediatric junior residents who had not attended any neonatal resuscitation training were eligible for enrollment. The study was approved by the ethics committee of the institute. Written informed consent was obtained from the parents for video recording the stabilization of their preterm infant. The trial was prospectively registered with the Clinical trial registry of India. Computer-generated random numbers were used for participant allocation. Serially numbered, sealed and opaque envelopes were used for allocation concealment. They were opened by an independent observer. Blinding was not possible; however, the co-investigator assessing outcomes was not aware of the group allocation. The training was done in the NICU as a single-day workshop in two sessions; each session having 12 participants. A pre-workshop knowledge assessment was done for all participants. After the initial session (interactive discussion by facilitators on physiology, equipment preparation, thermal care and respiratory support) and skill training (on equipment preparation, thermal care and respiratory support); participants were randomized into two arms: the SBE and the CE. SBE was delivered as an orientation (including equipment pre-brief), actual scenario run and debriefing

session in which the participants performed as a team in a realistic scenario with appropriate fidelity. The manikin used for SBE was of moderate fidelity (Premature Anne with Sim Pad Plus, Laerdal Medical, Norway) with realistic chest expansion, breath sounds, intubation, chest compressions, vascular access and touch screen interface with integrated data log. The participants in the CE group did self- demonstrations on task trainers (NeoNatalie newborn simulator, Laerdeal Medical), received feedback from facilitators and clarified their doubts in the defined session. The duration of interaction and the participant facilitator ratio was the same in both groups. The skill scores were assessed on the same day after the training session by the respective facilitators and was marked as done or not done based on predetermined objective criteria. The evaluation of performance score included assessment of team behavior and assessment of actual clinical performance in real-time while the participant stabilized a preterm neonate ($31^{0/7}$ to $36^{6/7}$ weeks) within 8 weeks of the training session. The principal investigator informed the identified participant of the anticipated preterm birth after which participant attended the delivery as the first resuscitator. A senior registrar always accompanied the participant for the delivery as an emergency backup. Team behavior was evaluated by a validated tool (Team STEPPS Team Performance Observation Tool (T-TPOT) [9,10] by an independent observer who was physically present in the delivery room. This score was evaluated on video recording (through a dedicated camera placed in delivery room) done at the time of delivery. The video was later seen by two independent assessors who evaluated the performance through Preterm Stabilization Performance Evaluation (PSPE) score. This was evaluated as percentage of correct steps performed by the participant (denominator being the total steps for clinical stabilization of the preterm infant). Any disagreement between the two assessors was sorted out by mutual discussion. The assessors were blinded to the intervention arm.

A pre-validated questionnaire recorded the satisfaction of trainers and trainees in SBE group. In a previous study from our own center, trainees' mean (SD) post-conventional training skill scores were 15.6 (2.5) (a maximum possible score of 25) [11]. We assumed that SBE should increase the skill scores by at least 20% (19.0), and with 90% power, the sample size for the current study was 12 in each group. Analysis was done using Stata 14.2 (Stata Corp).

RESULTS

The flow of the study is shown in **Fig. 1** where 12 residents completed the study in each arm. The key baseline characteristics of participants and the preterm neonatal births on which performance scores were evaluated in real-time, were comparable between the two groups (**Table I**). The skill scores for each assessment station as well as the overall skill scores and PSPE scores were similar in the two groups (**Table II**). The knowledge scores increased from 22.8 (2.5) to 27.2 (1.2) in SBE group and 20.4 (5.2) to 25.7 (1.7) in CE group, with comparable intergroup difference (**Table II**).

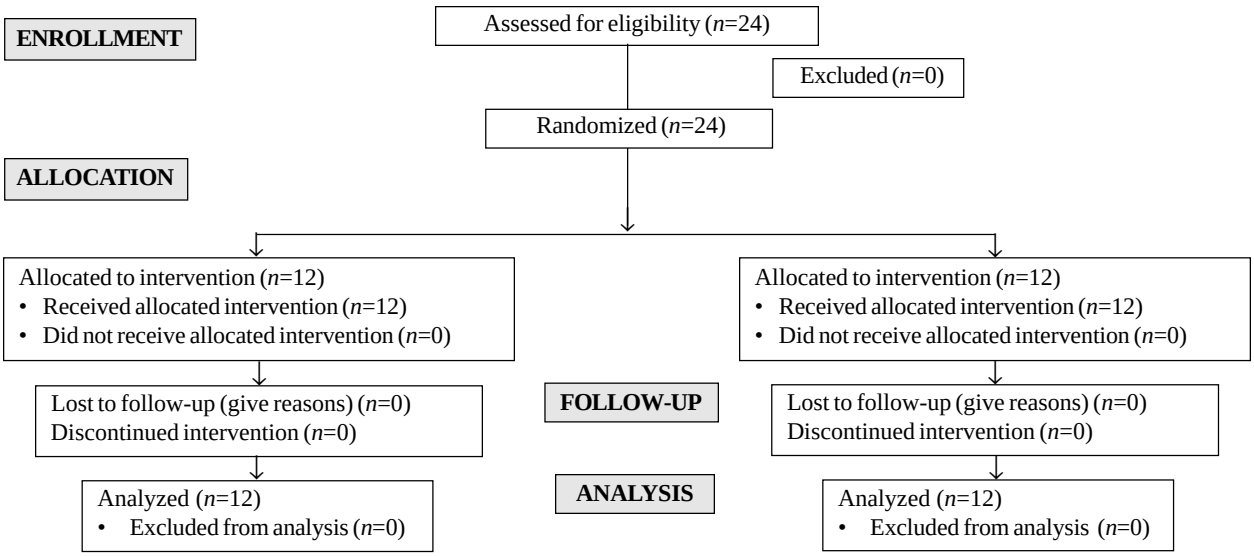

Fig. 1 Flow of the Study.

Table I Baseline Characteristics of the Participants and Enrolled Neonates

Variable	*Simulation-based training group*	*Conventional training group*	*P value*
Participants	(*n*=12)	(*n*=12)	
Male residents	6 (50)	5 (41.7)	0.68
Age (y)[a]	26 (1.5)	26 (1.2)	1.0
Posting in NICU (mo)[a]	3.8 (1.6)	3.4 (1.3)	0.50
Confidence in leading neonatal resuscitation	6 (50)	4 (33.3)	0.40
Mean knowledge score before training[a]	22.8 (2.5)	20.4(5.2)	0.16
Neonatal characteristics	*(n=12)*	(*n*=12)	
Gestation (wks)[b]	34 (33-35)	34 (33- 35)	1.0
Birth weight (g)[a]	2258 (821)	2175 (472)	0.76
Apgar 1 min[b]	8 (7-9)	9 (7-9)	0.72
Apgar 5 min[b]	9 (8-9)	9 (8-9)	0.39
Apgar 10 min[b]	8 (8-8)	7 (7-7)	0.32
Male	7 (58.3)	2 (16.7)	0.03
Oxygen by hood/prongs	3 (25)	5 (41.7)	0.39
CPAP requirement at birth	3 (25)	4 (33.3)	0.65
PPV requirement at birth	2 (16.7)	0	0.14

Data expressed as n (%), [a]mean (SD) or [b]median (range). CPAP: continuous positive airway pressure, PPV: positive pressure ventilation.

Table II Skill, Performance and Knowledge Gain Scores of the Study Participants

OSCE	*Simulation-based training (n=12)*	*Conventional training (n=12)*	*Mean difference (95% CI)*	*P value*
Skill score (Total)	51.1 (8.1)	46.5 (7.8)	4.6 (-2.1, 11.3)	0.17
OSCE 1	4.5 (1.7)	3.6 (1.1)	0.8 (-0.4, 2)	0.16
OSCE 2	8.3 (1.5)	7.6 (1.3)	0.6 (-0.6, 1.8)	0.30
OSCE 3	6.7 (1.1)	5.5 (1.8)	1.3 (-0.01, 2.5)	0.05
OSCE 4a	14.2 (3.3)	13.3 (3.7)	0.9 (-2.0, 3.9)	0.52
OSCE 4b	8. 7 (2.1)	7.8 (2.5)	0.9 (-1.1, 2.9)	0.34
OSCE 5	8.8 (3.1)	8.8 (3.0)	-0.1 (-2.4, 2.6)	0.94
Performance assessment scores	80.2 (14.2)	82.9 (10.2)	-2.68 (-8.3, 13.71)	0.62
Knowledge gain	4.4 (1.9)	5.3 (4.1)	0.9 (-1.8 to 3.6)	0.49

Data expressed as mean (SD). OSCE – Objective Structured Clinical Examination, 1-5; equipment checklist and team preparation, thermal care, initial steps, PPV using T piece, PPV using bag and mask, CPAP, respectively.

Trainees (*n*=12) exposed to SBE expressed satisfaction in teachers' ability and quality of education when tested on a pre-validated questionnaire. Trainers' (*n*=5) in SBE when tested on a pre-validated questionnaire expressed that the learning environment was relaxed and conducive and that they would recommend similar activities to other facilitators.

DISCUSSION

The current study evaluated the effect of simulation-based education vs conventional education in improving the practices and knowledge of pediatric residents for stabilization of preterm neonates in the delivery room. There was no difference in the knowledge, skill or performance scores between the two groups.

We evaluated the participants' skill scores immediately after the learning session on the same day and performance scores in real-time while the preterm newborn was stabilized in the delivery room within 8 weeks of training sessions. A time period of 8 weeks was chosen because literature suggests a reasonable deterioration in skills thereafter [12]. We ensured equal time, similar facilitator participant ratio, and skill training with feedback in both arms to ensure that simulation-based learning

WHAT THIS STUDY ADDS?

- One-time session of simulation-based training for junior residents, when controlled for confounding by duration of training, does not improve participants' skills, performance, or knowledge scores compared with conventional task training.

experience was the only differentiating factor between the two arms. Previous studies which suggested improvement in these scores either had only didactic teaching in the control arm [13], or the duration of intervention in the two arms was not mentioned with obvious incremental time in simulation arm, thus leading to a potential bias in the results [14,15].

Lastly, a likely chance of contamination between the participants cannot be ruled out given the timeline of 8 weeks in between the training session and the actual recording of performance scores in real-time with video-based analysis, though they consented for non-disclosure of the technique or the methodology of teaching beforehand.

We tested participants' performance as the first resuscitator on a defined gestation range of stable preterm neonates ($31^{0/7}$ to $36^{6/7}$ weeks) till the trigger of requirement of positive pressure ventilation. In the aforementioned instances, the senior registrar intervened and took over as the team leader. Perhaps evaluating higher-end psychomotor skills (evaluating the performance at the time of initiation of PPV or even beyond that) could have shown a meaningful difference. We limited the performance evaluation till the indication of CPAP if needed for obvious reasons.

This study had some limitations like a risk of cross-contamination between the two participant groups. We limited the gestation of preterm infants for enrollment to a defined category to include stable preterm infants for ethical reasons. One-time simulation and debriefing sessions might have been inadequate to delineate the actual difference produced by SBE. The strengths of the study included assessment of real-time performance of participants and equal time allocation and equal participant facilitator ratio in the two intervention groups. An observer bias was removed as the neonatologists who evaluated the performance score were blinded to the intervention group.

In conclusion, a one-time session of SBE for junior residents, when controlled for confounding by duration of training, did not improve participants' skills, performance, or knowledge scores compared with conventional task training. Future research should focus on the effect of SBE on teamwork and leadership in other neonatal emergencies as well as the effect of repeated simulation training on the skills of pediatric residents.

Acknowledgements: Dr Ankit Verma, Dr Pratima Anand, Dr Srikant Kulkarni, Dr Deena Thomas, Dr Raja Ashok, Sister Meena Joshi, Sister Swati (Nurse Educator) for their contribution to the execution of the study, teaching sessions and assessment of the two groups. Dr Vinay M Nadkarni, Medical Director, Center for Simulation, Advanced Education and Innovation, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA, for his critical inputs at the time of inception of the study and for critically reviewing the final manuscript.

Ethics clearance: IEC, AIIMS, New Delhi; No.IECPG-513/ 29.11.2017, dated Dec 27, 2017.

Contributors: DN: participated in the conceptualization and designed the study, recruited the participants, collected all the data, analyzed data and drafted the initial manuscript; AS: participated in the conceptualization and design of the study, aided with data collection and helped in interpretation of data; AT: conceptualized and designed the study, supervised the collection and analysis of data. MJS: participated in the design of the study, helped in statistical analysis of the data, RA: participated in the design of the study, provided interpretation of data; AKD: conceptualized and designed the study, provided interpretation of data; DN,AS,AT,MJS,RA,AKD: critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted

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

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RESEARCH PAPER

Sunlight Exposure vs Oral Vitamin D Supplementation for Prevention of Vitamin D Deficiency in Infancy: *A Randomized Controlled Trial*

ANISHA GOYAL,[1] AASHIMA DABAS,[2] DHEERAJ SHAH,[1] RAJEEV KUMAR MALHOTRA,[3] POOJA DEWAN,[1] SV MADHU,[4] PIYUSH GUPTA[1]

From Departments of [1]Pediatrics and [4]Endocrinology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi; [2]Department of Pediatrics, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi; and [3]Delhi Cancer Registry, Dr BRA-InstituteRotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi.

Correspondence to: Dr Piyush Gupta, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi 110095. prof.piyush.gupta@gmail.com

Received: February 12, 2022; Initial review: April 16, 2022; Accepted: September 10, 2022

Objective: To compare the efficacy of sunlight exposure and oral vitamin D3 supplementation to achieve vitamin D sufficiency in infants at 6 months of age.

Design: Open-label randomized controlled trial.

Setting: Public hospital in Northern India (28.7°N).

Participant: Breastfed infants at 6-8 weeks of age.

Intervention: Randomized to receive sunlight exposure (40% body surface area for a minimum of 30 minutes/week) or oral vitamin D3 supplementation (400 IU/day) till 6 months of age.

Outcome: Primary - proportion of infants having vitamin D sufficiency (>20 ng/mL). Secondary - proportion of infants developing vitamin D deficiency (<12ng/mL) and rickets in both the groups at 6 months of age.

Results: Eighty (40 in each group) infants with mean (SD) age 47.8 (4.5) days were enrolled. The proportion of infants with vitamin D sufficiency increased after intervention in the vitamin D group from 10.8% to 35.1% (*P*=0.01) but remained the same in sunlight group (13.9%) and was significant on comparison between both groups (*P*=0.037). The mean (SD) compliance rate was 72.9 (3.4)% and 59.7 (23.6)% in the vitamin D and sunlight group, respectively (*P*=0.01). The geometric mean (95% CI) serum 25(OH) D levels in the vitamin D and sunlight group were 16.23 (13.58-19.40) and 11.89 (9.93-14.23) ng/mL, respectively; *(P*=0.02), after adjusting baseline serum 25(OH)D with a geometric mean ratio of 1.36 (1.06-1.76). Two infants in sunlight group developed rickets.

Conclusion: Oral vitamin D3 supplementation is more efficacious than sunlight in achieving vitamin D sufficiency in breastfed infants during the first 6 months of life due to better compliance.

Keywords: *Calcium deficiency, Compliance, Rickets, Ultraviolet rays*.

Trial registration: CTRI/2018/11/016443

Published online*:** September 22, 2022; ***PII: S097475591600459

Vitamin D deficiency is a significant problem across all ages in India, especially infants due to associated maternal vitamin D deficiency, poor vitamin D content in breastmilk, and inadequate vitamin D content of traditional complementary foods in the first year of life [1,2]. Given the concern of increasing prevalence of vitamin D deficiency during infancy, Global Consensus [3], and the Indian Academy of Pediatrics (IAP)[4], recommend routine vitamin D supplementation to breastfed infants at a dose of 400 IU per day till 12 months of age. However, with an easier, natural, and inexpensive alternative for vitamin D being available through sunlight exposure, it becomes pertinent to explore the efficacy of this natural source in tropical countries like India.

The efficacy of vitamin D supplementation was reported to be higher than sunlight exposure with a mean difference ranging from 2.4-11 ng/mL in older children and adults [5-9]. Similar comparative studies were not available in infants. An earlier study estimated that an afternoon sun exposure of 30 minutes per week for 16-18 weeks (starting from 6 weeks) over 40% of exposed body surface may be able to achieve sufficient serum 25(OH)D (≥20 ng/mL) levels in infants at 6 months of age. The median observed sun-exposure duration was 17 minutes weekly over median 6% (range 2-40%) body surface area predominantly in summer months in northern India [10], similar to earlier conclusions on sunlight exposure in infants by Specker, et al. [11]. However, the adequacy of this duration of sunlight exposure in comparison to routine vitamin D supplementation has not been evaluated.

Invited Commentary: Pages 835-36.

We conducted this study to compare the efficacy of sunlight and oral vitamin D3 supplementation (400 IU/day) in achieving vitamin D sufficiency at 6 months of age. The

mean change in serum 25(OH)D levels and proportion of infants with vitamin D deficiency or rickets were also compared between both the groups.

METHODS

This was an open-labeled randomized controlled trial conducted between November, 2018 and April, 2020, in a public hospital in Northern India (28.7°N). An approval from the ethics committee of the institute was obtained. Written informed consent was obtained from the parents for participation. The trial was registered with the clinical trial registry of India.

We enrolled infants between 6-8 weeks of age during the first immunization visit from the outpatient clinic including those residing within a 5 km radius of the hospital to ensure uniform latitude, season, and geographical location. Infants who were born at term gestation (37-41 weeks), appropriate for gestational age, and exclusively breastfed were included. Any child with chronic systemic illness, congenital malformations, genetic syndrome, history of hospitalization in neonatal care unit for more than 48 hours, history of intake of calcium or vitamin D preparations, skin disorders, active rickets, mothers on vitamin D supplements, or history of intake of mega dose of vitamin D (6 lakh IU or >1000 IU/day) in preceding 12 weeks, and growth faltering as per WHO growth charts [12], were excluded. No changes in inclusion criteria were made after the commencement of the trial.

Participants were enrolled between March and July (during summer months) for a six month intervention period till September-December, keeping in mind the Indian equinox. The relevant clinical information on antenatal complications, maternal intake of calcium, or vitamin D supplements, and birth details of the baby were recorded. The socio-demographic characteristics of the household including the socioeconomic status and type of house were recorded. The infant's weight, length, and head circumference were recorded by standard techniques using calibrated equipment in a pre-designed proforma. WHO reference [12], was used for determining weight-for-age *z*-score (WAZ), length-for-age *z*-score (LAZ), weight-for-length *z*-score (WLZ) using AnthroCal software [13].The feeding history of the infant with a history of intake of vitamin D supplements was recorded on the proforma. The infant was clinically examined for rickets by a pediatrician. They were clinically evaluated for skin color according to Fitzpatrick skin color scale into six types, where type I was the fairest and type VI was the darkest skin [14].

Infants were randomized using block randomization of varying block sizes (*www.randomization.com*) to receive either of the following interventions till 6 months of age: *i*) Sunlight group: Sunlight exposure over 40% body surface area (BSA) for a minimum of 30 minutes/week, and *ii*) Vitamin D group: Oral vitamin D3 supplementation (400 IU/day).The random number sequence was generated by a third person not involved in the study. Allocation concealment was done by the sealed envelope technique which was prepared by a third person different from the person who generated the randomization sequence. This was an open-label study.

In the sunlight group, mothers were counseled to expose infants to direct (unfiltered) sunlight over 40% body surface area (BSA) for 30 minutes per week. The mothers were advised to lay infants in direct sunlight in a prone position wearing only diapers for 5 min/day preferably between 1000-1100 hours or 1430-1500 hours for 6 days every week excluding Sundays. Exposure on cloudy days was not advised; it was compensated by adding the duration of the missed day/s on the next day within seven days. Compliance was checked by a daily record of BSA exposure with mention of exact duration (in minutes) and time of the day (as per clock time) of sun exposure in a modified Lund and Browder chart [15] that was collected once a month. In the sunlight group, percent compliance was calculated by dividing the total duration (in minutes) for which the baby was exposed to sunlight by the total duration (in minutes) for which sunlight was prescribed.

