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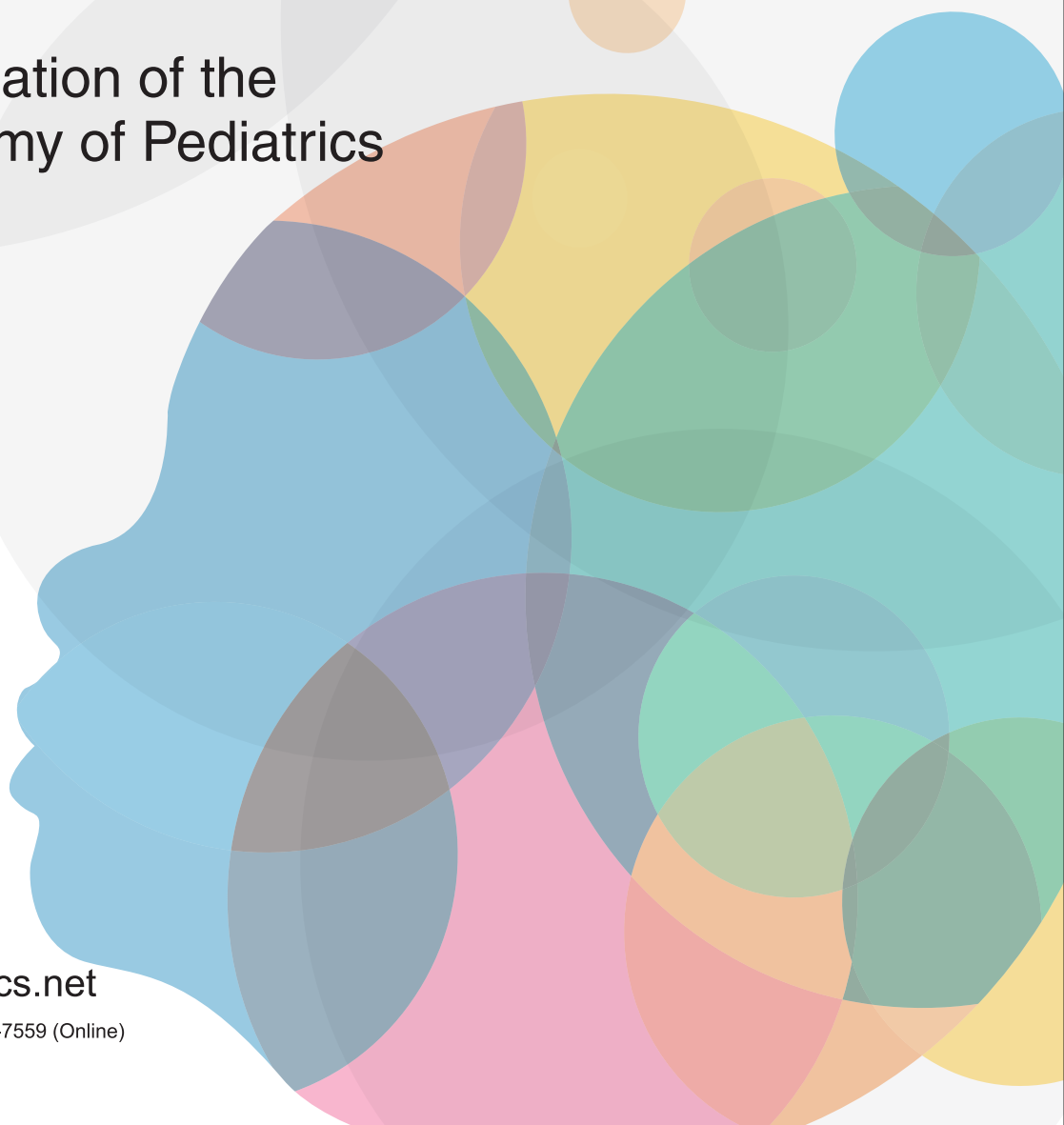

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IAP Guidelines for pediatric skincare

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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CONTENTS

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Child Health and the Environment