In the vitamin D group, mothers were counseled to administer 400 IU/day of oral vitamin D3 as 0.5 mL/day (1 mL=800 IU in 30 mL pack, Arbivit-3 forte drops, Raptakos Brett & Co Ltd) using a standardized dropper supplied within the bottle. The drug was obtained from the manufacturers directly and distributed by the study investigators. The mothers were asked to report the missed doses by marking on calendar dates in the format provided to them and return with used supplement bottles during their monthly visits for measuring any leftover medicine. The percent compliance was calculated by dividing the number of days oral vitamin D3 was given in recommended dosage to the baby by the total number of days prescribed. They were not counseled for or against sunlight exposure but were asked to record the same.

Compliance in both the groups was ensured telephonically every week and was defined as low at <50%, moderate at 50-80%, and high at ≥80%. Infants were physically followed up at 10 and 14 weeks at consecutive immunization visits and then additionally at 6 months (± 2 weeks) of age. Anthropometry of infants was performed at each visit. Infants were also examined for clinical signs of vitamin D deficiency/ rickets (anterior fontanelle measures, rachitic rosary, frontal bossing, and wrist widening).

Infants developing clinical rickets during follow-up were treated as per standard guidelines [4]. Mothers were asked to report adverse events, if any, at each visit.

Venous blood (2 mL) from mother and infant was drawn at baseline for estimation of serum 25(OH)D levels; and from the infant at the end of 6 months (3 mL) for estimation of serum 25(OH)D, serum calcium, serum phosphorus, and serum alkaline phosphatase (ALP). Serum calcium, phosphorus, and ALP levels were measured at baseline within 24 hours of collection. Serum was stored at -20 degrees Celsius for estimation of baseline serum 25(OH)D levels and were measured with serum 25(OH)D levels collected at six months. Additionally, in the vitamin D group, a spot urinary sample was taken for determining urinary calcium creatinine ratio (U-CaCr) to detect hypercalciuria. Serum calcium, phosphorus, and ALP were estimated by UniCelDxC 600 automatic analyzer (Beckman Coulter India, Pvt. Ltd.) Total serum 25(OH)D was estimated by the Beckmann Coulter radio-immunoassay method. Urinary calcium creatinine ratio (U-CaCr) was measured in a spot freshly void urine sample by UniCelDxC 600 automatic analyzer (Beckman Coulter India Pvt. Ltd.) using the Colorimetric method. A U-CaCr cut-off of >0.6 mg/mg was taken as abnormal. Vitamin D status was defined as sufficient if >20 ng/mL, insufficient 12-20 ng/mL, and deficient <12 ng/mL [3,4].

The outcomes were measured at 6 months ± 2 weeks of age. The primary outcome was proportion of infants having serum 25(OH)D levels >20 ng/mL. The secondary outcomes were serum 25(OH)D levels, the proportion of infants developing clinical rickets, and vitamin D deficiency (<12 ng/mL).

In a previous study [16], the observed proportion of infants being administered 400 IU of oral vitamin D3 daily (from birth) to achieve serum 25(OH)D level ≥20 ng/mL at 6 months of age was 97.5%. Considering less compliance in our population, we expected 85% to achieve serum 25(OH)D level >20 ng/mL at 6 months. With 15% absolute difference with sunlight group on either side of oral vitamin D group, type-I error 5% and 80% power, we needed 36 participants per group (non-inferiority). Assuming 10% attrition, we planned to enrol 40 infants per group.

Statistical analysis: Data were analyzed by using SPSS software (version 11). Descriptive data were presented as mean or median (IQR). Baseline continuous characteristics were compared between the groups using unpaired t-test and categorical with Chi-square/Fisher exact test. Normality of serum 25(OH)D data was tested using the Shapiro Wilk test and found right-skewed distribution. The natural log transformation was applied to make distribution normal and results are reported in geometric mean with a 95% confidence interval. Analysis of covariance was applied to compare serum 25(OH)D at 6 months between the groups taking baseline serum 25(OH)D as a covariate and also with compliance. The interaction between the groups and covariates was tested and subgroup analysis was performed in case of a significant interaction. McNemar test was used to compare the proportions within the group before and after the intervention and Chi-square/Fisher exact test was performed to compare two groups. Intention to treat analysis was used for comparison between intervention and control groups. The missing values were substituted by the baseline value of serum 25(OH)D for final analysis. Pearson correlation was used to check the correlation between two continuous variables. *P*-value <0.05 was considered significant.

RESULTS

Participant enrolment and follow-up are depicted in **Fig. 1**. A total of 80 (49 boys) infants were enrolled [mean (SD) age 47.8 (4.5) days; birth weight 2805.8 (313.6) g]. Infants

Table I Baseline Parameters in Sunlight and Vitamin D Groups

Parameters	*Sunlight (n=40)*	*Vitamin D (n=40)*
Age at enrolment (d)	47.9 (4.7)	47.7 (4.3)
Birth weight (g)	2790.3 (314.6)	2821.3 (315.8)
Gestation (wk)	37.8 (1.1)	37.9 (1.0)
Anthropometry		
Weight at enrolment (g)	4375.5 (421.0)	4415.8 (383.8)
Length at enrolment (cm)	55.8 (1.6)	56.0 (1.6)
Weight for age *z*-score	-0.96 (0.69)	-0.82 (0.63)
Length for age *z*-score	-0.28 (0.80)	-0.04 (0.82)
Weight for length *z*-score	-1.03 (0.76)	-1.04 (0.65)
Skin Fitzpatrick score[a]		
Type III	6 (15)	9 (22.5)
Type IV	26 (65)	25 (62.5)
Type V	8 (20)	6 (15)
Socioeconomic status[a]		
Upper middle	2 (5)	2 (5)
Lower middle	8 (20)	6 (15)
Upper lower	20 (50)	27 (67.5)
Lower	10 (25)	5 (12.5)
Maternal serum 25(OH) D (ng/mL)[b]	9.76 (8.81-10.80)	9.31 (8.27-10.47)
Infant serum 25(OH) D (ng/mL)[b]	10.93 (9.24-12.93)	10.87 (9.44-12.52)
Month of enrolment[a]		
March to May	35 (87.5)	37 (92.5)
June-July	5 (12.5)	3 (7.5)

Data expressed as mean (SD), [a]no.(%) or [b]Geometric mean (95% CI). 25(OH)D-25 hydroxyvitamin D. All P>0.05.

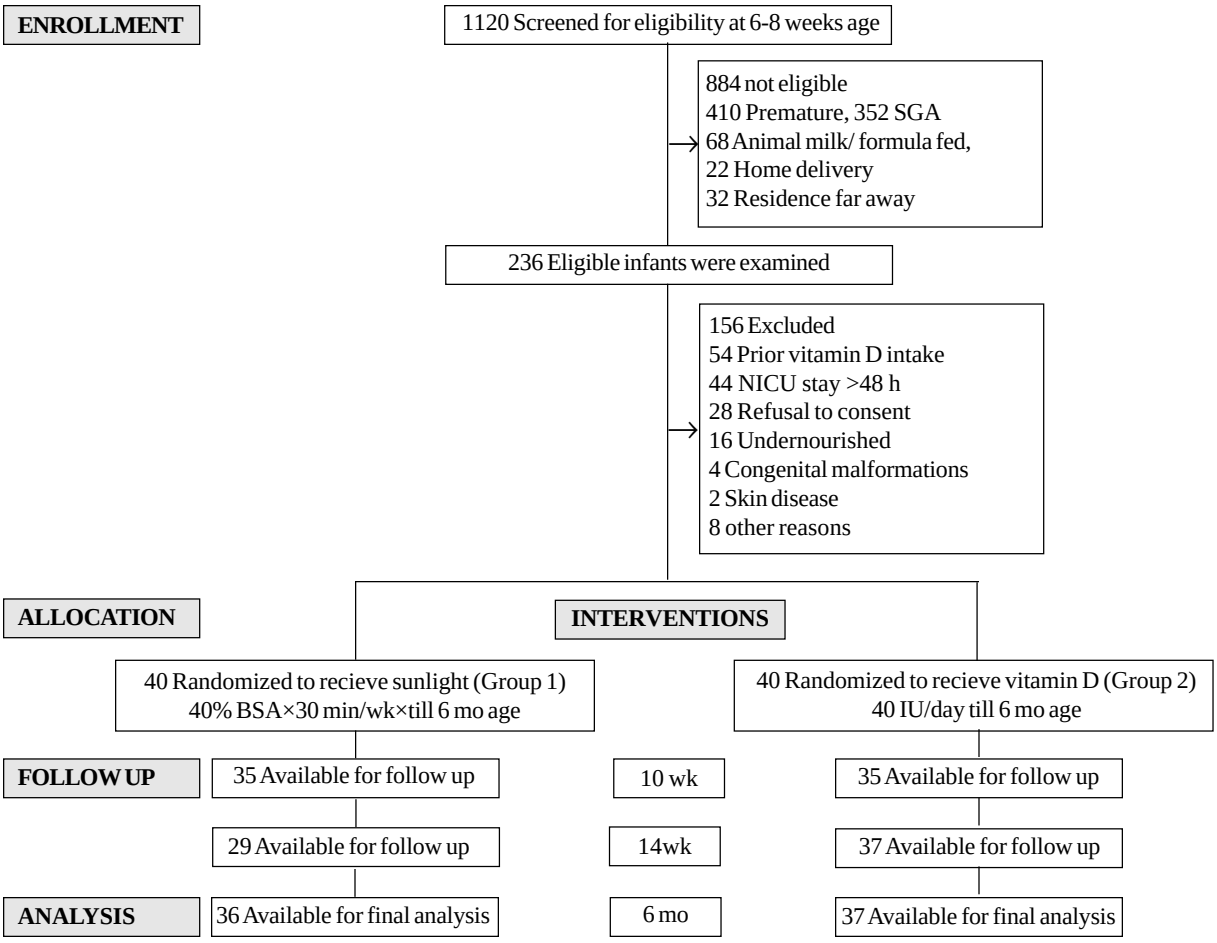

Fig. 1 Study flow chart

belonged to Fitzpatrick skin type III 15 (18.8%), IV 51 (63.8%), or V 14 (17.5%).

Vitamin D deficiency, insufficiency and sufficiency at baseline were seen in 57 (71.2%), 22 (27.5%), and 1 (1.3%) mothers, and in 49 (61.2%), 21(26.3%), and 10 (12.5%) infants, respectively. The baseline characteristics of infants in the two groups are shown in **Table I**. All infants were exclusively breastfed till six months of age and did not receive calcium or vitamin D supplements from any other source.

The mean (SD) compliance was 72.9 (3.4)% in the vitamin D group and 59.7 (23.6)% in the sunlight group (P=0.01) and 17 (45.9%) and 6 (16.7%) infants had ≥ 80% compliance in both groups, respectively. The mean (SD) WAZ score at follow-up in two groups was comparable [-0.19 (0.56) and -0.24 (0.66), respectively; P=0.726]

Table II Vitamin D Status Before and After Intervention in Sunlight and Vitamin D Group

Vitamin D status	*Group*	*Before intervention*	*After intervention*	*P value*
Vitamin D sufficient [a]	Sunlight (n= 36)	5 (13.9)	5 (13.9)	1.0
	Vitamin D (n= 37)	4 (10.8)	13 (35.1)	0.01
Vitamin D deficient [b]	Sunlight (n= 36)	22 (61.1)	17 (47.2)	0.45
	Vitamin D (n =37)	22 (59.5)	13 (35.1)	0.04

Values in no. (%). Vitamin D sufficient as serum 25 (OH) D levels >20 ng/mL. Vitamin D deficient as serum 25 (OH) D levels <12 ng/mL. [a]P value between two groups before intervention P=0.74 after intervention P=0.037; [b]P value between two groups before intervention P=0.88, after intervention P=0.294.

Vitamin D status of participants at baseline and after the intervention is compared within group and between groups in **Table II.** In the sunlight group, five infants with serum 25(OH)D levels >20 ng/mL had >50% compliance. In the vitamin D group, 11 out of 13 (84.6%) infants with serum 25(OH)D levels >20 ng/mL had ≥80% compliance. Values of four and three participants were missing in the sunlight and vitamin D group, respectively, that were substituted for baseline values for statistical analysis. On analyzing the primary outcome by replacing the missing values, there was no change in the results.

We did not observe any significant correlation between the log-transformed maternal serum 25(OH)D values and serum 25(OH)D values of the infant, both before (r=-0.128; P=0.258) and after intervention (r=-0.089; P=0.456). There was no statistical significant association found for change in vitamin D and both serum calcium and phosphorus in both groups at six months (data not shown).

The mean (SD) serum calcium in the sunlight and vitamin D group were 8.86 (1.03) and 9.08 (0.93) mg/dL, respectively (P=0.335); serum phosphorus 5.24 (0.87) and 5.57 (0.75) mg/dL, respectively (P=0.09); and serum ALP 226.6 (75.6) and 245.3 (48.91) IU/L, respectively (P=0.158).

The geometric mean serum 25(OH)D level at 6 months of age was higher ng/mL in the vitamin D group than sunlight group after adjusting baseline serum 25(OH)D level as a covariate with a geometric mean ratio of 1.36 (95% CI: 1.06-1.76) (**Table III**). Analysis of covariance (ANCOVA) found a significant interaction between the group and compliance percentage (P=0.045) revealing the dependence of vitamin D values at 6 months on the compliance percentage **(Web Fig. 1)**. A post-hoc analysis was performed to assess the effect of vitamin D by dividing the study subjects into ≥80% (high) and <80% (low and moderate) compliance. The ANCOVA models were performed taking serum 25(OH)D levels at 6 months as dependent and group as the fixed factor with baseline serum 25(OH)D levels as the covariate (**Table III)**.

Two infants in the sunlight group developed rickets (diagnosed clinically and confirmed with biochemical and radiological tests) while none developed rickets in the vitamin D group. Four infants (baseline mean (SD) serum 25(OH) D 13.12 (3.6)ng/mL) in the vitamin D group had U-CaCr >0.6 mg/mg with mean (SD) serum calcium 9.25 (0.54) mg/dL and serum 25(OH)D levels 20.97 (10.0) ng/mL, without any clinical or biochemical evidence of vitamin D toxicity.

DISCUSSION

The present study showed a higher proportion of infants with vitamin D sufficiency after daily vitamin D3 supplementation for six months than daily sunlight exposure. Vitamin D sufficiency in both groups was significantly related to compliance which was better in the vitamin D group than the sunlight group.

Studies have shown that serum vitamin D level increases after both, sunlight and supplementation. A systematic review reported a significant increase in serum 25(OH) D levels after exposure to artificial UV light which was dependent on UV-B dose and baseline serum 25(OH)D [17]. A recent study showed that infants with <30 min/day sunlight exposure were five times likely to develop vitamin D insufficiency than those with >30 min/day [18].

However, vitamin D3 supplementation results in a more predictable increase in serum 25(OH)D levels than sunlight as seen in adults [19-21]. A systematic review of seven studies in adults reported a higher mean difference of 8.56 nmol/L (95% CI 4.15-12.97) with vitamin D supplementation (400-5000 IU/day) than sunlight (duration 8-48 weeks). This difference remained statistically significant irrespective of the duration of therapy and was higher with the use of natural sunlight [9]. In another RCT from China, adolescents with low baseline serum 25(OH) D(15.5-16.5 nmol/L), were randomized to receive oral 800 IU/day vitamin D3 or more than 30 min/day of outdoor exposure between 9 am and 3 pm and compared with a control group. A significantly higher reduction was observed in the proportion of subjects with vitamin D deficiency in the first two groups [8]. The present study also reported greater efficacy of vitamin D3 supplementation than sunlight exposure to achieve a higher proportion of vitamin D sufficiency in infants.

Table III Serum 25(OH)D Levels Six Months After Intervention Among Children in the Two Groups

	Sunlight group		*Vitamin D group*		*OR (95% CI)*	*P value*
	n	*25 (OH) D levels*	*n*	*25 (OH) D levels*[a]		
All children[a]	36	11.89 (9.93-14.24)	37	16.23 (13.58-19.40)	1.36 (1.06-1.76)	0.02
≥80% compliance	6	15.61 (11.36-21.44)	17	24.28 (20.11-29.31)	1.57 (1.08-2.27)	0.03
<80% compliance	30	11.25 (9.30-13.56)	20	11.54 (9.18-14.53)	1.03 (0.77-1.37)	0.86

Vitamin D levels as geometric mean (95% CI) in ng/mL. [a]*Interaction between group and baseline* serum 25(OH)D *was not significant (P>0.05).*

Harsher summer in Northern India probably limits time spent outdoors, while increasing air pollution with poor UV index limits sunlight penetration during winters even when sun exposure is preferable [22]. A cross-sectional survey from Ethiopia reported poor knowledge, attitude, and practices towards sunlight exposure of infants in mothers [23]. Most families being nuclear in structure can offer limited time for supervised sun exposure for their infants. These variances are unlikely to be seen with vitamin D3 supplementation suggesting it to be a more reliable and effective strategy. Also, rickets developed in infants in the sunlight group unlike in the vitamin D group reiterating the role of vitamin D supplementation in the prevention of rickets as reported in an earlier study [24]. However, vitamin D supplementation carries its concerns of added costs, adherence, and risk of side-effects/toxicity unlike sunlight exposure which is a natural and effective endogenous source of vitamin D. There may occur interpersonal variations in adherence to universal vitamin D supplementation practices [25]. Moreover, at present the Government agencies do not endorse any routine infant supplementation.

The lack of direct observation of interventions, lack of objective measurement of sunlight with the solar meter or quantification of standard erythemal dose, and collection of information on sunlight exposure on questionnaire alone may be perceived as the limitations in the present study. Repeat urine samples were not collected to confirm elevated calcium excretion as part of this study. However, this study explores the role of sunlight in Indian infants where sunlight is replete and may be utilized for optimizing serum 25(OH)D levels after accounting for environmental and personal host factors.

We conclude that oral vitamin D3 supplementation of 400 IU/day was more efficacious than daily sunlight exposure to achieve vitamin D sufficiency in infants; the effect was mainly modified through better compliance to oral vitamin D3 supplementation than sunlight. Daily vitamin D supplementation has added costs with the need for administration, while sunlight exposure is an unpredictable source of vitamin D. Further epidemiological studies are needed to evaluate the practical implementation and cost-effectiveness of these public health strategies.

Ethics approval: Ethics Committee of University College of Medical Sciences; No. HR/2018/36/105, dated Oct 15, 2018.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributions: PG, DS: Study conception, data analysis, manuscript review and final editing; AG, AD: Data collection and analysis, manuscript drafting and writing; RKM: Data analysis, manuscript writing and review; PD: Study conception, manuscript drafting; SVM: Laboratory analysis, manuscript review and editing; All authors have read and approve the final contents of the manuscript.
Funding: Intramural grant from the University College of Medical Sciences, Delhi; *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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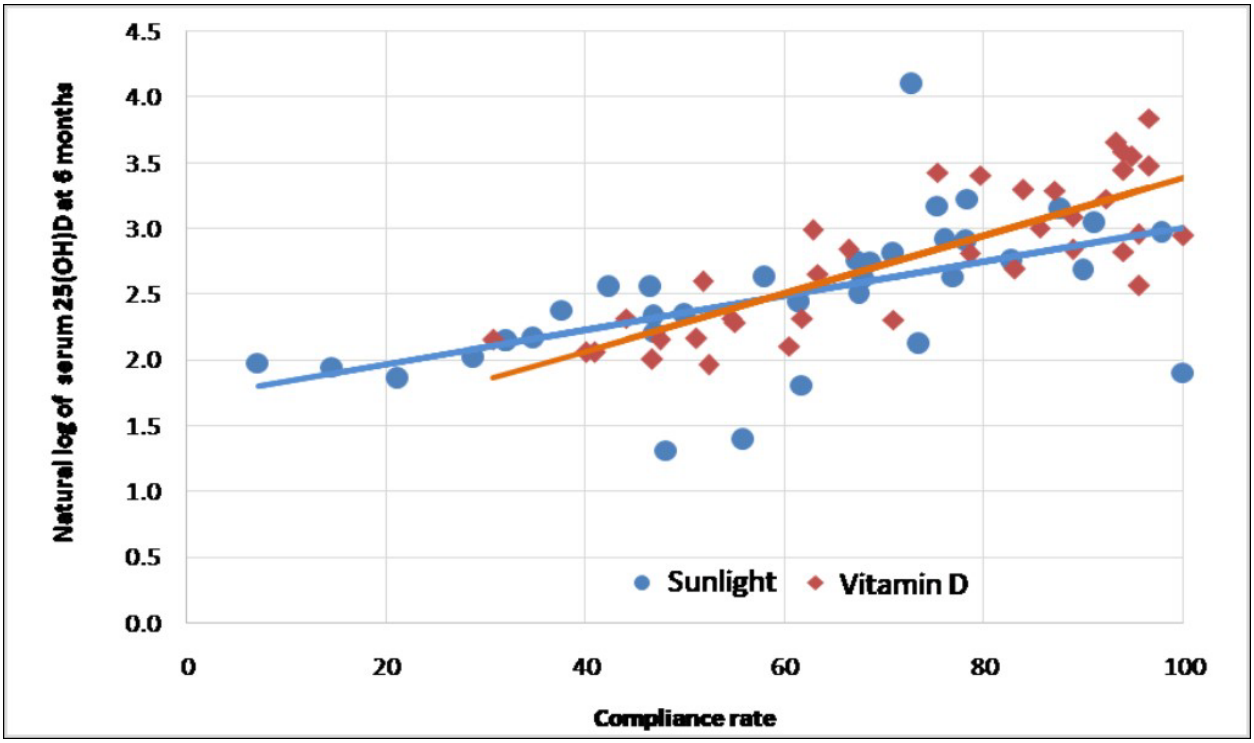

Web Fig. 1 Interaction between compliance rate and the natural log of infant's serum 25(OH)D at 6 months.

RESEARCH PAPER

Risk Factors of Delirium in Children in Pediatric Intensive Care Unit

BHAVESH MOTWANI, UMESH PANDWAR, AMIT AGRAWAL, JYOTSNA SHRIVASTAVA
From Department of Pediatrics, Gandhi Medical College and Kamla Nehru Hospital, Bhopal, Madhya Pradesh.

Correspondence to:
Dr Umesh Pandwar,
Associate Professor,
Department of Pediatrics,
Gandhi Medical College and Kamla Nehru Hospital, Bhopal,
Madhya Pradesh.
umeshpandwar@gmail.com
Received: May 27, 2022;
Initial review: July 19, 2022;
Accepted: August 18, 2022.

Objectives: To determine the prevalence of delirium and its risk factors among children admitted to a Pediatric intensive care unit (PICU). **Method**: A descriptive study in which consecutive patients admitted to the PICU over a period of 12 months were screened daily for delirium using the Cornell Assessment of Pediatric Delirium (CAPD) score. Treatment-related and demographic variables were collected and analyzed. The statistically significant risk factors for delirium were analyzed by multivariable logistic regression for independent associations. **Results:** Among the 476 screened patients, 96 (20.2%) developed delirium. The independent risk factors associated with the development of delirium were respiratory failure (P<0.001), administration of benzodiazepines during PICU stay (P<0.001), and presence of multiple (≥2) risk factors for delirium (P<0.001). The mean length of PICU stay was significantly higher among delirious subjects with P<0.001. **Conclusion:** Delirium is a frequent complication in critically ill children, and recognition of associated factors may assist in early diagnosis and focussed management.

Keywords: *Benzodiazepine, Outcome, Respiratory failure, Unconscious.*

Published online*:** August 26, 2022; ***PII: S097475591600449

Delirium is a manifestation of acute cerebral dysfunction due to a serious underlying illness. It has been linked to increased mortality, prolongation of hospital stay, and long-term disabilities [1]. The pathophysiology of delirium is com-plex and involves multiple factors, including alterations in cerebral blood flow, energy metabolism, neurotransmission, and disordered cellular homeostasis. It is a result of the synergism of three events: the underlying disease itself, adverse effects of the treatment, and the highly stressful intensive care environment [1].

The available pediatric studies [2,3] have found a varying prevalence of delirium in critical patients, ranging from 17.3% to 25%. The various risk factors found to be associated with the development of delirium in these studies are age ≤2 years, developmental delay, the severity of illness, mechanical ventilation, and administration of vasopressors, benzodiazepines, anticholinergics and narcotics, and use of physical restraints [2,3]. We studied the prevalence of delirium in the pediatric intensive care unit (PICU) and the associated risk factors.

METHODS

This descriptive study was conducted at a public sector tertiary care hospital, after obtaining approval from the institutional ethical committee. Between 1 April, 2020 to 31 March, 2021, all patients with ages ranging from 1 month to 14 years, admitted to the PICU for at least 24 hours were included in the study, after taking informed consent from a guardian of the child. Demographic data, including age, sex, and developmental status were collected at admission in the PICU.

All children included in the study were screened once daily by observing the patient over the entire duty shift by a single investigator, using the Richmond Agitation-Sedation Scale (RASS score), followed by the Cornell Assessment of Pediatric Delirium (CAPD score) for assessment of delirium during their entire PICU stay. The RASS is a validated scale in critical pediatric patients for accurate assessment of awareness in mechanically ventilated and spontaneously breathing patients [4]. The RASS score ranges from –5 (unarousable), through 0 (alert and calm), to +4 (combative). It was used to assess the level of awareness and classify the subtype of delirium in this study. The CAPD is a rapid, observational screen, validated for the detection of delirium in PICU setting. It consists of eight items that correlate with the diagnostic domains of awareness and cognition from the DSM-5, and also includes psychomotor symptoms. It has a high over-all sensitivity (94.1%) and specificity (79.2%) for critically ill patients. In developmentally delayed patients, it has low specificity (51.2%) but high sensitivity (96.2%) [5].

As per the calculated scores, subjects were categorized into 'Comatose' (subjects with a RASS score of -4 or -5 at any point of time during their PICU stay, who were under

deep sedation or unarousable to verbal or physical stimulation and therefore impossible to assess for delirium), 'Delirious' (CAPD score ≥9 at any point of time during their PICU stay) or 'Non-delirious'. Comatose patients were excluded from the study. The subtype of delirium was categorized based on the RASS score of the delirious patient, as Hypoactive delirium (RASS score of 0 to -3), Hyperactive delirium (RASS score of +1 to +4), or Mixed delirium (RASS score crossing both sides of 0).

The risk factors for the development of delirium assessed clinically for individual subjects over their PICU stay were the presence of significant developmental delay (clinical assessment and/or developmental problems that led to severe impairment in the ability to communicate with caregiver in age-appropriate ways), respiratory failure (presence and persistence of any of the following: respiratory acidosis, SpO2 < 90% or PaO2 < 60 mm Hg, tachypnea, increased work of breathing) [6], cardiac failure (based on clinical and radiological criteria) [7], shock [8], cyanotic spells, renal failure [9], and administration of benzodiazepines during PICU stay. Duration of delirium was defined as the number of days for which the patient was delirious during the PICU stay.

Statistical analysis: The statistical tests used were the chi-square test and Fisher exact test for analysis of risk factors, and unpaired t-test for comparison of PICU length of stay. *P* value <0.05 was considered statistically significant in univariate analyses. All factors which were found to be significantly associated with the development of delirium in univariate analysis were entered in the multivariable logistic regression analysis to identify independent associations.

Table I Characteristics of Children Admitted in the PICU and Enrolled in the Study

Characteristics	*Delirious (n=96)*	*Non-delirious (n=380)*	*P value*
Male sex	55 (57.3)	210 (55.3)	0.73
Age			
<2 y	55 (57.3)	144 (37.9)	0.001
2-5 y	14 (14.6)	108 (28.4)	
6-10 y	18 (18.7)	81 (21.3)	
>10 y	9 (9.4)	47 (12.4)	
Developmental delay	40 (41.6)	43 (11.3)	<0.001
Respiratory failure	40 (41.6)	3 (0.8)	<0.001
Cardiac failure	9 (9.4)	23 (6.1)	0.25
Shock	34 (35.4)	8 (2.2)	<0.001
Cyanotic spells	2 (2.1)	4 (1.1)	0.34
Renal failure	2 (2.1)	2 (0.6)	0.18
Benzodiazepine administration	55 (57.3)	26 (6.9)	<0.001
Multiple risk factors for delirium	79 (82.3)	44 (11.6)	<0.001
Outcome of PICU stay			
Discharge	50 (52.1)	325 (85.5)	<0.001
Death	38 (39.6)	9 (2.4)	
Other	8 (8.3)	46 (12.1)	

Data expressed as n (%). PICU pediatric intensive care unit.

RESULTS

We screened a total of 534 children for eligibility during the study, of which, parents of 11 children refused consent and 47 children had coma (GCS<8). Thus, 476 children (55.6% males) were enrolled, of which 20.2% (*n*=96) screened positive for delirium (**Table I**). The most common subtype of delirium was the hypoactive type (44.8%) followed by hyperactive (29.2%) and mixed types (26%).

The risk factors that were found in a significantly higher proportion in delirious patients were age less than 2 years (*P*=0.001), developmental delay (*P*<0.001), respiratory failure (*P*<0.001), shock (*P*<0.001), administration of benzodiazepines during PICU stay (*P*<0.001), and presence of multiple (≥2) risk factors (*P*<0.001) (**Table I)**

In the multivariate logistic regression analysis, independent risk factors found to be associated with the development of delirium were respiratory failure (*P*<0.001), administration of benzodiazepines during PICU stay (*P*<0.001), and presence of multiple (≥2) risk factors (*P*<0.001) (**Table II**). The mean (SD) length of PICU stay was significantly higher in delirious subjects as compared to non-delirious subjects [5.75 (2.71) and 2.74 (1.61) days; *P*<0.001, respectively].

DISCUSSION

We found the incidence of delirium to be 20.2% among children in the PICU. The independent risk factors found to be associated with the development of delirium were respiratory failure, administration of benzodiazepines during PICU stay, and presence of multiple (≥2) risk factors for delirium.

Delirium is a commonly occurring condition in critically ill patients, as they are predisposed to environmental and

Table II Multivariate Logistic Regression Analysis of Risk Factors Associated With the Development of Delirium

Characteristics	*Adjusted OR (95% CI)*	*P value*
Age <2 y	1.21 (0.54-2.71)	0.62
Developmental delay	1.75 (0.72-4.24)	0.21
Respiratory failure	14.03 (3.24-60.74)	<0.001
Shock	2.21 (0.66-7.31)	0.19
Benzodiazepine administration	7.31 (3.31-16.11)	<0.001
Multiple risk factors	6.30 (2.33-17.04)	<0.001

WHAT THIS STUDY ADDS?

- Delirium is a common phenomenon in the PICU, and is commonly associated with respiratory failure and benzodiazepine administration.

metabolic risk factors for delirium such as disturbed sleep, immobility, infections, withdrawal, noise disturbances, and sensory overload [10]. The findings of our study are in accordance with the range of prevalence of delirium in previous pediatric studies [2,3]. The varying prevalence of delirium among these studies may be due to different patient populations, varying reasons for admission, use of different tools for diagnosis of delirium, differences in sedation practices, or other unknown factors. Among the subtypes of delirium, incidence of hypoactive delirium was found to be similar (46%) in another study [2], but they reported the incidence of hyperactive delirium as only 8%, which is in contrast to our study. Another study that was performed among adult medical ICU patients concluded that mixed delirium was the most common subtype (54.1%) [11]. The risk factors found to be associated with delirium in our study are consistent with previous pediatric and adult studies [1-3,12,13]. A two-times longer length of PICU stay was reported among delirious subjects in one study [2], and few other studies have reported similar results [1,13].

The limitations of the study include assessment of delirium could be performed only once daily, so any fluctuations or diurnal variations in the state of delirium could not be analyzed. The tool for diagnosis of delirium which is used in this study was CAPD, which is a well-validated screening tool for pediatric patients with high sensitivity, but its specificity is low in developmentally delayed children, which could lead to an under-diagnosis of delirium in that subset of patients [5]. The causality of association for the risk factors of delirium also could not be established.

To conclude, delirium is a lesser known but prevalent condition in the PICU. It is associated with risk factors like respiratory failure and administration of benzodiazepines and it also leads to a longer length of PICU stay. Further multi-institutional studies on various aspects of delirium, including its effects on patient outcomes and long-term neurocognitive impairment, are required to improve our understanding of pediatric delirium. Another area of future research could be focused on the evaluation of interventions to reduce the incidence of delirium, as well as its effect on patient outcomes.

Ethics clearance: IEC, Gandhi Medical College, Bhopal; No. 530/MC/IEC/2020, dated Jan 04, 2020.
Contributors: BM: Acquisition and interpretation of data, data analysis, drafting the article, and literature review; UP: Concept, interpretation of data and data analysis, drafting the article, literature review, and revising the article critically for important intellectual content; AA: Drafting the article, literature review, and revising the article critically for important intellectual content; JS: Interpretation of data and data analysis, literature review, and revising the article critically for important intellectual content. All the authors approved the final manuscript.
Funding: None; *Competing interests*: None stated.

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RESEARCH PAPER

Ocular Toxicity of Ethambutol During Both Intensive and Continuation Phases of Anti-Tubercular Therapy in Children

SUSHANT S MANE, ANINDITA MANDAL, MANAS PUSTAKE, MOHAMMAD KASHIF ALI, NISHA YADAV

From State Pediatric Center of Excellence for TB, Grant Government Medical College and Sir JJ Group of Hospitals, Byculla, Mumbai, Maharashtra 400008.

Correspondence to:
Dr Manas Pustake,
State Pediatric Center of Excellence for TB, Grant Government Medical College and Sir JJ Group of Hospitals, Byculla, Mumbai, Maharashtra.
pustakemanas@gmail.com
Received: March 26, 2022;
Initial review: April 25, 2022;
Accepted: September 02, 2022 .

Objective: The study was conducted to evaluate the ocular toxicity of ethambutol given in both intensive and continuation phases of treatment in children with drug-sensitive tuberculosis. **Methods:** A prospective study of 94 eyes from 47 patients receiving an ethambutol-containing regimen was conducted between 1 December, 2018 and 31 August, 2020. Visual acuity, visual field, visual evoked response (VER), contrast sensitivity, colour perception, and retinal nerve fiber layer (RNFL) thickness [using optical coherence tomography (OCT)] were tested for each patient before, during, and after the treatment. **Results:** On follow-up, visual acuity, color vision, contrast sensitivity, fundus, and visual fields were not affected in any of the patients. There was no statistically significant increase in the mean latency of the P(100) wave at any point in time. On OCT, no significant loss of mean RNFL thickness was detected. **Conclusions:** Ethambutol is safe to use up to a dose of 20 mg/kg/day throughout the entire course of anti-tubercular therapy in children with drug-sensitive tuberculosis.

Keywords: *Adverse effects, Optic coherence tomography, Outcome, Visual evoked response*.

Ethambutol is an important drug for the treatment of tuberculosis due to less propensity to develop resistance, and good distribution in all body tissues (except the central nervous system) with minimal adverse effects. Most frequently, it causes retrobulbar neuritis, which affects either the axial or, less commonly, peri-axial fibres [1]. The onset of ocular symptoms is usually delayed and may begin weeks to months after the start of therapy. Other than early detection and stopping the drug, no specific treatment is available for the optic neuropathy caused by ethambutol. Most patients recover after stopping the drug; though rarely, vision may fail to recover even after the drug is stopped [2].

In 2016, the World Health Organization (WHO) approved including ethambutol for both the intensive and continuation phases of tuberculosis therapy, even in infants, with recommended dosages [3]. Previously, research has concentrated on the analysis of optic neuropathies arising after signs and symptoms of toxicity have manifested [4]. There is limited data on ethambutol-induced ocular toxicity, especially in children, after the WHO approved its use in both the intensive and continuation phase for the treatment of tuberculosis [5]. This study was conducted to evaluate the spectrum and associated factors of ocular toxicity with ethambutol in children with drug-sensitive tuberculosis when used in both the intensive and continuation phases of the treatment.

METHODS

This was a prospective, observational study conducted at a tertiary care institute in India, after institutional ethics committee clearance. Participants were enrolled between 1 December, 2018 and 31 August, 2020 from the in-patient and outpatient facility in the department of pediatrics. Eligibility criteria were age 6 months to 12 years at enrolment, advised six-month RNTCP (Revised National Tuberculosis Control Programme) regimen with two months of HRZE (intensive phase) and four months of HRE (continuation phase) [6] for a confirmed diagnosis of drug-sensitive tuberculosis (pulmonary, extra-pulmonary or disseminated) and whose parents/caregivers gave consent. For neurological and spinal tuberculosis, the total duration of treatment was 12 months, with ten months of the continuation phase. All critically ill patients, those with other co-morbid systemic conditions, or those with previously diagnosed ophthalmologic comorbidities were excluded. All the children were given ethambutol at a dose

of 20 mg/kg/day as a single daily dose of the child-friendly dispersible tablet. The cumulative dose for each child was 3600 mg throughout treatment (7200 mg in case of CNS or spinal TB).

Data were collected through a predesigned questionnaire. On the day of examination, parents were told to bring the child with a clean scalp and hair, enough sleep the previous night (minimum 6 hours), and a light meal. Data related to vision and serum ethambutol levels were collected at the baseline, at the end of the intensive phase, at the end of the continuation phase, and two months after the end of the continuation phase. Only those children who manifested ocular toxicity were subjected to serum ethambutol levels two months after completion of the entire regimen. A brief ophthalmological history was taken for each participant, with a review of their past medical records. Before beginning the eligible patients on ethambutol, baseline tests were done. The visual field was measured using standardized perimetry. Confrontation perimetry and finger counting in quadrants of the visual field were used for younger children. For school-aged children, Goldmann Perimetry was used [7]. The visual acuity in infants was measured using age-appropriate methods [7]. Each patient underwent visual evoked potential (VEP), fundus photography, and optical coherence tomography (OCT). Serum ethambutol levels were measured in serum by a modified microbiological vertical diffusion test [8].

Statistical analysis: The data were analyzed using the IBM Statistical Packages for Social Sciences (SPSS software version 22). *P* value less than 0.05 were considered statistically significant.

RESULTS

Of the 74 patients diagnosed with tuberculosis during the study period, 63 patients were enrolled, and 47 were finally analyzed. Of these, 14 patients were CNS or spinal tuberculosis, so the duration of treatment for these patients was 12 months. The characteristics of the patients are shown in **Table I**.

The serum ethambutol levels of participants are shown in **Table I**. Seven patients were found to have serum ethambutol concentration of >1 µg/mL at the end of the continuation phase, but all of them had undetectable levels two months after stopping the treatment. An eight-year-old male child with pulmonary tuberculosis had a serum ethambutol level of 1.44 µg/mL at the end of the intensive phase, which decreased to 0.76 µg/mL after the continuation phase. Serum ethambutol levels in all the other children in both evaluations were <1 µg/mL.

There were no complaints of impaired vision or other subjective ocular signs from any of the patients at any point during the study. None of the parameters (visual field, visual acuity, colour perception, and contrast exposure) showed significant differences throughout the course of treatment as compared to the baseline. Throughout the study duration, perimetry, visual acuity, colour perception, and contrast exposure demonstrated no noticeable difference from baseline.

Measures of subclinical toxicity are given in **Table II**. At the end of the intensive phase, two patients had increased latency of VEP. No patient developed a further increase in latency. RNFL thickness or VEP latency did not show a significant difference over time. Factors found to

Table I Characteristics of Children With Tuberculosis Receiving Ethmbutol (*N*=47)

Age (y)[a]	6.5 (4-10)
Male sex	23 (47)
Type of infection	
Pulmonary	17 (34.7)
Extra-pulmonary	18 (36.7)
Disseminated	14 (28.6)
Serum ethambutol level (< 2 µg/mL)[b,c]	
End of intensive phase (*n*=48)	
0-1	42 (89.5)
1-2	5 (10.5)
End of continuation phase (*n*=47)	
0-1	40 (85.1)
1-2	7 (14.9)

Data in no. (%) or [a]median (IQR). [b]No patient had levels > 2 µg/mL; [c]Levels were available for only 7 patients two months after stopping the drug, and were between 0-1 µg/mL in two.