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A famous quote which we often come across these days is, "*We do not inherit the Earth from our ancestors, we borrow it from our children*." Of late, the Earth's environment has emerged as one of the foremost concerns of humankind. Not a single day passes without a mention of issues like global warming, climate change, pollution, plastic and hydrocarbons. The cars that we drive are slated to go electric by the end of this decade. We are advised not to use plastic carry bags. Local municipal bodies educate us regarding the proper disposal of household waste. The world seems to be opening its eyes to the multitude of problems that plague our beleaguered planet. A constant messaging tool is the appeal to safeguard the environment for the sake of our future generations. So this begs the question: have we pediatricians, being the custodians of future generations, opened our eyes to the perils of environmental threats to child health? In what way does the environment impact the health of children? What can we do to reduce the adverse effects? I, herein, present an overview of the issue.

THE IMPACT OF THE ENVIRONMENT ON CHILDREN

The focus of pediatrics thus far has been on improving child mortality using different parameters like perinatal, neonatal, and Under 5. Having made good progress in these spheres, we have extended our reach via different subspecialties to address other issues too. The new domain which seeks our urgent intervention has to do with the impact of the environment on child health. While we have successfully addressed the traditional threats to children's health, the question of environmental impact on child health is a relatively new one and goes hand in hand with global threats posed by environmental issues. As a recent article [1] points out, "*Climate change is affecting every person on earth, with rising temperatures and sea levels, increased water and air pollution, and extreme weather events having an impact on our health, wellbeing, and stability. Children, in particular, bear the brunt of these devastating consequences.*" The article [1] further asserts: "*There is no child health without planetary health. The child health community must step up its efforts, both individually and collectively, to protect the environment for all children and adolescents.*"

According to UNICEF, an estimated 26% of deaths in children under five years old can be prevented by addressing environmental risks [2]. "*Climate change and environmental degradation threaten to reverse progress on child and adolescent survival, health and well-being we have achieved over the years. Environmental hazards have been linked to a range of significant health risks for children. For example, the global rise of cancer, diabetes, neurodevelopmental disorders and asthma has accompanied a surge in air pollution, e-waste and the use of harmful chemicals in everyday products* [2]."

Figures published by the United Nations [2] reveal that reducing environmental risks could prevent 1 in 4 child deaths. In 2012, 1.7 million child deaths in under five were attributable to the environment. These included 570,000 deaths from respiratory infections, 361,000 deaths from diarrhoea, 270,000 deaths from neonatal conditions, 200,000 deaths from malaria and 200,000 deaths from unintentional injuries. The World Health Organization (WHO) estimates that three million children under the age of 5 die annually from environmentally related diseases [3].

ENVIRONMENTAL PEDIATRICS

From all available indications, children are the most vulnerable segment with regard to environmental impact on health [4].

- Children are constantly growing. They breathe more air, consume more food, and drink more water than adults do, in proportion to their weight.
- Children's systems are still developing. This includes their central nervous, immune, reproductive, and digestive systems. At certain early stages of development, exposure to environmental toxicants can lead to irreversible damage.
- Children behave differently from adults, and this means there are different ways they can be exposed to environmental risks. For example, young children crawl on the ground, where they may be exposed to dust and chemicals that accumulate on floors and soils.
- Children have little control over their environment. Unlike adults, they may be both unaware of risks and unable to make choices to protect their health.

All these factors have resulted in environmental causes drawing the attention of Pediatrics. As a result, a new domain called 'Environmental Pediatrics' has emerged over the last decade as a new subspeciality. The aforementioned paper [4] observes that environmental exposure is among parents' top health concerns for children. It goes on to state that the study of the effects of environmental exposure on health outcomes is a developing field, and clinicians feel inadequately prepared to address these concerns. The WHO created the first international Task Force for the Protection of Children's Environmental Health in 1999. That same year, the first edition of the American Academy of Pediatrics (AAP)'s Handbook of Pediatric Environmental Health was published, gathering together available evidence in the field. Three years later, the first formal fellowships in Pediatric Environmental Health were established across the United States and the WHO held the first International Conference on Environmental Threats to the Health of Children. This led to the development of the Bangkok statement, which established priorities and commitment for action.