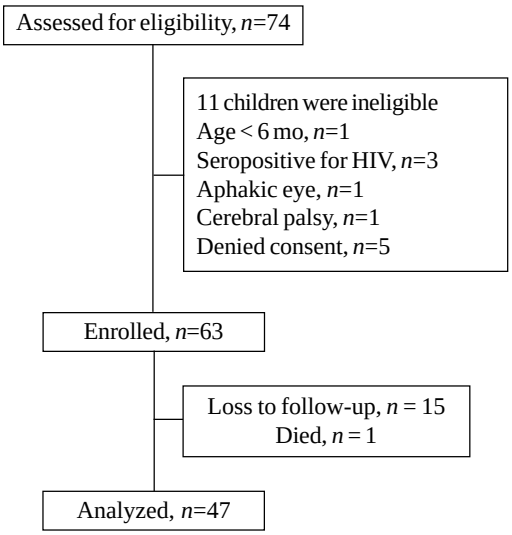

Fig. 1 Flow of patients in the study.

Table II Visual Characteristics of Children With Tuberculosis Receiving Ethambutol at Various Timepoints

Parameter	*Baseline* Mean (SD)	Range	*End of intensive phase* Mean (SD)	Range	*End of continuation phase* Mean (SD)	Range	*2 mo after treatment completion* Mean (SD)	Range
	n=114		*n=96*		*n*=86		*n*=84	
Visual acuity (logMAR)	0.04 (0.08)	0.02-0.32	0.05 (0.06)	0.01-0.32	0.04 (0.08)	0.05-0.31	0.05 (0.14)	0.03-0.22
Contrast sensitivity	1.71 (0.21)	0.80-2.81	1.67 (0.22)	0.79-3.11	1.68 (0.21)	0.80-2.92	1.57 (0.32)	0.79-2.3
VEP	94.13 (9.63)	61-105.42	93.98 (11.21)	61.22-118.14	95.24 (10)	67-118.72	89.71 (2.46)	77-98.66
RNFL thickness (µm)	*n*=126		*n*=98		*n*=94		*n*=92	
Average	100.9 (8.6)	80.8-114.2	101.1 (7.7)	81.2-114.3	101.1 (10.2)	79.6-115.7	101.1 (10.2)	79.6-115.7
Inferior	138.3 (16.9)	111-181	135.4 (14.8)	111.2-172.3	134.8 (19.0)	105.3-170.7	127.2 (11.9)	104.1-148.4
Superior	134.0 (17.6)	98-168	135.0 (18.1)	97.3-189.7	144 (15.1)	93.2-179.5	143.8 (14.8)	92.5-168.9
Nasal	86.3 (26)	44-133	87 (14.2)	46.5-134	98.9 (21)	45-135.2	100.2 (19.2)	64.4-135.3
Temporal	71.8 (11.8)	54-114	72.3 (11.7)	53.8-130.2	71.8 (12)	48.1-107.4	73.2 (8.6)	51-107.8

P>0.05 for comparison of all parameters between baseline, end of intensive phase, end of continuation phase and 2 mo after treatment completion.

be associated with the appearance of subclinical toxicity (increased latency on VEP) in univariate analysis (age, sex, serum ethambutol concentration (at baseline and 6 months), and type of tuberculosis infection) were subjected to multivariate logistic regression. After multivariate logistic regression, none of the variables exhibited a statistically significant relationship with the development of subclinical toxicity.

DISCUSSION

The prevalence of ethambutol-induced optic neuropathy has been estimated to be greater than 1% in adults [9]. This issue is less explored in the pediatric population but the available evidence in children indicates that the oculotoxicity of ethambutol is <1% [10]. Oculotoxicity from ethambutol presents as painless loss of central vision and ceco-central scotomas in the visual field. The toxicity is usually reversible on stopping the treatment. Hence, it is advisable to closely monitor for oculotoxicity among the patients taking ethambutol [11].

After the intensive phase, only two patients (4%) showed objective evidence of affection for vision. However, they did not have any visual signs or symptoms. In three similar studies from India, no visual symptoms, clinical or subclinical, were reported in doses between 15-25 mg/kg/day [12]. In a study conducted by Thee, et al. [14] ocular toxicity was monitored every four weeks during treatment, where 4 (0.7%) children were found to have visual complaints, like changes in colour perception. However, no change in fundoscopy, perimetry, or visual evoked potential was detected [13].

It was thought that the difference in the oculotoxicity between adults and children must be due to different doses of ethambutol in these studies. Hence, we tried to correlate the serum levels of ethambutol with ocular toxicity. However, we couldn't get any conclusive evidence on the association of serum levels of ethambutol with ocular toxicity.

Ethambutol toxicity, as previously stated, is dose-dependent. We gave our patients a 20 mg/kg/day dose, as recommended by the WHO, with an excellent response to the therapy without any significant toxicity. Hence, larger ethambutol doses may be unnecessary.

We measured serum ethambutol concentrations only once at two hours after the dose. The peak serum levels of ethambutol may likely have reached later than two hours. However, we do not consider this to be a significant limitation because the toxicity is dose-dependent rather than serum concentration-dependent. There may be bias or lack of physician error in the objective assessment of ophthalmic evaluation in children.

WHAT THIS STUDY ADDS?

- Ethambutol is a safe medication in children with drug-sensitive tuberculosis, when given in a daily dose of 20 mg/kg/day, both in the intensive and continuation phases of tuberculosis treatment.

Ethambutol is a safe medication in children with drug-sensitive tuberculosis when given at a daily dose of 20 mg/kg/day, throughout the entire course of anti-tubercular therapy, both in the intensive and continuation phases of treatment.

Contributors: SM, AM, MP: Concept and designed the study, analysed data and drafted the manuscript, collected the data and helped in data analysis. SM, AM, MP, MKA, NY: Helped in the data collection, statistical analysis and revising of the final draft of the manuscript. All authors approved the final version of the manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.

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RESEARCH PAPER

Characteristics of Siblings With Celiac Disease Diagnosed by Family Screening

BILGE S AKKELLE, BURCU VOLKAN, ENGIN TUTAR, DENIZ ERTEM

From Marmara University School of Medicine, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Istanbul, Turkey.

Correspondence to:
Prof Dr Deniz Ertem, Chief,
Division of Pediatric Gastroenterology
Marmara University School of
Medicine, Bahýbüyük Campus,
Maltepe Bahibüyük Yolu Sok. No:9/1,
34854 Maltepe – Istanbul.
denizertem@marmara.edu.tr
Received: May 07, 2022;
Initial review: June 13, 2022;
Accepted: Sept. 10, 2022.

Objective: The aim of this study was to evaluate the features of asymptomatic siblings of index celiac patients who were diagnosed with celiac disease (CD) at the initial screening. **Methods:** We reviewed hospital records of 210 children with CD. The characteristics of sibling celiacs (*n*=24) were compared with index celiacs (*n*=186). **Results:** At diagnosis, sibling celiacs were older than index celiacs (mean (SD) 10.4 (2.7) vs 8.2 (4.3) years; *P*=0.02). There were no significant differences between sibling and index celiacs in terms of serum anti-tTG IgA titer (≥10xULN, 83.3% vs 85%), and most of the patients had moderate/severe villous atrophy in both groups. The rates of iron deficiency anemia, folic acid deficiency, wasting and stunting were comparable between sibling and index celiac patients. **Conclusions:** Siblings with CD were older than index children with CD at diagnosis, and their characteristics were similar to symptomatic index children with CD, despite not having any complaints.

Keywords: *Asymptomatic, Serology, Silent disease*

Published online*:** September 22, 2022; ***PII: S097475591600458

Celiac disease (CD) is an immune-mediated enteropathy, triggered by ingestion of gluten and related prolamines in genetically predisposed individuals. It has been known that CD may display different phenotypic expressions, and clinical manifestations can occur at any age [1-3]. Some individuals with CD-related conditions (i.e., first-degree relatives of patients with CD, autoimmune diseases, Down/Turner syndrome, and selective IgA deficiency) may be asymptomatic despite positive celiac serology and histopathology compatible with CD [4]. The condition with the presence of positive CD-specific antibodies, and HLA, specific small-bowel biopsy findings but without sufficient symptoms and signs to warrant clinical suspicion of CD was defined as silent celiac disease by the current pediatric guideline [5]. Considering that celiac disease may present with a wide spectrum of clinical manifestations, it is doubtful how 'silent' the condition actually is.

First-degree relatives of celiac patients are individuals with high risk for CD and the prevalence of CD varies from 2% to 20% among them [5-8]. Siblings have a common genetic background and shared environment, and it has been suggested that they have a higher risk for CD compared to other family members [8,9]. However, there is scarce data concerning the characteristics of CD in siblings of pediatric celiac patients. The aim of this study was to investigate the features of asymptomatic siblings of index celiac patients who were diagnosed with CD as a result of family screening.

METHODS

The study was approved by local ethics committee of Marmara University School of Medicine.

The data children with CD who were followed up in our tertiary care center between 2014 and 2020, were retrospectively analyzed. Patients with an established diagnosis of selective IgA deficiency, Down/Turner syndrome, concomitant chronic/autoimmune disease such as type 1 diabetes mellitus and hypothyroidism were not included in the study. The patients were categorized into two groups: Group 1 consisted of asymptomatic siblings of index celiac patients diagnosed with CD as a result of screening; and Group 2 consisted of patients with CD who were symptomatic at presentation.

All patients included in the study had positive celiac serology and histopathology compatible with CD. A positive celiac serology is defined at our center if the level of anti-tissue transglutaminase (anti-tTG) IgA antibody is above the upper limit of normal on a gluten consuming diet. Anti-tTG IgA titer is measured in serum samples by

using a micro-enzyme-linked immunosorbent assays (ELISA) method (Euroimmun AG) with a cut off set at 20 U/mL. Individuals with a positive serology undergo upper gastrointestinal endoscopy. The intestinal biopsies are examined by the pathologist who is blind to the clinical and laboratory data. The modified Marsh (Oberhuber) classification system is used for grading mucosal histopathology [10].

Group 1 and 2 were compared regarding demographic and anthropometric features, nutritional deficiencies (iron, folic acid), serologic and histopathology findings at diagnosis. Lower limits of normal for age were used for hemoglobin to assess the presence of iron deficiency anemia [11]. Folic acid deficiency was defined if serum folic acid value below laboratory normals. Anthropometric data (Body mass index (BMI) and height for age (HFA) *z*-scores) are used to assess growth status in all patients. Furthermore, the BMI and HFA *z*-scores at admission and at 12th month of follow-up were compared in Group 1.

Statistical analysis: For statistical analyses, SPSS software version 22.0 was used. Descriptive analyses of the cohort is reported as proportions, means, standard deviations or medians. Continuous data were compared using Student *t*-test or the Wilcoxon rank sum test was applied when the data was ordinal. Categorical variables were compared using chi-square, Fisher exact or McNemar test. Value of $P<0.05$ was considered as statistically significant.

RESULTS

In this cohort, 24 out of 210 celiac patients (11.4%) were in Group 1 while the remaining 186 (88.6%) were in Group 2 (**Fig. 1**). The gender distribution between the groups was comparable ($P=0.33$). The mean age at diagnosis was higher in Group 1 compared to Group 2 ($P=0.02$) (**Table I**).

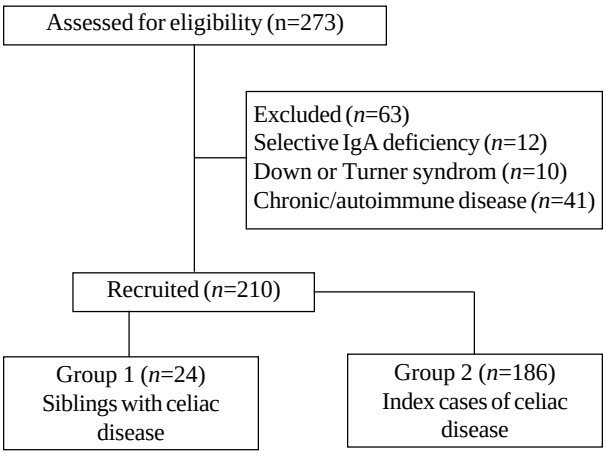

Fig.1 Flow chart of the study.

Table I Characteristic of Children With Celiac Disease and Their Asyptomatic Siblings Diagnosed by Family Screening

Characteristics	*Asymptomatic siblings (n=24)*	*Index cases (n=186)*	*P value*
Female gender	17 (70.8)	113 (60.8)	0.33
Age (y)[a]	10.4 (2.7)	8.2 (4.3)	0.02
BMI *z*-score <-2	7 (29.1)	34 (18.3)	0.22
HFA *z*-score <-2	6 (25)	49 (26.3)	0.90
Hemoglobin (g/dL)[a]	11.1 (1.5)	10.9 (1.7)	0.24
Iron deficiency anemia	11 (45.8)	85 (45.5)	0.97
Folic acid deficiency	6 (24)	29 (15.6)	0.21
Anti-tTG IgA (x10 ULN)	20 (83.3)	158 (85)	0.75
Histopathology			
Marsh III C	9 (37.5)	95 (51)	0.13
Marsh III B	12 (50)	52 (28)	0.03
Marsh III A	3 (12.5)	25 (13.4)	0.84
Marsh II	0	7 (3.7)	-
Marsh I	0	7 (3.7)	-

Values in no. (%) or [a]mean (SD). BMI-body mass index; HFA-height for age.

In both groups serum anti-tTG IgA titer was more than 10 times of upper limit of normal in most of the patients (83.3% vs. 85%; $P=0.75$). All of the patients in Group 1 and most of the patients in Group 2 had histopathologic alterations that were compatible with Marsh III (**Table I**).

The hemoglobin values and the role of iron deficiency anemia and folic acid deficiency values were similar in both groups. At diagnosis, 29.1% of the children in Group 1 and nearly 20% of the children in Group 2 were wasted, but the difference between the groups was not significant. Similarly, there was no significant difference between the groups regarding the rate of being stunted (**Table I**).

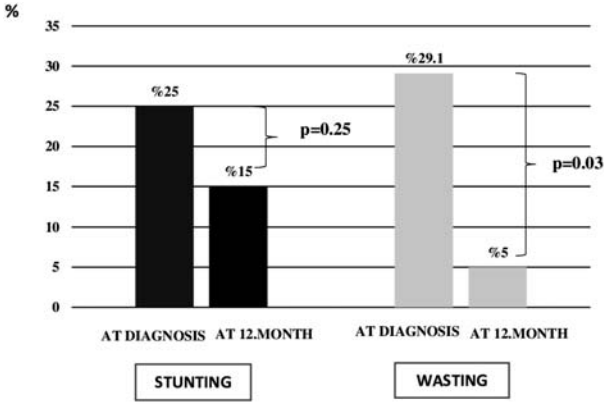

Fig.2 The change in the rates of stunting and wasting in siblings with celiac disease (Group 1) after one year follow-up on gluten free diet.

WHAT THIS STUDY ADDS?

- The clinical manifestations in asymptomatic siblings diagnosed with celiac disease were not different from the symptomatic index celiac patients in terms of growth retardation, micronutrient deficiencies and the presence of severe mucosal damage in their biopsies.

After 1 year on gluten-free diet, anthropometric parameters could be reassessed in only 20 (86%) siblings with celiac disease whose data were available. There was a significant improvement in the mean *z*-score for BMI [from -1.3 (1.7) to -0.3 (0.9), and the rate of wasting (29% to 5%). The difference between the rates wasting at diagnosis and follow-up in Group 1 was statistically significant. The mean (SD) *z*-scores for HFA also improved [from -1.2 (1.06) to -0.9 (1.05)] and the rate of stunting decreased (from 25% to 15%) among sibling celiacs at 12 month of follow-up on GFD (**Fig. 2**).

DISCUSSION

In this hospital record review of 210 children with celiac disease, 11.4% of the patients were asymptomatic siblings of index celiac patients diagnosed with CD through screening.

The malabsorption that occurs in CD is the cause of 'typical' symptoms (abdominal pain, diarrhea, abdominal distension, etc.) associated with the gastrointestinal tract, and can easily be recognized. However extraintestinal manifestations and unusual symptoms or signs can easily be overlooked [12]. The results of anthropometric and micronutrient evaluation in our study revealed that malnutrition and nutritional deficiencies in asymptomatic sibling celiac patients were similar to symptomatic index celiac patients. Moreover, siblings of our index celiac patients who were diagnosed with CD by screening were older than index celiac patients at diagnosis. Therefore, findings that may be warning signs for CD in those asymptomatic siblings had been overlooked until the index celiac patient had been diagnosed in the same family.

According to the results of our study, the titer of anti-tTG IgA in more than 80% of sibling celiacs was more than 10 times the upper limit of normal, as in index celiacs. Moreover, most of the patients in both groups had moderate/severe villous atrophy. Despite our sibling celiacs were diagnosed at the initial screening, serological and histopathological findings showed that they has already been living with CD. It has been known that micronutrient deficiencies due to malabsorption are common in celiac patients [13]. Almost half of the patients in both groups had iron and folic acid deficiencies possibly secondary to malabsorption, which is consistent with published figures [14].

Since growth retardation may be the primary or sole manifestation of CD, current guidelines recommend serological screening of the children with growth retardation [4]. In a recent meta-analysis, the pooled prevalence of biopsy-confirmed CD in children presenting with idiopathic short stature was reported as 11% [15]. In our study, a significant proportion of celiac patients in both groups had malnutrition, and a quarter of sibling celiacs had short stature consistent with stunting. In sibling celiac patients, a remarkable improvement in growth was observed under GFD treatment, although statistically not significant. These data support that screening not only enables the identification of new pediatric celiac patients, but also prevents CD-related complications in those so-called asymptomatics.

In our study, we evaluated the characteristics of sibling celiacs in a cohort of celiac patients diagnosed over a 6-year period. The fact that our cohort consisted of patients with biopsy-proven CD enabled the evaluation of histopathological features. Relatively small number of patients in the sibling celiac group was the main limitation in this single-center study.

Our results demonstrated that, sibling celiacs diagnosed by screening had a high rate of growth retardation, micronutrient deficiencies, and severe mucosal damage, and were similar in characteristics to symptomatic index celiacs. It seems that CD in the siblings of celiac patients may not be 'silent' even if they do not have any complaints. Given the importance of physical and mental development, the diagnosis of CD in early childhood will reduce the negative impact on growth and development.

Ethics approval: IEC, Marmara University School of Medicine; No. 9022.78, dated Jan 07, 2022 .
Contributors: BSA,DE,BV,ET: designed the study, analzsed and the data, revised the manuscript; BSA: wrote the first draft of the manuscript; BV,ET: gathered the data; DE: revised the manuscript critically for important intellectual content. All authors approved the final manuscript to be published and agreed to be responsible for all aspects of the work.
Funding: None; *Competing interests*: None stated.

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RESEARCH PAPER

Risk Factors of First Episode Simple Febrile Seizures in Children Aged 6 Month to 5 Year: *A Case Control Study*

P LEELA KUMARI, K RAJAMOHANAN, AS AJITH KRISHNAN
From the Department of Paediatrics, SAT Hospital, Govt Medical College, Trivandrum, Kerala.

Correspondence to: Dr Leela Kumari P, Associate Professor, Department of Paediatrics, SAT Hospital, Govt Medical College, Trivandrum, Kerala. leela_suresh2005@yahoo.co.in
Received: February 21, 2022; Initial review: April 22, 2022; Accepted: September 21, 2022.

Objective: To study the risk factors of first episode simple febrile seizures in children. **Methods**: This case control study was conducted at the pediatric department of our tertiary care hospital. Cases were children of age group 6 months to 5 years presenting with first simple febrile seizures (*n*=214), and Controls were children of same age group presenting with short febrile illness but without any seizures (*n*=214). Blood investigations were done to diagnose iron deficiency, which was diagnosed by adopting cut off of hemoglobin value <11 g/dL, serum ferritin < 12 ng/mL and red cell distribution width >15%. Other risk factors studied included age, gender, socioeconomic status, prematurity, family history of febrile seizure and epilepsy in first degree relatives, consanguinity, neonatal hospital admissions, day care attendance (for >1 mo), under nutrition, and immunization status of the child. Univariate analysis for crude odds ratio and multivariate analysis (logistic regression) was performed to study the adjusted odds ratio and independent risk factors. **Results**: The significant risk factors for first episode simple febrile seizure were iron deficiency [OR (95% CI) 5.78 (3.56-9.38); *P*=0.001], family history of febrile seizure [OR 4.31 (2.37- 7.83), *P*<0.001] or epilepsy [OR 4.25(2.21-8.19), *P*<0.001] in first degree relatives, day care attendance for >1 month [OR 4.81 (2.41-9.59), *P*<0.001], and prematurity at birth [OR 5.18 (2.48-10.84), *P*<0.001]. **Conclusion**: Iron deficiency, family history of febrile seizure and epilepsy in first degree relatives, day care attendance and premature birth are the risk factors for first episode simple febrile seizures in children.

Keywords: *Hemoglobin, Iron deficiency, Serum ferritin, Epilepsy*.

Febrile seizures are the most common type of seizures in children. It occurs in 2-5% of children in the age group of six months to five years. Febrile seizures is defined as seizures associated with fever (body temperature >38^0C or 100.4^0F), occurring in children of 6 months to 5 years with no evidence of central nervous system infection, metabolic abnormality or any other CNS insult to account for the seizures (i.e., in otherwise neurologically healthy children) with no prior history of afebrile seizures [1,2].

Both genetic and environmental factors are reported as risk factors of febrile seizures in children. Alterations in genes coding for gamma amino butyric acid (GABA) receptor and sodium voltage gated channel alpha sub unit (SCN1A) are known to be associated with febrile seizures [4,8]. Pathologically, febrile seizures are characterized as response of an immature brain to fever. Iron deficiency is reported as risk factor for febrile seizures in many studies [5, 6]. Other reported risk factors for first febrile seizures are maternal factors like smoking, alcoholism, stress, premature birth, prolonged neonatal intensive care (NICU) stay, day care attendance, febrile seizures in first degree relatives, afebrile seizures in first degree relatives, micro-nutrient deficiencies like iron and zinc deficiency [7-10].

There is a scarcity of studies focusing on all risk factors of first episode simple febrile seizures in Indian setting. This study was planned to identify the risk factors of first episode simple febrile seizures in children.

METHODS

This case control study was done in the pediatrics department of a tertiary care referral centre for a period of three and half years from August, 2012 to February, 2016. Ethics clearance was obtained from Institutional ethics committee and a written informed consent was taken from parents or the caregiver. Cases were children of age 6 months to 5 years presenting with first episode simple febrile seizures as per the American Academy of Pediatrics (AAP) guidelines [2]. Controls were children of age 6 months to 5 years presenting with short duration fever but without any seizures. Children with complex febrile seizures, afebrile seizures, chronic neurodevelopmental

problems, metabolic abnormalities, central nervous system infections, and diagnosed cases of other hematologic problems, those on iron supplement, chronic systemic diseases, and very sick children were excluded from the study. Consecutive cases and concurrent controls were selected from the same setting in a ratio of 1:1.

Sample size was calculated from the statistical software EpiInfo and using the sample size calculation formula of unmatched case control studies with assumptions of α error 5%, β error 20% (power of study 80%), prevalence of exposure (iron deficiency) among controls as 30% (obtained from a preliminary (pilot) study in the same setting and also literature evidence), and 95% confidence. Calculated sample size was 200 cases and 200 controls. After informed consent, clinical history was elicited, physical examination was performed, and relevant laboratory investigations were carried out among the study participants. Iron deficiency was the major exposure factor studied. Blood investigations done to diagnose iron deficiency include hemoglobin estimation and red cell distribution width (RDW) using an automated hematology analyzer (Sysmex Kx -21) and serum ferritin estimation using ELISA method (Acubind ELISA). Iron deficiency was diagnosed by WHO cut offs of hemoglobin value <11 g/dL, serum ferritin < 12 ng/mL and red cell distribution width >15% [3]. Other risk factors studied were age, gender, socioeconomic status, prematurity, family history of febrile seizure and epilepsy in first degree relatives, consanguinity, neonatal intensive care unit (NICU) admissions, day care attendance (for >1 month), undernutrition, and immunization status of the child.

Statistical analysis: This was done using the software SPSS version 27. Analyses included descriptive statistics, univariate analysis for crude odds ratio and multivariate analysis (logistic regression) to study the adjusted odds ratio and independent risk factors.

RESULTS

A total of 214 cases and 214 controls were recruited in the study. Mean age (in completed months) of cases and controls were comparable [18.66 and 18.79; P = 0.635]. Proportion of boys in both groups were also comparable [52.8% vs 55.1%; P=0.628]. There was no statistically difference in the socio economic status of cases and controls (P=0.77).

Significant association was found between iron deficiency and first episode simple febrile seizures in univariate (**Table I**) and multivariate analysis (**Table II**). The odds ratio of iron deficiency with simple febrile seizure adjusted for other covariates was 5.78 (95% CI 3.56-9.38) (P <0.001). Other risk factors found to be significant are family history of febrile seizures in first degree relatives [aOR (95% CI) 4.31 (2.37 -7.83), P <0.001], family history of epilepsy in first degree relatives [aOR (95%CI) 4.25l (2.208 -8.193) P <0.001], day care attendance for more than one month [aOR (95% CI) 4.81 (2.41-9.59) P<0.001] and prematurity at birth [aOR (95% CI) 5.18 (2.48-10.84); P <0.001]. No statistically significant difference was noted among cases and controls for neonatal hospital admissions (NICU) (P=0.61), immunization status of child (P=0.26) and undernutrition (P=0.79).

Table I Risk Factors for First Episode of Simple Febrile Seizure in the Enrolled Children

Variable	*Cases n=214*	*Controls n=214*	*Crude OR (95%CI)*
Iron deficiency[a]	128 (59.8)	51 (23.8)	4.76 (3.13-7.21)
Family history			
Febrile seizure[a]	71 (33.2)	22 (10.3)	4.33 (2.56-7.32)
Epilepsy[a]	58 (27.1)	17 (7.9)	4.31 (2.41-7.69)
Daycare attendance[a]	46 (21.5)	17 (7.9)	3.17 (1.75 -5.74)
Preterm birth[a]	35 (16.4)	15 (7)	2.59 (1.37-4.91)
Male gender	113 (52.8)	118 (55.1)	0.91(0.62-1.33)
Age <15 mo	107(50)	111(53.2)	0.93 (0.63- 1.35)
Socioeconomic status			
Middle	97(45.4)	94 (43.9)	0.94(0.64-1.38)
Lower	117 (54.6)	120 (56.1)	
Not fully immunized	19 (8.9)	12 (5.6)	1.64 (0.77-3.47)
Undernutrition	36 (16.8)	33 (15.4)	1.10 (0.66-1.86)

All values in no. (%). [a]P<0.005.

DISCUSSION

This case control study was done to identify the risk factors of simple febrile seizures in children. Iron deficiency, family history of febrile seizures and epilepsy in first degree relatives, day care attendance, and prematurity were found to be the independent risk factors. No statistically significant association was found between outcome variable and gender of child, socioeconomic status, neonatal hospital admissions (NICU), immunization status and undernutrition.

Table II Multivariate Logistic Regression Analysis for Risk Factors for First Simple Febrile Seizure

Variable	*Cases n=214*	*Controls n=214*	*Adjusted OR (95% CI)*
Iron deficiency	28 (59.8)	51 (23.8)	5.78 (3.56-9.382)
Family history			
Febrile seizure	71 (33.2)	22 (10.3)	4.31 (2.37-7.83)
Epilepsy	58 (27.1)	17 (7.9)	4.25 (2.20-8.19)
Daycare attendance	46 (21.5)	17 (7.9)	4.81(2.41-9.59)
Preterm birth	35 (16.4)	15 (7)	5.18 (2.48-10.84)

All values in no. (%). P All <0.001.

WHAT THIS STUDY ADDS?

- Iron deficiency, family history of febrile seizures and epilepsy, day care attendance, and prematurity were independent risk factors for first episode simple febrile seizure in children.

Both genetic and environmental factors are reported as risk factors for febrile seizures [1,2]. Genetic predisposition, certain viral infections and certain vaccines are more frequently associated with febrile seizures. Common viral infections are Human herpes virus 6, Influenza virus, Para influenza virus and Adenoviruses [8]. It was reported by Butilã, et al. [4] that mutations in genes that encode for voltage gated sodium channels and GABA receptors can cause febrile seizures. The vulnerability of immature brain for the fever induced seizures and genetic background of febrile seizures is reported in other studies also [5,6].

Smith, et al. [7] reported that family history of febrile seizure in first degree relatives is an independent risk factor for febrile seizures in children. Other risk factors reported were family history of afebrile seizure, neonatal intensive care admissions, day care attendance, and in utero exposures (maternal smoking). All these factors except NICU admissions and maternal smoking were found to be significant in the present study as well. Similar risk factors are also reported by other authors [8-12]. Sharvat, et al. reported male gender to be significantly associated with the risk of a febrile seizure [11]; although, others have not found a similar association [12]. We also did not find a significant association between gender of child and first febrile seizures.

In the case control study done by Rajwanti, et al. [13], it was found that the mean serum ferritin was significantly low in children with febrile seizures compared to controls. In our study also iron deficiency was noted as an independent risk factor for simple febrile seizures. Iron is essential for brain energy metabolism, myelination and neurotransmitter metabolism. So, a child with iron deficiency may be more prone for fever induced seizures [14, 15].

As it was a hospital based study, the prevalence of exposure and outcome variables may be different from a community setting. Serum ferritin, a nonspecific acute phase reactant, can rise in any inflammatory conditions; although, both cases and controls were having fever at the time of enrolment. It may be interesting to explore the genetic background for the identified risk factors. The strengths of our study include standardized criteria for diagnosing cases and controls and strict adherence to this during selection procedure and thus controlling the selection bias. Similarly, standardized definitions were adopted to define iron deficiency anemia and other risk factors thus augmenting the comparability of the results. Information was collected from the most reliable informant and hospital/personal records were also examined for getting the authentic data and thus recall bias was controlled.

Results of the present study favor the early detection and timely correction of iron deficiency, which may prevent febrile seizures. Anticipatory guidance can be given to parents of children with family history of febrile seizure and epilepsy in first degree relatives, day care attendance and premature birth.

Ethics clearance: IEC, Government Medical College, Thiruvananthapuram; No. IEC 01/36/2012, dated Jan 17, 2012.
Contributors: PLK: designed the study, done literature search, collected, analyzed and interpreted the data and prepared the manuscript; RK: supervised and helped in data collection and analysis, reviewed the manuscript; AK: helped in data analysis and manuscript writing.
Funding: None; Competing *interests*: None stated.

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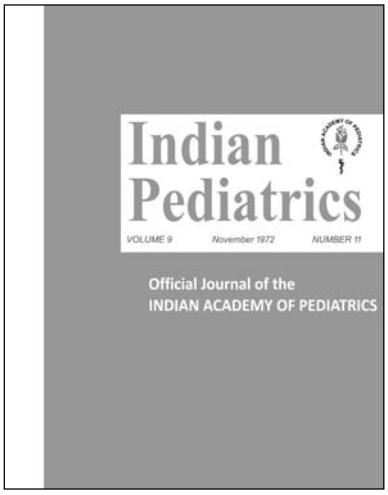
Progress in Diagnosis and Management of Intellectual Disability in India: A Journey Over Half-a-Century !

Sunita Bijarnia-Mahay[1], Sapna Sandal[1], Praveen Suman[2]
From [1]Institute of Medical Genetics & Genomics, and [2]Institute of Child Health, Sir Ganga Ram Hospital, New Delhi.
Correspondence to: Dr Sunita Bijarnia-Mahay, Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi.
bijarnia@gmail.com

Over the last half century, our country has witnessed enormous progress in medical practice. Prominent reasons for this include advancements in technology, pioneering research, and general awareness amongst practitioners. The same is true for the field of intellectual disability, which has come a long way, from being a relatively ignored field to rapidly becoming one of the more relevant ones in child health. We celebrate this welcome change by commemorating 50 years of publication of an article by Professor Sinclair on 'Etiological diagnosis in mental retardation' in the same journal [1]. The study, published in the summer of 1972, was remarkable at that time, as it showed a real world picture of the status of 'mental retardation' in India. Looking back, the assignment of a diagnosis of 'mental retardation' was largely clinical, based on history, examination and a few basic investiga-tions [1]. A lot has changed since then, starting from the definition and terminology used for the medical con-dition. It is no longer 'mental retardation', removing the derogatory connotations, and replaced by a more apt term of 'intellectual disability' or ID [2].



The etiological diagnosis of global developmental delay or GDD (GDD/ID) is now more precise and it has changed the way these children are managed. Four major aspects of GDD/ID are being highlighted in this paper to depict the major transformation that has occurred over the last 50 years, in India and abroad. These are: definitions, the clinical spectrum, diagnostic modalities/facilities available, and the management component.

Definitions

Intellectual disability: ID is applied to children >5 years of age with significant deficits in intellectual and adaptive functioning and onset in early developmental period (<18 years). The intellectual functioning is assessed by measuring intellectual quotient (IQ) using age-appropriate standardized tests and includes individual's ability to reason, judgement, problem solving, planning, abstract thinking, academic and experiential learning. The adaptive functioning includes person's communication and social skills, and the ability to work independently [3,4].

Global developmental delay: GDD is applied to children <5 years of age with significant delay (>2 SD below the mean with age-appropriate standar-dized tests) in two or more develop-mental domains including gross/fine motor skills, cognition, speech/lang-uage, social/ personal, and activities of daily living [3,4].

Clinical Spectrum

The advent of the new era of diagnostics has allowed for many more specific etiological diagnoses in patients with GDD/ID. The clinical spectrum of patients seeking diagnosis and management has also changed drastically, with reduction in incidence of birth-related adverse events (perinatal asphyxia, infections etc). Prominently, autistic spectrum disorders have risen multifold, even in the last decade. We looked at the spectrum of disorders in children presenting with GDD/ID at two clinics at our hospital – child development clinic and genetic clinic, and noted two different types of spectrums. The children attending child development clinic showed a varied spectrum – from pre and perinatal factors to genetically determined GDD/ID. The spectrum today is starkly different from what it was 50 years ago. Previously, etiological factors were divided simply into natal, post-natal and multiple factors. The

autistic spectrum disorders find no mention in 1972 data, but were seen in at least 28% of children in child developmental clinic presenting with GDD/ID. ASD is increasingly being recognized to occur, either alone or in associated with GDD today. Indian guidelines recommend that each child with GDD be screened for ASD at initial diagnosis and again at 3 years of age [5]. Other notable differences from the previous study [1] were the significant reduction in cases with congenital infections or teratogenicity [1]. Birth related events also seem to have reduced, but prematurity and low birth weight continue to be a significant part of GDD group. In a consecutive sample of 100 children with GDD presenting to our genetic clinic, 38% had no etiological diagnosis. Of the remaining 62, 18 had chromosomal disorders (Down syndrome in 10, other microdeletion syndromes), 11 had an inborn error of metabolism, 30 had other confirmed monogenic causes, and 4 were identified to have an imprinting disorder (PWS/Angelman syndrome). This shows the vast improvement in genetic diagnosis and refinement in diagnosis that is possible today. In the older study, Down syndrome and Turner syndrome were the only chromosomal disorders mentioned, with no microdeletions. The inborn errors of metabolism that were observed in the older study were homocystinuria and phenylketonuria, which were diagnosed non-specifically using basic urine chemical tests, whereas presently such cases are being genetically and biochemically proven, and may be a spectrum from MTHFR deficiency, glutaric acidemia type 1, phenylketonuria and arginase deficiency.

Diagnosis of GDD/ID

Evaluation of a case of GDD/ ID

Screening: Recent guidelines give developmental surveillance and screening recommendations for pediatricians to assess children with GDD/ID. It is recommended to do developmental surveillance which includes detailed history and examination at routine immunization visits by primary pediatrician till two years of age [5]. The commonly used developmental screening tools include Denver developmental screening test (DDST-II), Developmental Profile (DP), and Ages and stages questionnaire (ASQ).

Developmental assessment tests: Significant advances have taken place in tools for developmental assessment. A formal developmental assessment is indicated after initial screening, and is performed using age-appropriate standardized tests. Various developmental assessment tools are now available e.g., Weschler intelligence scale for children (WISC) and its Indian adaption Malin's intelligence scale for children (6-18 years), Binet Kamat Test of Intelligence (BKT) (>3 years), Development Assessment Scale for Indian Infants (DASII) (<30 months), and Vineland Social Maturity Scale (VSMS) (<15 year) [3,5]. The children with GDD/ID are classified into mild (IQ ≥ 50-69), moderate (IQ ≥35-49), severe (IQ≥20-34) and profound (IQ < 20) (ICD-10) [6].

Assessment of Comorbidities

Increased knowledge and awareness in care and management of GDD/ID has made it mandatory to assess for comorbidities today. The common associated comorbidities include seizures, ASD, vision impairment, and hearing impairment. A comprehensive evaluation for these associated comorbidities needs to be done in every child with ID/GDD. Neuroimaging is often indicated, based on history and physical examination e.g., abnormal head size, neurocutaneous stigmata, and seizures. Magnetic resonance imaging (MRI) with MRS (magnetic resonance spectroscopy) is preferred over computerized tomography (CT) scan [4,5]. None in the older study had any MRI or CT scan done, and the only radiological investigation performed in almost all cases was *X*-ray of the skull [1].

Diagnostic Tests

The field of diagnostics has evolved significantly in the last half century. The diagnostic tests mentioned in the 1972 study were limited to basic urine metabolic tests (e.g., ferric chloride), *X*-rays, serological tests for congenital infections, and karyotyping, which was only performed wherever indicated [1].

The etiology of ID/GDD is now understood to be quite heterogeneous with nearly equal contribution acquired and genetic causes, a thorough investigation is mandated. Genetic causes contribute up to 50% cases of GDD/ID. Sometimes an early postnatal injury can mask an underlying genetic cause [4,5]. The genetic etiology of ID is highly diverse, including cytogenetic abnormalities affecting the entire chromosomal to sub-microscopic copy number variants and single nucleotide variants in single genes. The genetic tests utilized are as follows:

Conventional genetic tests: The genetic testing can be approached in two ways. It may be phenotype driven or performed upfront as a blanket testing with use of molecular and cytogenetic tests. It is phenotype driven when history and examination is highly suggestive for a recognizable syndrome e.g., Down syndrome. In such a scenario, targeted testing can be offered such as conventional genetic tests like karyotyping for Down syndrome, fluorescent in situ hybridization (FISH)/ Multiplex ligation probe amplification (MLPA) for as targeted copy number variants e.g., 7q11.23 del, 22q11.2 del and PWS/Angelman syndrome. Karyotyping has a diagnostic yield of 3% excluding Down syndrome. Fragile

X syndrome accounts for 2-7% cases of ID based on patient selection and can be tested by methylation studies/ triplet-primed PCR [5].

Chromosomal microarray (CMA): In 2010, American college of Medical Genetics and Genomics (ACMG) recommended chromosomal microarray (CMA) as a first-tier test in children with unexplained ID/GDD and congenital anomalies [7]. The diagnostic yield of chromosomal microarray is between 14-20% in different studies and similar yield of 14.2% is reported from India [8].

Next generation sequencing (NGS): Over the past two decades, massive parallel sequencing based next generation sequencing (NGS) technology has entered as the newer diagnostic frontier for ID. The reported yield for large gene panels and exome/genome sequencing is between 8-20% [9,10] and 25 to >50% [11-13] in different studies. In 2021, ACMG expert panel recom-mended exome sequencing /genome sequencing (ES/GS) can be considered as a first or second tier test for pediatric patients with ID/GDD/congenital anomalies [13].

However, there remain many challenges with genetic testing in India, including cost of testing and un-availability of tests at many centers.

Testing for inherited metabolic causes: Testing for metabolic disorders is indicated based on neonatal screen, family history, consanguinity, neuroregression, episodic decompensation, physical examination (coarse facies, rash, peculiar odor), and neuroimaging. Biotinidase deficiency is a common treatable cause of ID and should always be ruled out. The other metabolic tests are ammonia, plasma amino acids, urine organic acids etc.

Treatable GDD/ID

The recognition of 'treatable' ID now forms major part of the management of GDD/ID, as there is more focus on treatment as compared to before. Treatable ID App is a digital tool launched in 2012, and recently updated in 2021, which provides information to clinicians on inherited metabolic causes of ID which are amenable to treatment [14]. The App provides information on 116 inherited metabolic disorders causing ID which have treatment available in form of nutritional therapy, pharmacological therapy, supplementation of vitamins/ trace elements, hematopoietic/stem cell transplant, enzyme replacement therapy and gene-based therapy [14].

In conclusion, after a long and hard journey over the last 50 years, we are now in a good position. There is far greater understanding about intellectual disability and global developmental delay. We have many more resources to dig deep and determine the etiology which then enables us to provide a more accurate and meaningful treatment. With vast expansion of the 'treatable ID', we can look forward to an era of newborn screening in our country, where at least the common and easily treatable disorders would be screened for, to give a better disease-free life to our future children. In the developed world, newborn screening has expanded in recent decades to >50 disorders and is already preventing deaths and disabilities in millions of children worldwide. With this note, we look forward to the next 50 years!

Acknowledgment: Dr Ashima Mehta helped in compiling the data from the child development clinic.
Contributors: SBM: writing the manuscript, collecting data from genetic clinic; SS: writing the manuscript, literature search; PS: collection of data from child development clinic, and assistance in writing. All authors read the manuscript and provided critical comments and suggestions to modify content.
Funding: None; *Competing interests*: None stated.

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Oral Faropenem Sodium – Implications for Antimicrobial Resistance and Treatment Effectiveness

DHANYA DHARMAPALAN,[1] SUJITH J CHANDY[2]

From [1]Pediatric Infectious Diseases, Apollo Hospitals, CBD Belapur, Navi Mumbai, Maharashtra; [2]Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, Tamil Nadu.
Correspondence to: Dr Dhanya Dharmapalan, Consultant in Pediatric Infectious Diseases, Apollo Hospitals, CBD Belapur, Navi Mumbai 400 614. drdhanyaroshan@gmail.com

Rising antimicrobial resistance (AMR) is causing therapeutic failures with antibiotics. Inappropriate use is a contributing factor. One such antibiotic on the radar is faropenem, a broad spectrum antibiotic approved in 2005 in India. Recently, faropenem sodium suspension was approved for use in children. There is a potential danger of overuse due to the convenience of oral administration. Other carbapenems such as meropenem are used parenterally. Overuse of faropenem may promote cross-resistance with other carbapenems making them ineffective.

Keywords: *AMR risk, Carbapenems, Rational use*.

The burden of antimicrobial resistance (AMR) is rising rapidly in the world and also among children and neonates [1]. Irrational antibiotic use is a major driving force towards rising resistance, and therefore, responsible use is paramount [2]. Respiratory infections are one group of infections where antibiotics are misused. Evidence-based National and International guidelines recommend use of amoxicillin as the first line antibiotic for community acquired respiratory infections due to its effectiveness against leading res-piratory pathogens such as *Streptococcus pneu-moniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* [3,4]. Severe cases of pneumonia need to be treated with injectable co-amoxiclav or ceftriaxone. Carbapenems, which have the broadest spectrum of activity among all the beta-lactam antibiotics, is usually reserved for use for multidrug resistant infections, especially caused by aerobic gram negative bacilli [3].

Faropenem is an oral beta-lactam antibiotic belonging to the same class as carbapenems. Faropenem is available in many countries including India and is increasingly being used. Unfortunately, there are also reports of faropenem resistance causing cross resistance to other carbapenems [5]. This raises serious concerns since the other carbapenems such as meropenem, imipenem and erta-penem are usually reserved as life-saving antibiotics, especially in situations where the patients are critically ill due to multi-drug resistance organisms. Widespread use of faropenem, which is oral and relatively cheaper, therefore may have dangerous implications towards rising AMR and treatment ineffectiveness. We will address some of these aspects with the aim to sensitize stakeholders regarding the need to curb the use of faropenem in the interest of the society.

THE MOLECULE AND ITS APPROVAL

Faropenem is structurally similar to the other carbapenems except for a sulfur atom at position one [6]. The Clinical and Laboratory Standards Institute (CLSI) classifies faropenem and carbapenems under the penem class of antibiotics. The World Health Organization classifies faropenem as a 'reserve' antibiotic and therefore not to be used routinely without laboratory evidence [7]. It is produced as an oral formulation of the prodrug faropenem medoxomil (also known as faropenem daloxate) and faropenem sodium. Similar to other beta lactam antibiotics, it exerts its bactericidal action by inhibiting the cell wall synthesis of bacteria. It has a broad spectrum of activity including non-penicillin-susceptible *S. pneumoniae* and β-lactamase *H. influenzae* and *M. catarrhalis*, Gram-negative bacteria, including extended spectrum beta-lactamase (ESBL)-producing Enterobacteriales and anerobic bacteria [8]. There are no clinical breakpoints defined by the CLSI or European Committee on Antimicrobial Susceptibility Testing (EUCAST) for routine antimicrobial susceptibility testing by laboratories [9]. The adverse effects reported are mainly mild in nature and include diarrhea, nausea and abdominal pain.

Faropenem was approved for use in Japan in 1997. However, the United States Food and Drug Administration in 2006 stated that the drug was "non-approvable" for the applied indications of acute bacterial sinusitis, community-acquired pneumonia, acute exacerbations of chronic bron-chitis, uncomplicated skin and skin structure infections and urinary tract infections [10]. Faropenem is also not in the public data base of the European Medicines Agency (EMA) containing all medicines authorized in Europe [11]. In 2010, the Central Drugs Standard Control Organisation (CDSCO) approved its use for the above conditions in India as tablet faropenem sodium in 2005, and recently in 2021, as its oral suspension [12].

IMPLICATIONS FOR AMR

India and China are leading consumers of faropenem [13]. The faropenem consumption as a proportion of total penems was estimated at 58.4% on average for India and 6.8% in China between 2005 and 2014 [13]. Between 2010 and 2014, faropenem consumption in India sky rocketed by 154% [14]. Both the above reports highlight the fact that the consumption of faropenem had exceeded the total consumption of other carbapenems in India.

The global faropenem sodium market size is projected to grow at a compound annual growth rate (CAGR) of 9.03% reaching USD 281.99 million by 2026 [15]. This rising trend could be due to the ease of use as an oral formulation, its relative low cost and aggressive marketing as an 'effective antibiotic.' In contrast, the other carbapenems such as meropenem, imipenem and ertapenem have to be used parenterally, often in intensive care situations, and are comparatively expensive. The increasing use of faropenem is of critical relevance due to the evidence that induced resistance by faropenem can lead to development of cross-resistance to carbapenems among *E. coli* isolates con-taining *CTX-M-15-type* ESBL enzymes [5]. Additio-nally, another factor which may contribute to resistance is that the faropenem sodium formulation available in India has poor oral absorption (20-30%) in comparison to its prodrug, faropenem medoxomil, which has much higher bio-availability (70-80%) [13]. Therefore there is an imminent risk of prolonged exposure of gut bacteria to this drug and increase in gut colonization of resistant gram negative bacteria amongst its consumers [16]. The wide usage of faropenem therefore can endanger the effectiveness of other carbapenems, which are used in life saving situations and when first and second line antibiotics are not effective due to rising AMR.

STRATEGIES FOR OPTIMAL USE

Antibiotic stewardship encourages compliance towards updated evidence based guidelines and the use of existing antibiotics over newer antibiotics unless there is a critical need. The Indian Council of Medical Research (ICMR) guidelines on treatment of infections do not mention the need for faropenem [3]. Faropenem is also not listed in the Essential medicines list of our country or the WHO list [17]. There is no pressing need for encouraging a broad spectrum new antibiotic for treatment of community acquired respiratory infections when other effective and narrower spectrum antibiotics are still available. The convenience of oral administration can facilitate easier widespread misuse of the antibiotic among children in the community, thereby fuelling AMR, and difficulty in treatment of critical infections with carbapenems unless strict stewardship measures are undertaken.

Urgent measures are therefore needed to limit the use of oral faropenem sodium among children and the wider community. Currently, faropenem is listed under Schedule H1 in the Drugs and Cosmetics Act, 1940 [18]. This means that faropenem is to be sold by registered retail pharmacies only with a prescription from a registered medical practitioner. Also, all sales of this drug and relevant details need to be maintained in a separate register by retail pharmacies. It would be interesting to ascertain whether this is being followed strictly in each state, and also whether compliance is being monitored on a regular basis. Over the counter use of faropenem will have a devastating impli-cation for rising AMR. It is also imperative that the Drug Controller General of India (DCGI) and ICMR have wider discussions with stakeholders on the risks and benefits of continuing with faropenem in the market. It is our hope that an urgent and balanced decision must be made taking into account the critical nature of rising AMR. Last, but not least, it is important that all stakeholders, including physicians, other healthcare professionals, policymakers, the media and the public, understand the implications of over-usage of faropenem. Imbibing a risk versus benefit approach, not just individually, but for the society, will hopefully change behavior and improve appropriate use.

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Defensive Medicine in the Context of the Indian Health System

ANKIT CHAUDHARY,[1] VIJAY KUMAR BARWAL[2]

From Departments of Community Medicine, [1]Dr Rajendra Prasad Government Medical College, Kangra; and [2]Indira Gandhi Medical College, Shimla; Himachal Pradesh.

Correspondence to, Dr Vijay Kumar Barwal, Assistant professor, Department of Community Medicine, Indira Gandhi Medical College, Shimla, Himachal Pradesh. barwalvk@gmail.com

Defensive medicine; although a recent concept, is slowly beginning to cement its place in the Indian health system. An interaction of multiple factors has paved way for this form of practice. Need for certainty of the diagnosis, lack of hierarchy in medical care, exponential growth of micro/super specializations and private/corporate health institutions, incentive-based practice, increasing incidences of violence against health personnel, rising trend of defamation suites against doctors, bad publicity by media, and interference by elected representatives have jeopardized the situation. This has led to decline in practice of clinical medicine, increased burden of investigations, especially in already compromised public facilities, and high out-of-pocket health expenditure. As much as ethical medical practice, standard patient management protocols, strict protection of interest of medical practitioners by law, responsible role of media and elected representatives are the need of the hour; we need to find ways to accept and incorporate defensive medicine into the modern medicine. Different stakeholders are required to come together and take substantial steps to understand the phenomenon and preserve the art and science of practicing medicine in its true form.

Keywords: *Malpractice*, *Medical Protection Act, Protocols, Violence against health personnel*.

In a period not long ago, physicians took pride in making a diagnosis based upon clinical knowledge supported by years of experience. The eyes, ears, nose and hands supplemented by the stethoscope were their diagnostic modalities. However, this art of palpating, percussing and auscultating is slowly vanishing; and the ever evolving science of modern medicine is becoming defensive day by day [1]. We explore factors about the evolution and phenomenon of practicing defensive medicine in the context of the Indian health system.

DEFENSIVE MEDICINE

Defined as "doctor's deviation from their usual behaviour or that is considered good practice, to reduce or prevent complaints or criticism by patients or their families"; the definition further encompasses the action of ordering investigations, procedures and visits, or avoidance of high-risk patients or procedures with the primary (but not sole) aim, of reducing malpractice liability [1,2].

REASONS FOR SHIFT TO DEFENSIVE MEDICINE

The foremost factor can be advancement in medical technology. Defensive medicine might actually be an evolutionary approach of minimizing clinical error and managing a patient through best diagnostic modalities available. Although, it might look more expensive and cumbersome to the masses, it may be enabling the physician to be absolutely sure while taking a decision for the patient's well-being [3].

India lacks a system of stratification of health care; meaning any patient can see a specialist or superspecialist bypassing a community physician or primary/secondary level doctor. The specialists then are extra cautious while dealing with such patients by means of ordering specific investigations. So, seeking specialized help for even minor illnesses may be an additional factor for the phenomenon [4]. A large number of corporate hospitals, private clinics and nursing homes have been providing quality services, but at a cost. The advanced and costly investigations tend to generate more revenue for the institution. Monetary gains can also be in the form of incentives or "cut money" to the referring physicians; though it cannot be generalized [5,6]. Here, the irony is that most of the times the patient and his relatives are satisfied that a specialist or super specialist is being called for further evaluation or treatment of even minor ailments. Many also think that more costly the investigation and medicines, the better is the physician [3].

The most recent, unfortunate and probably the most significant cause is the workplace violence which medical professionals are facing on a routine basis [7]. This practice has instilled fear in the minds of doctors; and therefore, they go for more expensive and invasive procedures, just to protect their skin in future [8]. So even if a physician knows that acute abdomen with which a patient has landed in emergency is mere gastritis just by history, examination and sound judgment, still he/she tends to write ultrasonography, just to avoid violence for missing any rare

cause. Due to this reason, some hospitals are denying admission to severely sick or injured patients, as it might induce violence in case the patient has an adverse outcome [9]. Moreover, in the age of internet, rather than giving history, patients give you diagnosis on the basis of superficial web search and self-prescribed, laboratory tests which they have already undergone [10]. Many a times, such patients request for specific tests, and also, sometimes drugs, like antibiotics. Physicians oblige them, for fear of losing the patient to a competing practice, or to avoid any argument with the patient and attendants [5,11].

Just like the Western world, Indian medical field is also witnessing a paradigm shift in terms of legal aspects of practising medicine. Health institutions and medical professionals are being sued for hefty compensation in the courts [12]. So practicing medicine, which was once an art and science, has become more of a professional obligation. The patients and attendants, who on arrival request a doctor for help, suddenly become violent and try to encash the adverse situation. The media has also played a role in the spread of this phenomenon. Without having a holistic view and supporting evidence, they flash big headlines on countless newspapers and television channels implying medical negligence [13]. Today, in the age of mobile technology, any person can shoot a video, play victim of medical negligence and defame a health institution or a professional in seconds. The media trial and comments that follow are enough to dampen the enthusiasm of a medical professional, and to drive him/her to play safe. Moreover, the undue and unwarranted interference by elected non-medical public representatives in health institutions has further worsened the situation. Lastly, medical professio-nals also have to take care of the ethics code, which have been framed for patient management and protecting the rights of sick and deprived against malpractice [14]. So, to avoid any controversy and conflict, modern day physicians rather than going with their judgment tend to go by the book.

CONSEQUENCES

The only real benefit of this phenomenon is the increased certainty of diagnosis. Hence there are decreased incidences of alleged medical negligence leading to lesser chances of health professionals and institutions being defamed as well as dragged to the court of the law. It also saves the physician from the violence driven mobs, occasionally seen after an adverse patient outcome [5,11]. Coming to the disadvantages, first is the increased out-of-pocket expenditure for the patients, insurers, and/or the exchequer [15]. Relying too much on external diagnostic and treatment aids, has led to the creation of micro-specializations and further handicapped medical science. To some extent, it has undermined the skills of budding physicians and even blunted the more experienced ones. The establishment of health insurance, as suggested, is likely to increase the practice of defensive medicine [16].

SOLUTIONS

The very first step is to acknowledge the existence of defensive medicine. The difference between need, desire and option of investigations must be highlighted. After consulting different scientific medical agencies, standard global guidelines for the need of investigations, use of technology, invasive procedures and use of drugs must be laid down and followed to the core. There should be regular medical audits of all health institutions [17]. The concept of community physician or family medicine must be revived and strengthened. Except emergencies, the primary health care facility should be the first point of contact of the patient and the chain of referral of should be maintained [18]. Tertiary care institutes with their expert professionals must be reserved for the advanced and complicated ailments. Unlike reality, the concept of quaternary prevention in health care, which protects the patient from over diagnosis and over medication is still alien in Indian system, and must be given due importance 19].

Perhaps the biggest cause of medicine going this defensive in India is violence against the health personnel [8]. The overall expenditure on health is low in India and it is one of the worst ranked countries in terms of health professional to population ratio [20]. The long-standing demand of Act for violence against medical professionals should be met at the earliest. Further Courts of Law are also requested to take obscuring factors like lack of facilities and health staff, low wages of professionals in the public health institutions while labelling medical conduct as negligence and passing judgment [12,21]. Media must also act responsibly in a non-judgemental way, and acknowledge the poor plight of healthcare workers [21]. All states of India have not formulated the Medical Protection Act. During the Covid-19 pandemic, an ordinance for amendment of epidemic act 1897 was brought to make violence against medical professionals a cognizable and non-bailable offence with monetary implications and imprisonment [22]. But it is just a temporary arrangement for the COVID-19 situation.

Political will and commitment are also the need of the hour. Autonomy of the institutes with professional independence, with necessary checks and balances, is need of the hour for proper functioning of academic institutions, and of those working in them [23]. Public representatives have every right to check the working of institutions and report wrong doings, but too much interference will make health professionals more defensive

leading to increased denial to admit sick patients, referrals and out of pocket expenditure. As the National Health Policy, 2017 recommends, India should spend 2.5% of its GDP on health; human resource must be recruited as per standards and taking enormous population of the nation into account [24]. Medical fraternity also needs to set a good example by doing ethical practice themselves [25].

Lastly, we may have to accept the fact that defensive medicine has evolved, thrived; will prosper in future and become a standard or norm. We may need to find ways to subtly incorporate this aspect into the modern medicine one way or another. The National Medical Commission has taken a step in right direction by incorporating the Attitude, Ethics and Communication (AETCOM) Competencies for the Indian Medical Graduate curriculum [26]. While teaching the AETCOM module, we can devote some time to defensive medicine also, thereby sensitizing the future doctors about this practice.

CONCLUSIONS

Its high time to acknowledge that defensive medicine has become a part and parcel of modern medicine and it may become the future of the medical care. Medical science is ever growing and advancing due to its practice of experimental, bold and evidence-based decision making. Although growth of health sciences should not be hampered and limited to a mere skin saving act; yet the interests of medical professionals cannot be ignored either. While some defensiveness is needed in today's context, too much of it will erode the ethos of medical practice. Benefit of doubt should always be given to the doctor when he takes a risk to save the life of a patient in emergency. It is a joint responsibility of Health professionals, Common man, Government, Judiciary and Administration to strike a balance between the different approaches of modern medicine.

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Concurrent Scrub Typhus and Dengue Fever Mimicking Acute Appendicitis

Both scrub typhus and dengue are known to independently cause acute abdominal pain, but it is seldom severe enough to mimic localized peritonitis necessitating surgery [1,4]. We report a child with both these conditions, who underwent a surgery due to suspected acute appendicitis.

A 9-year-old girl presented with abdominal pain, anorexia, high-grade intermittent fever and non-bilious vomiting of two days. History of recent travels or contact with coronavirus disease (COVID-19) was absent. She appeared sick, and her temperature was 38ºC, pulse rate was 110/min and respiratory rate was 30/min. Local tenderness with guarding (McBurney sign) was elicited in the right iliac fossa. She did not have peripheral lymphadenopathy or organomegaly.

Her hemoglobin was 9.7 g/dL, leukocyte count was 15.8×10^9/L (with 81% neutrophils), and urine had traces of albumin and 12-15 red blood cells per high power field. Serum levels of electrolytes, urea, creatinine, bilirubin and liver enzymes were within normal limits. Ultrasonography revealed probe tenderness and a non-compressible aperistaltic tubular structure in the right iliac fossa, suggestive of acute appendicitis. Calculated 'pediatric appendicitis score' was 9 out of 10. She was scheduled for emergency appendicectomy.

During surgical preparation, a small black eschar of 1 x 0.5 cm was noted in the right hip and it raised the suspicion of scrub typhus. On surgical exploration, the appendix and peritoneal cavity were found to be normal. There were no subserosal petechiae. Non-specific mesenteric lymphadenopathy was noted. The operation was concluded without performing appendicectomy. After 8 hours of surgery, she was started on oral doxycycline (4 mg/kg/day).

Enzyme linked immunosorbant assay (ELISA) done on the first post-operative day was positive for IgM antibodies against scrub typhus. Dengue IgM antibody titers and NS1 antigen titers were positive, while dengue IgG titer was negative. Reverse transcriptase polymerase chain reaction (RT-PCR) of nasal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative, but COVID-19 antibody was equivocally positive. Peripheral smear was negative for malarial parasites. Urine and blood cultures were sterile.

Thirty six hours after surgery, she developed respiratory distress, hypotension (BP 80/50 mmHg) and drop in oxygen saturation (SpO_2 85%). Blood gas analysis revealed respiratory alkalosis. Platelet count, which was 155×10^9/L on admission, dropped to 58×10^9/L. Activated partial thromboplastin time was 28 sec and prothrombin time was 19 sec (International normalized ratio 1.4). Serum D-dimer was 2585 ng/mL. ECG recorded sinus tachycardia. Echocardiography revealed dilatation of all four cardiac chambers with left ventricular ejection fraction of 44%. Chest radiograph showed diffuse haziness with mild pleural effusion. Systemic inflammatory response to infectious fever was diagnosed. She was treated with ionotropes (noradrenalin), frusemide and oxygen by nasal prongs. Broad spectrum antibiotics (piperazillin and tazobactum) were also empirically started, and continued until the negative blood culture reports. Defervescence occurred 42 hours after surgery, and doxycycline was continued for 7 days. On the fourth postoperative day, her hemodynamic status and coagulation profile became normal. On the eighth day, she was discharged and is presently healthy at one year of follow-up.

Abdominal pain without physical signs of peritonitis is a common presenting symptom in children with scrub typhus (32%) and dengue fever (77%) [1,4]. However, pain severe enough to mimic acute surgical abdomen is rare in both. A Sri Lankan study [4] reported that only 17 out of 3309 patients (0.5%) suffering from dengue fever presented with features of peritonitis. A review of English literature could identify only six patients (all adults) with scrub typhus presenting as acute abdomen [5]. As compared to adults, abdominal pain is generally infrequent in children with scrub typhus [1].

The association of acute abdominal pain and infectious fevers is well known. This combination can be classified into three distinct etiopathological types namely coincidental (type 1), causal (type 2) and mimicry (type 3). During febrile episodes, several patients experience acute exacerbation of pre-existing calculus cholecystitis (type 1b) or chronic pancreatitis (type 1c). Coincidental true appendicitis (type 1a) during dengue fever has also been reported [6]. Infectious fevers are known to cause widespread serositis and systemic inflammation. By this mechanism, they may precipitate peri-appendicitis (type 2a), peri-cholecystitis (type 2b) and acute pancreatitis (type 2c). In contrast to transmural appendicitis, only the seromuscular layer is inflamed in peri-appendicitis [4,7]. Spontaneous rupture of enlarged spleen and bowel perforation due to vasculitis may also cause general peritonitis (type 2d) in infectious fevers [8,9].

The most perplexing clinical presentation is that of the mimickers (type 3). Exact mechanism is not known as to how acute signs and symptoms are caused in the absence of actual inflammation. Several hypotheses have been proposed to explain this phenomenon [4,7,10]. Cytokines released during febrile episodes may cause mucosal edema (interstitial plasma leakage) or smooth muscle spasm of tubular structures such as the cystic duct, pancreatic duct or appendix. The resultant luminal obstruction may lead to the sequence of pent-up secretion, over-distension, superadded bacterial infection, serosal stretching and acute pain [7]. Sonographic visualization of the distended appendix in our patient may support this hypothesis. Other proposed mechanisms include subserosal bleeding (petechiae) due to thrombocytopenia or leukocytoclastic vasculitis, ischemic

reperfusion injury following recovery from circulatory shock, over-distended gall bladder (cholestasis) due to 'nil per oral' status, drug- or disease- induced mucosal ulceration of the gut, mesenteric lymphadenitis, associated hepatitis and referred pain from pleurisy [7,10]. Regional lymphadenopathy at the bite site is a characteristic feature of scrub typhus seen in 10-60% of patients [1]. As per the lymphatic anatomy, eschar of the right hip will cause enlargement of ipsilateral iliac nodes. In our patient, this could have contributed to localized tenderness in the right iliac fossa.

Omitting a laparotomy in the presence of actual inflammation would constitute medical negligence; while on the other hand, an unnecessary operation done in the presence of febrile illness is potentially hazardous and avoidable. To resolve this dilemma, several scoring systems have been proposed.

We consider SARS-CoV-2 antibodies noted in our patient to be due to the well documented phenomenon of serological cross-reactivity with dengue [11]. Despite performing laparotomy, we avoided excision of non-inflamed appendix as it may increase the risk of wound infection and add to the morbidity without any additional benefits. This case highlights the need to consider co-infections and rare complications in children with uncommon presentations.

JAN AMRITHA,[1] VENKATACHALAM RAVEENTHIRAN[2]*
From Departments of [1]Pediatrics and [2]Pediatric Surgery, Government Cuddalore Medical College, Chidambaram, Tamil Nadu.
**vrthiran@gmail.com*

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Recurrent Generalized Scleredema in an Adolescent Girl With Uncontrolled Type 1 Diabetes Mellitus

Scleredema is a non-pitting induration of the skin and connective tissue, usually secondary to intrinsic disease or infection, rare in children, and generally reversible on treating the primary disease [1]. The main associations of scleredema in children are infections [2-4]. Sceleredema as a manifestation of uncontrolled diabetes in children and adolescents is rarely reported in India [5]. We report recurrent generalized scleredema in an adolescent girl having poorly controlled type 1 diabetes mellitus (T1DM).

A 13-year-old girl presented with generalized swelling over the whole body for six months. The swelling started from the arm followed by the abdomen and gradually involved the face, chest and legs. She also complained of pain in the abdomen, arms and legs for one month. There was stiffness of facial muscles and difficulty in opening the mouth and difficulty swallowing food for 15 days. There was no history of cold, cough, fever with rash, morning stiffness in joints, no history of Raynaud phenomenon, or eating raw or undercooked pork. She was diagnosed as T1DM at 9 years of age but was poorly compliant to the prescribed insulin injections. Her documents showed persistent hyperglycemia and frequent hospitalization for diabetic ketoacidosis. She weighed 35 kg, and on examination was alert, afebrile, with heart rate of 90/min, respiratory rate 20/min, blood pressure 108/68mm Hg, and diffuse swelling was seen over the face, thorax, abdomen, bilateral upper and lower limbs. Swelling was diffuse, tense, waxy, hard, non-tender, indurated, non-pitting and could not be pinched. Her face was blank, mask-like, with abolition of skin linings and folds. The rest of the general and systemic examinations were normal.

She was hospitalized and started on insulin as a split-mix regime along with symptomatic treatment. Investigations revealed total leucocyte counts 12.3×10^9/L, hemoglobin12.3 g/dL, alanine aminotransferase 64 U/L, aspartate aminotransferase 28 U/L, total protein 6.6 mg/dL, serum albumin 4.2 g/dL, total cholesterol 192 mg/dL, triglycerides 176 mg/dL, TSH 1.36 µIU/mL, blood urea 26 mg/dL, serum creatinine 0.64 mg/dL, ionized calcium 7.9 mg/dL, serum potassium 4.25 meq/L, sodium 136.2 meq/L . Her random blood glucose was 554 mg/dL, urine glucose

3+and glycated hemoglobin was 13%. Arterial blood gas analysis revealed compensated metabolic acidosis. The HIV serology was negative, rheumatoid factor was 5 IU/mL (normal), anti-streptolysin titer 40 IU/mL and anti-ds DNA titer was negative. Chest radiograph and ultrasonography of abdomen were normal. Skin biopsy from the back of chest was suggestive of sceleredema. The biopsy was stained with alcin blue which revealed normal epidermis, mucin filled thickened collagen bundles with deposition of acid hyaluronidase. Fundoscopy revealed diabetic retinopathy in her both eyes and surgery was recommended.

After one week of achieving normoglycemia, the scleredema started reducing from the abdomen, and upper and lower limbs. She was discharged with scleredema persisting on her face. On follow-up, after two months, her weight reduced to 33 kg and sceleredema resolved completely as nasolabial folds and wrinkles on the forehead reappeared.

After 8 months, she again presented with generalized scleredema all over the body, more on the face as compared to the abdomen and limbs, with poor acceptance of meals. The mother associated worsening of sclererderma with glargine insulin and improvement if glargine insulin was replaced with regular or mixtard insulin. She was admitted and insulin was started as a split-mix regimen. Her blood glucose was high and glycated hemoglobin was 16.8%, liver function tests, renal function tests, erythrocyte sedimentation rate and C-reactive protein were normal. The repeat ASO titer and Anti-ds DNA titer were negative. During recurrence, skin biopsy was not performed due to unavailability of consent from parents. After a few days, blood glucose was controlled, oral intake improved and she was discharged on split-mix regime on mixtard insulin, with advice regarding strict diet and blood glucose control. After two months, on follow up, scleredema was diminished from the abdomen and limbs but persisted on the face. She continues to remain under follow-up subsequently.

Scleredema necessitates morphological classification as a generalized or localized type. Generalized sceleredema can be described as diffuse affection of the entire body, like the face, thorax, abdomen, and upper and lower limbs with less skin hardening. It is common in children irrespective of precipitating etiology [2-5]. Localized scleredema can be explained as a patchy and randomly distributed lesions over either upper or lower half of body or involving non-contiguous multiple sites. Skin thickening and hardness is more in localized type, refractory to treatment, usually seen in obese adults having prolonged poorly controlled type 1 or type 2 diabetes mellitus known as scleredema diabeticorum.

The skin shows hyperplasia of fibroblast and excess collagen synthesis in sclererderma, that can get triggered due to hyperinsulinemia or prolonged hyperglycemia with resistance to insulin [6]. Skin tightening, swelling and hardness found in scleredema mimics scleroderma, scleromyxedema, and trichinella. These were distinguished in this child by confirmation of scleredema on histology, normal TSH, non-ingestion of pork and absence of fibrotic or sclerotic changes in skin. Normal ASO titre and absence of pyoderma, tonsillopharyngitis, common cold, cough, fever with rash demarcated it from infections like streptococcal, influenza, scarlet fever, measles, rubella and mumps.

Non-resolution of scleredema within a year necessitates work up for secondary causes like multiple myeloma, monoclonal gammopathy, paraproteinemias, Sjogren syndrome and hyper-parathyroidism. Normal cardiac, renal and nervous system examination along with normal laboratory reports in the index child excluded these causes. She remained well over the next one year and didn't have any new symptom.

In diabetic obese males older than 40 years of age, scleredema is10 times more prevalent and starts in adulthood [6], which is contrary to the index case who was a 13-year-old slim girl. Chronic and prolonged diabetics on insulin injections having retinopathy are prone to develop scleredema as observed in index child and earlier also [5]. Recurrent episodes are unusual and under-reported, but our patient also experienced a second episode of generalized scleredema associated with glargine insulin. Type of insulin may affect the development of scleredema as is reported earlier [5], where NPH insulin flared scleredema while Lente insulin reduced.

Treatment of scleredema depends on eliminating or controlling the triggering factor [2,5]. A high index of suspicion is needed for diagnosing scleredema in children with chronic diabetes with microvascular complications. The strict control of blood glucose is the mainstay of treatment. It is a rare entity and its reappearance is a rarest possibility.

PRAMILA VERMA,[1*] GARIMA AGRAWAL VARSHNEY,[1] NANDINI DIXIT,[1] SANJAY AGRAWAL[2]

From Departments of [1]Pediatrics and [2]ENT, Nandkumar Singh Chouhan Government Medical College, Khandwa, Madhya Pradesh.

**drpramilav@yahoo.com*

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Pulmonary Renal Syndrome: Perilous Presentation in Pediatrics

Pulmonary renal syndrome (PRS) is life threatening condition manifesting as rapidly progressive glomerulonephritis (RPGN) with diffuse alveolar hemorrhage (DAH), which needs to be timely recognized and aggressively managed. We report PRS in a child with steroid dependent nephrotic syndrome on levamisole therapy.

A five-year-old girl (disease onset at three and half year), was diagnosed with steroid dependence and put on treatment with levamisole (2 mg/kg alternate day) along with prednisolone. After one-and-half years on levamisole, she presented to us with moderate fever for 20 days and gross hematuria for two days. There was no history of trauma, burning micturition, exposure to coronavirus disease (COVID-19) or environmental toxins. Her blood pressure was 116/62 mm Hg (Stage I hypertension). She had severe pallor, but no edema, lymphadenopathy, icterus nor clubbing. She did not have any cutaneous lesions. Systemic examination was normal.

Investigations showed hemoglobin of 4.1 g/dL, total leukocytes $26X10^9$/L, platelets $332X10^9$/L, 355.5 mg/d proteinuria, serum creatinine 0.67 mg/dL (eGFR 97.1 mL/min/1.73m^2) with normal coagulation profile, serum electrolytes, and liver function tests. Urine examination showed 20-25 red blood cells (RBCs)/ high power field with >20% dysmorphic RBCs but no pus cells. Urine culture was sterile. C3 level was normal (136mg/dL). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverese transcriptase-polymerase chain reaction (RT-PCR) was negative; however, SARS-CoV-2 IgG antibody was positive (4.9 AU/mL).

Levamisole was stopped due to neutropenia. Packed RBCs were transfused. Fever resolved with antibiotics after seven days. After seven days of admission, she had hemoptysis for two days. Computed tomography (CT) chest showed patchy areas of consolidation with adjacent ground glass opacities (suggesting DAH) with no cavitation or nodules in whole respiratory tract. Anti-glomerular basement membrane (GBM) antibody and p-ANCA were negative. c-ANCA (1:20) and ANA (53.84 Units) were positive. ELISA for myeloperoxidase (MPO), proteinase 3 (PR3) and human neutrophil elastase (HNE) were not available at our center. Renal biopsy showed eight glomeruli with focal necrotizing glomerulonephritis. Two out of eight glomeruli (25%) had crescents (one cellular, one fibro-cellular). Immunofluorescence showed <2+ glomerular immunostaining for immunoglobins (pauci-immune) and smudgy IgM and C3 in areas of fibrinoid necrosis. Provisional diagnosis of ANCA associated vasculitis (AAV) was made.

Injectable methylprednisolone 500 mg/d (approx. 25 mg/kg/d) for three days was followed by prednisolone (2 mg/kg/day in two divided doses for 15 days) that was tapered to 1 mg/kg/day on alternate days for four weeks. Injectable cyclophosphamide (0.75 g/m^2) was started on third day of methylprednisolone and continued monthly for six doses. Hemoptysis did not recur and hematuria resolved in four days. Repeat CT thorax after 15 days showed resolution of opacities. Proteinuria resolved after five weeks. c-ANCA became negative after six months.

AAV is characterized by necrotizing inflammation of small to medium vessels with autoantibodies against cytoplasmic region of neutrophil (ANCA). Chapel Hill nomenclature classifies systemic vasculitis based on size of the affected vessel and associated clinical, radiological and pathological manifestations without accounting for pathogenic mechanisms [1]. AAV occurs either as primary autoimmune conditions or secondary to malignancy, sepsis, drug reactions, irradiation or connective tissue diseases. Interaction of genetic and extrinsic factors have also been incriminated. There are some reports of PRS following Covid infection [2].

Levamisole induced vasculitis (LIV) is diagnosis of exclusion. Features suggestive of LIV include *i*) prolonged history of levamisole therapy; *ii*) fever, night sweats, weight loss, arthralgia; *iii*) retiform purpura; *iv*) renal manifestations of hematuria, proteinuria, raised creatinine, pauci-immune glomerulonephritis; *v*) Pulmonary manifestations of bronchitis, bronchiolitis, interstitial pneumonia, nodules, hemorrhage *vi*) leucopenia, neutropenia; and *vii*) low complements, positive ANCA, ANA, ds-DNA, lupus anticoagulant, APLA [3]. Previous studies have shown resolution of constitutional symptoms, arthralgia, neutropenia on stopping levamisole. AKI shows transient improvement with immunosuppression but requires dialysis in long run. Pulmonary lesions and mild kidney involvement respond to immunosuppression [4]. Other adverse effects of levamisole therapy include general malaise, fatigue and hypersensitivity [5]. We could not find any report of PRS associated with levamisole therapy, especially in children.

Neutrophil extracellular traps (NETs) comprise of a scaffold of chromatin DNA intermingled with histones and cytoplasmic granules (MPO, PR3, HNE), released from activated neutrophils in response to various stimuli, including intact pathogens, pathogen components, ROS, antibodies and antibody-antigen complexes. NETs provide source of intact antigen capable of inducing adaptive immunity, linking innate and adaptive immune systems by producing ANCAs [6]. NETs induce direct endothelial damage, activate alternative complement and coagulation pathway and provide structural support to thrombi [3]. Levamisole induces disorganized NETs resistant to homeostatic mechanisms and induces loss of tolerance to multiple antigens within neutrophil granules, resulting in clinical disease [3,4,6]. As HNE shares epitopes with PR3, antibodies to HNE result in falsely positive anti-PR3 immunoassay resulting in high titers of p-ANCA in LIV [4].

AAV (60%), Goodpasture's syndrome (20%) and other primary systemic vasculitis associated with cryoglobulinemia, SLE, systemic sclerosis, antiphospholipid syndrome, environmental factors and drugs are all known to cause PRS [7]. Patients who present with elevated baseline glomerular filtration rate (eGFR) >30 mL/min/m2 and low degree of chronicity/ interstitial fibrosis fare better as compared with patients who present with low eGFR (<30 mL/min/m2) and moderate to severe chronicity/fibrosis [6].

In conclusion, childhood-onset PRS is a fulminant disease but improvement occurs over time in renal outcome. Pediatricians should be aware of early diagnosis and treatment of this disease.

ANUBHA SHRIVASTAVA,[1*] AMBUJ TRIPATHI,[1] ARPIT GUPTA,[1] VARSHA KUMAR,[2] ARJUMAND JAHAN[3]
Departments of [1]Pediatrics, [2]Pathology and [3]Radiology, MLN Medical College, Prayagraj, Uttar Pradesh.
**anubhashrivastava@rediffmail.com*

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OBITUARY

Dr Dilip Mahalanabis

(12 November, 1934 – 16 October, 2022)

While oral rehydration solution (ORS) as a simple, effective remedy for dehydration is known around the world, Dr Dilip Mahalanabis, the man who pioneered the treatment is less famous, and passed away at a Kolkata hospital on October 16, 2022. The sad demise is a great loss to Indian pediatric fraternity, as well as to the children all over the developing world. His death marks the end of an era.

Born on November 12, 1934 in West Bengal, Dr Mahalanabis studied in Kolkata and London, and joined the Johns Hopkins University International Centre for Medical Research and Training in Kolkata in the 1960s, where he carried out research in oral rehydration therapy. Oral rehydration is still the mainstay of treatment for diarrheal diseases in children. Before the use of ORT, the only treatment was intravenous fluid infusion, which was neither cost-effective nor easy. Due to Dr Mahalanabis's persistent efforts, ORT was made a household name.

From 1975 to 1979, Dr Mahalanabis worked in cholera control for the World Health Organization (WHO) in Afghanistan, Egypt and Yemen. During the 1980s, he worked as a WHO consultant on research on the management of bacterial diseases. In 1983, he was made a member of the WHO's Diarrhoeal Diseases Control Programme. He remained in that role for over five years. He was also associated with Kolkata's National Institute of Cholera and Enteric Diseases (NICED) and the Institute of Child Health.

In 2002, Dr Dilip Mahalanabis along with Dr Nathaniel F Pierce was awarded the Pollin Prize by Columbia University (considered the equivalent of Nobel in Pediatrics). Later, he also received the Prince Mahidol Award (2006).

His was a life full of compassion, dedication and true acts of generosity. Our pediatric fraternity mourns the loss of a great researcher and human being in every sense of the word. His exemplary dedication to child health and his zest to innovate to save lives in the battlefield makes him a true hero for mankind.

Does COVID-19 Not Have Any Impact on Children With Tuberculosis?

We read with interest the recent paper by Mane, et al. [1] on coronaviruses disease 2019 (COVID-19) and tuberculosis. We have a few concerns, clarifications on which might be helpful for the readers.

COVID-19 and tuberculosis may have a similar presentation; however, they differ in many respect. Simultaneous testing of TB and COVID-19, though promising, is not mandatory. The World Health Organization (WHO) has recommended a country-specific testing strategy for tuberculosis or COVID-19 based on history, clinical features, and local TB burden [2].

There is a significant disparity in the clinical features between the two groups. In the TB group, 93.5% (101/108) of children were asymptomatic, while only 10.6% (13/122) were asymptomatic in the non-TB group. This may be due to the inclusion of an antibody test for diagnosing COVID-19. In the TB group, the majority (94%, 102/108) were diagnosed with positive COVID-19 antibody tests, while it was positive in only 9.1% (11/122) in the non-TB group. Moreover, including new and old patients could be another reason for more asymptomatic cases in the TB group, as children might have visited the hospital for routine follow-up and may not necessarily have acute symptoms at presentation. Furthermore, it would be interesting to know COVID-19 outcomes in new versus old tuberculosis patients, as some children may have completed antitubercular therapy and might be free from diseases. Moreover, the outcome of tuberculosis may be different in pulmonary versus extra-pulmonary TB. Thus, more details of tuberculosis patients are likely to be helpful.

It would be informative to know details about children in the non-TB group, their primary diagnosis, underlying risk factors, and reason for hospital visits, as most children were symptomatic in this group.

We feel that due to these disparities, it is difficult to compare the COVID-19 outcome in the two groups.

PRAWIN KUMAR,* JAGDISH P GOYAL
Department of Pediatrics,
All India Institute of Medical Sciences,
Jodhpur, Rajasthan.
**drprawin484@gmail.com*

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AUTHORS' REPLY

We thank the readers for their interest. Mandatory bidirectional screening for tuberculosis and COVID-19 was very much in existence in India during the collection of data for this research (*https://tbcindia.gov.in/WriteReadData/l892s/60159559755DODDG_NTEP%20%20Response_Full.pdf*;h*ttps://www.mohfw.gov.in/pdf/1TBCOVIDscreeningguidancenote.pdf*; *https://tbcindia. gov.in/showfile.php?lid=3598*).

We would like to mention here that we have not included children with tuberculosis who had completed their antitubercular therapy and/or were free from tuberculosis disease.

The baseline characteristics like age, sex, and RTPCR–positive for groups were not similar for TB group and Non-TB group. A majority of cases of tuberculosis in children in India are picked up in the adolescent and pre-adolescent age group. Also, in the early pandemic, data was very limited regarding this topic, so we tried our best to perform the study and match the control group, but we could not do so. We acknowledge this limitation.

We had taken severe acute coronavirus 2 (SARS-CoV-2) antibody-positive children in our study, which may be indicative of recent or past infection. We included these children as one of our aims was to see if the asymptomatic nature of COVID-19 infection in children was similar in either of the groups i.e., TB or non-TB. In all the SARS-CoV-2 antibody-positive children, we had inquired about their symptom history in the past six months. Due to the word limit restriction, we could not add this to the methods in our manuscript.

The difference in the proportion of asymptomatic patients in both groups might be attributable to the difference in the epidemiological settings, susceptibility of the population, and differences in the immunological responses to infection in India and other Western countries. We do not have many papers studying these two infections in children from India. Hence, the results between these different epidemiological settings may not be comparable. The scope of the information asked in children in the non-TB group was beyond the scope of this manuscript, and would be published in another detailed paper.

SUSHANT MANE, MANAS PUSTAKE*
Centre of Excellence for Pediatric TB,
Grant Government Medical College and
Sir JJ Group of Hospitals, Byculla,
Mumbai, Maharashtra.
**pustakemanas@gmail.com*

COVID-19 and Tuberculosis in Children

We read the recent article on coronavirus diseases 19 (COVID-19) [1] with special interest. Tuberculosis in children in the era of COVID-19 pandemic needs attention due to the huge burden of this disease in India. We would like to draw attention to a few aspects of this article:

i) Baseline characteristics like age, sex and reverse transcriptive-polymerase chain reaction (RT-PCR) positivity status in both COVID-19 groups (with and without tuberculosis) are not similar. It might have an impact on the study results.

ii) Authors have included severe acute coronavirus 2 (SARS-CoV-2) nucleocapsid antibody positive children in this study. Antibody detection in serum might be a feature of recent or past infection, which could last 3-12 months or longer [2]. Therefore, clinical features and outcome assay may not be accurate at that point in time.

iii) Reports from previous studies indicate that the severity of COVID-19 in children could be bimodal with an increased rate of hospitalization in those younger than 1 year and older than 10 years of age. Approximately 21% of children with COVID-19 are asymptomatic and 58% of patients have only one symptom [3]. However, 93.5% of patients were found to be asymptomatic in this study in the tuberculosis group as compared to 36.1% observed in the non-TB group, which is discordant. This could be attributed to a larger group of patients diagnosed with COVID-19 based on antibody status. The authors did not mention the rate of hospitalization in both groups, which could have added another aspect of the problem.

iv) Symptoms like fever, cough, and respiratory distress are similar in both COVID-19 and untreated tuberculosis, and are really difficult to distinguish in the early course of illness. Whether these patients were diagnosed during the onset of tuberculosis or the maintenance phase of therapy is important to mention in this context.

SAROJ KUMAR TRIPATHY, SARTHAK DAS*
Department of Pediatrics,
All India Institute of Medical Sciences,
Deoghar, Jharkhand.
**drsarthakdas2222@gmail.com*

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AUTHORS' REPLY

We thank the authors for their interest in our work [1]. Most of the concerns have been addressed in the reply to a previous correspondence [2].

The nature of symptoms in pulmonary tuberculosis is more chronic i.e., fever, cough, weight loss/no weight gain is present for a period of two weeks or more, for it to be considered as a presumptive case of pulmonary TB.

Symptoms of COVID-19 are more acute in onset, and non-severe infections do not last for more than two weeks. While enrolling the cases of tuberculosis who were recently diagnosed, this difference in the natural history of both infections was duly considered by us, and any doubtful cases or those with overlapping symptoms were excluded. The rest of the enrolled patients with tuberculosis were in the maintenance phase of the antituberculous therapy and were asymptotic for the symptoms of the TB. Due to word limits, we could not describe this in the methods in detail [1].

SUSHANT MANE, MANAS PUSTAKE*
Centre of Excellence for Pediatric TB,
Grant Government Medical College and
Sir JJ Group of Hospitals,
Byculla,
Mumbai,
Maharashtra.
**pustakemanas@gmail.com*

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Asthma Prediction Tool for Pre-school Children

At present modified asthma predictive score (mAPI) can be used in children aged less than three-years presenting with ≥4 wheezing episodes per year, to predict the likelihood of development of asthma. Although, it has some limitations, such as need of blood eosinophil levels and allergy skin prick tests which are difficult to perform in young children. Therefore, a team of researchers from University of Toronto and McMaster University developed a symptom-based screening tool to identify the children at risk of persistent asthma at 5 years of age, known as CHILDhood Asthma Risk Tool (CHART). On the basis of history of number of wheezing episodes, use of asthma medications, and visit to emergency department or hospitalizations for wheeze before three of age, CHART categorizes children into "high risk", "moderate risk" or "low risk", groups and predicts the risk of future asthma.

The predictive performance was tested among the participants of CHILD Study cohort (*N*=2511), CHART assessment surpassed the physician assessment and mAPI in predicting persistent wheeze and asthma diagnosis in these children at 5 years. For external validation, CHART was applied to a general population cohort (Raine Study [Australia], *N*=2185) and a high-risk cohort (CAPPS [Canada], *N*=349). Similar prediction for persistent wheeze was obtained in the Raine Study in children at 5 years of age and CAPPS at 7 years of age.

This simple tool could be incorporated for routine screening in primary care to identify children at high risk of asthma to take steps for timely control of symptoms and introduction of preventive therapies. (*JAMA Network Open, 06 October 2022*)

Impact of Air Pollution on Cardiac Health of Adolescents

Studies have documented the negative effects of air pollution on the cardiovascular health in the adult population. A team from the Pennsylvania State University College of Medicine analyzed the data collected from participants (322 adolescents) of the Penn State Child Cohort (PSCC) during the follow-up, to evaluate the impact of breathing fine particulate matter on heart rhythms of adolescents.

For data collection, nephelometer were used for obtaining the 24 hour PM2.5 concentrations for each participant, simultaneously 24 hour ECG data was obtained using a Holter monitor to identify cardiac arrhythmias, including premature atrial contractions and premature ventricular contractions (PVCs). Study findings revealed that PM2.5 exposure was associated with an acute increase in number of PVCs, while no association was found with premature atrial contractions. An increase of 10 $\mu g/m^3$ in the PM2.5 was associated with the 5% (95% CI, 1%-10%) increase in PVC counts within 2 hours after exposure in this population based sample of adolescents. Thus, by improving the quality of air the risk of SCD can be reduced in adolescents. (*Journal of the American Heart Association, 14 September, 2022*)

Maternal Consumption of Ultra-processed Food and Overweight/Obesity in Offspring

Childhood obesity is rising at an alarming rate all over the world. Sedentary lifestyle along with the high consumption of the ultra-processed food is an important cause. Development of obesity can be attributed to the combined influence of genetic susceptibility and environmental factors. Studies have shown an association between maternal intake of healthy diet during pregnancy and lowered risk of childhood obesity in the offspring. In a population based prospective cohort study, published from the Harvard Medical School, USA,association between maternal intake of ultra-processed food during pregnancy and child rearing period, and risk of overweight or obesity in the offspring during childhood and adolescence was assessed. Among the 19,958 mother-child pairs with a median (IQR) follow-up of 4 (2-5) years, 2471 (12.4%) offspring developed overweight or obesity. Authors reported that after adjusting for established risk factors in mother and offspring, maternal consumption of ultra-processed foods during the child rearing period was associated with overweight or obesity in offspring. No significant association was found between peri-pregnancy intake of ultra-processed food and risk of overweight and obesity in offspring. These findings highlight the need to modify the dietary recommendations for the women in reproductive age group, to improve the offspring health. (*BMJ, 05 October, 2022*)

Bionic Pancreas in Type 1 Diabetes

The current automated insulin delivery systems need continuous input of the amount of mealtime carbohydrates consumed and adjustment of settings to deliver the right amount of insulin. Solution for this problem has been found by a team from Boston University in the form of "Bionic Pancreas"–an automated insulin delivery system which uses next-generation technology to deliver insulin with minimal user input. Recently, the effectiveness of Bionic Pancreas was assessed in a multicentric, randomized control trial involving person with type 1 diabetes aged between 6 to 79 years. Participants were assigned in a 2:1 ratio into group 1 (receiving bionic pancreas treatment with insulin aspart or insulin lispro, *N*=219) or group 2 (receiving standard care i.e.any insulin-delivery method with unblinded, real-time continuous glucose monitoring, *N*=107). At 13 weeks, the use of a bionic pancreas was associated with a statistical significant reduction in the glycated hemoglobin level than standard care. No significant difference was noted in the number of severe hypoglycemia events between the two groups. (*NEJM 29 September, 2022*)

RAJESH KUMAR MEENA
raj.mamc@gmail.com

A behavior change model to address caregiver hesitancy around COVID-19 vaccination. (Vaccine. 2022.16;40:5664-9)

This semi-structured telephone interview was conducted to better understand the perspectives of vaccine hesitant caregivers, and develop targeted recommen-dations for health care workers and policymakers to engage in more effective vaccine discussions. Twenty three caregivers were recruited from a Pediatric infectious diseases clinic, including a subset of patients referred to discuss vaccine hesitancy. Barriers and facilitators were mapped to the World Health Organization 3C's (confidence, complacency, convenience) model of vaccine hesitancy as well as the COM-B (capability, opportunity, motivation) behavior change model. Barriers included mistrust in authorities, misperception of the risk of COVID-19 in children, and perceived health contra-indications and negative previous vaccine experiences. Facilitators included positive relationships with healthcare workers, the promise of a ''return to normal", and societal pressures to immunize. The authors concluded that efforts to increase vaccine uptake in the Pediatric population must target specific barriers and facilitators to immunization expressed by caregivers.

SMS reminders for childhood immunization in low income and middle-income countries (BMJ Global Health 2021;6:e005035)

Childhood vaccine delivery services in the low- and middle-income countries (LMICs) are struggling to reach every child with lifesaving vaccines. Short message service (SMS) reminders have demonstrated positive impact on a number of attrition-prone healthcare delivery services. Authors aimed to evaluate the effectiveness of SMS reminders in improving immunization coverage and timeliness in LMICs. PubMed, Embase, Scopus, Cochrane CENTRAL, CINAHL, CNKI, PsycINFO and Web of Science including grey literatures and Google Scholar were systematically searched for randomized controlled trials (RCTs) and non-RCTs that evaluated the effect of SMS reminders on childhood immunization and timeliness in LMICs. 18 studies (13 RCTs and 5 non-RCTs) involving 32712 infants (17135 in intervention groups and 15577 in control groups) from 11 LMICs met inclusion criteria. Pooled estimates showed that SMS reminders significantly improved childhood immunisation coverage (RR=1.16; 95%CI: 1.10 to 1.21; I^2 =90.4%). Meta-analysis of 12 included studies involving 25257 infants showed that SMS reminders significantly improved timely receipt of childhood vaccines (RR=1.21; 95%CI: 1.12 to 1.30; I^2=87.3%).

Safety and efficacy of COVID 19 vaccines in children and adolescents: A systematic review of randomized controlled trials (J Med Virol. 2022;94:4644-53)

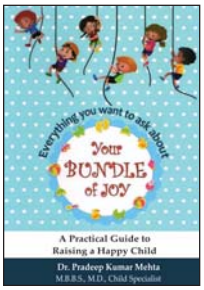
This systematic review of randomized controlled trials was done to assess the safety and efficacy of coronavirus disease 2019 (COVID 19) vaccines in children and adolescents. PubMed, EMBASE, Web of Science, Cochrane Library databases, the International Clinical Trials Registry Platform (ICTRP), the Chinese Clinical Trials Registry (ChiCTR), and ClinicalTrials.gov website were searched to collect accessible randomized controlled trials (RCTs) about the safety and efficacy of human COVID-19 vaccines in children and adolescents until May 1, 2022. COVID-19 vaccines were evaluated in a total of 10 950 children and adolescents in seven published studies and over 49 530 participants in 26 ongoing randomized controlled trials. The overall, local, and systemic adverse events following immunization (AEFIs) reported in most trials were similar between the vaccine and placebo groups. Most of the reactions reported were mild to moderate, whereas a few were severe. Few clinical trials reported serious adverse events, but most of them were unrelated to vaccination. In terms of efficacy, the investigated messenger RNA (mRNA) vaccine was found to be 90.7%-100% efficacious in preventing COVID-19 among children and adolescents, revealing good efficacy profiles in this age group. Among children and adolescents, the safety of current COVID-19 vaccines is acceptable.

Prevention of Typhoid Fever by Existing Improvements in Household Water, Sanitation, and Hygiene, and the Use of the Vi Polysaccharide Typhoid Vaccine in Poor Urban Slums (Am J Trop Med Hyg. 2022;7;106:1149-55)

Modest improvements in household water, sanitation, and hygiene (WASH) and typhoid vaccination can reduce typhoid risk in endemic settings. A total of 62,756 persons residing in 80 clusters in a Kolkata slum were allocated randomly 1:1 to either the typhoid Vi polysaccharide (ViPS) vaccine or hepatitis A (Hep A) vaccine. Surveillance was conducted for 2 years before and 2 years after vaccination. Households were classified as having "better" or "not better" WASH. The prevalence of better WASH households in clusters was calculated using previously validated criteria. Protection by better household WASH, better household WASH prevalence, and ViPS vaccination against typhoid in all cluster members present at baseline was evaluated using Cox proportional hazard models. Overall, ViPS vaccination was associated with a 55% (P, 0.001; 95% CI, 35–69) reduction of typhoid risk and was similar regardless of better WASH in the residence. Living in a better WASH household was associated with a typhoid risk reduction of 31% (P 5 0.16; 95% CI, –16 to 59) overall. The reduction was 48% (P 5 0.05; 95% CI, –1 to 73) in Hep A clusters, 6% (P 5 0.85; 95% CI, –82 to 51) in ViPS clusters, and 57% (P, 0.05; 95% CI, 15–78) in the population during the 2 years preceding the trial. This analysis highlights the importance of assessing the combination of WASH in conjunction with typhoid vaccines, and has implications for the evaluation of new-generation typhoid conjugate vaccines.

ARADHANA
draaradhanasingh@gmail.com

BOOK REVIEWS

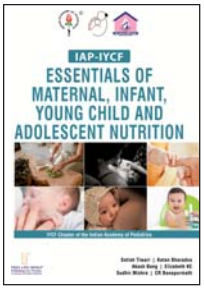


Your Bundle of Joy

PRADEEP KUMAR MEHTA
IVYNIB Communications Pvt Ltd, New Delhi
Pages: 189; Price: Rs. 395/-.

This book by Dr Mehta is truly a treasure house of information, from the desk of a pediatrician with longstanding experience of 'involved' office practice. It is not often that one comes across a book which addresses all the possible FAQs of parents with the fragrance of personal experiences. The author's style of presenting it in first person relates directly to the reader and he feels to "spoken to." Some facts on nutrition may not go in tandem with the IAP's recommendations – but on the whole, the book written in simple language with a few vernacular expressions is a delightful read and a must for young parents and young pediatricians. Young physicians will find it useful to structure their advisories for new, anxious parents. The last chapter consists of tips from the author's own parenting experiences.

S SITARAMAN
Director
Newton Institute of Child & Adolescent Development
Jaipur, Rajasthan.
drsraman.jp@gmail.com



Essentials of Maternal, Infant, Young Child and Adolescent Nutrition

SATISH TIWARI, KETAN BHARADVA, AKASH BANG, KE ELIZABETH, SUDHIR MISHRA, CR BANAPURMATH
Tree Life Media, 2022,
Pages: 764; *Price: 2495/-.*

Nutrition is the key element for physical and mental development of infants, children and adolescents. This book aims to empower students in the field of medicine and nutrition, as well as parents, by providing them scientific and unbiased information about childhood nutrition. This voluminous book provides an in-depth account of the subject through its 100 chapters divided in 10 sections and an Appendix. Though, the book aims to cover the topic of nutrition throughout the lifecycle of a child, the emphasis is on infant and young child feeding (IYCF), mainly breastfeeding. Regarding IYCF, not only the concept and recommendations are covered well, the traditional practices, myths, available support, practical issues, and feeding in difficult situations are also mentioned adequately. There is one chapter regarding adolescent nutrition that too covers only the outline and summary of the topic. Similarly, nutrition for children beyond two years of age is also covered only at few places along with nutritional requirements, and few disorders such as undernutrition and obesity. Besides covering above in detail, the future editions will also benefit from inclusion of chapters on nutritional management of common disorders of children such as celiac disease and persistent diarrhea. Other suggestions for future editions include ensuring uniform style of presentation of tables, boxes, figures, reference etc., and avoiding overlaps. The production quality is good, and flow diagrams and pictures are simple and easy to understand. I recommend this book for public health professionals, nurses, and postgraduate trainees in the field of nutrition, public health and pediatrics.

DHEERAJ SHAH
Director-Professor, Department of Pediatrics,
University College of Medical Sciences and
GTB Hospital, Delhi 110 095, India.
dshah@ucms.ac.in

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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