In 2007, the WHO teamed up with the International Pediatric Association and launched the International Pediatric Environmental Health Leadership Institute to train healthcare providers. In 2012, a group of international experts contributed to the first Textbook of Children's Environmental Health. The AAP defines environmental pediatrics as a new and still developing subspecialty of pediatrics. It is the study of how environmental exposures, genetic influences and psychosocial experiences interact with each other and the helpful or harmful effects they might have on children's health. It is the practice of anticipatory guidance for parents about exposures in their children's environment.

AAP presents the view that human beings are subject to a macro environment, which is shared by the population, and a micro environment, which is unique to each person at each point in time. The environment consists of the atmosphere, including the air we breathe, the soil and ground, bodies of water and rain, the plants and animals that share our environment, and man-made environments where we live, work, and play. It also includes a person's psychosocial situation. This holistic approach was well embraced by IAP when we initiated ECHG – the Environment and Child Health Group of Indian Academy of Pediatrics in 2007. This sub specialty Group has been working relentlessly to make the Pediatric fraternity of our country to focus much more on environmental health issues related to child health. IAP currently looks at child health from an entirely new perspective and the future of pediatrics is sure to become more broad-based than at present.

TAKING CHILDREN BACK TO NATURE

While researching on this topic, I came across something called 'Nature deficit disorder', which is an interesting new term coined by the author Richard Louv, in his book *Last Child in the Woods* to describe what happens to children who become disconnected from their natural world. Louv, who is a co-founder of the Children & Nature Network, argues that human beings, especially children, are spending less time outdoors than they have in the past, and that this change results in a wide range of behavioral problems. He associates this separation from nature with some of the disturbing childhood trends, such as the rise in obesity, attention disorders, and depression. This so-called disorder is not recognized in any of the medical manuals for mental disorders, and there has been no systematic research undertaken to authenticate the concept. However, some preliminary research is said to indicate that a lack of time outdoors does have negative effects on children's mental well being.

While the ideas proposed by Louv may be debatable, there is no doubt that spending more time with nature does have good therapeutic and developmental value. For children, in particular, more time spent outdoors does fulfill their deepest need for activity, experience, interaction, and experimentation. Most modern kids living in the larger cities are deprived of these simple joys of life due to being cramped in the concrete jungle and having a highly regimented life.

More work might be needed to integrate the various ideas randomly discussed above and make them into cohesive, clinically adaptable concepts. Both IAP and individual pediatricians will have to keep their eyes open for more developments in this new and very promising field.

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INVITED COMMENTARY

Secular Trends in Birthweight

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Secular trends in birth weight have been reported over a wide range of time periods, some dating back to as early as the initial years of the 20th century or even earlier [1,2]. However, changes in demographic profile, socio-economic status, environ-mental conditions, disasters, medical interventions, and health systems are expected to have an impact on these secular trends. Most of the reports on secular changes in birth weight (as also other anthropometric profiles such as length and head circumference) have largely come from Europe or North America; very few from low-and-middle-income countries (LMIC). The article in this issue of the *Indian Pediatrics* [3], which presents changes in birth weight from a tertiary care hospital in North India over a 40-year period may be a useful addition to information from LMICs. Most of the published data on secular trends span the period 1950 to 2010; large proportion being population based in comparison to hospital-based reports.

Celind, et al. [4] reported secular trends in birth weight amongst boys from 1950-2010 from Sweden which comprised a cohort of 46,548 boys. While the analysis for the entire period was noted to be stable (only a minimal negative secular trend was noted: -0.4 g/year; $P<0.01$), distinct trends were noted during sub-periods: a decrease during 1950-1980, an increase during 1980 -2000 and again a decrease from 2000-2010. Domagala, et al. [5] reporting on 7510 neonates born in the Polish City of Wroclaw between 1950s-2000 observed a minimal but insignificant increase in birth weight. They too observed periods of increase and decrease in the trends of birth weight over specific time periods; particularly notable being the deceleration in 1970s and 1980s which corresponded with the economic crisis and political transformations in Poland. Similar observations have been reported from Japan. Oishi, et al. [6] reported on birth weights of 6563 term singleton neonates born between 1962-1988 in a Municipal maternity hospital in Nagasaki prefecture. They observed an increase in size at birth from 1960s to 70s but not thereafter, which the authors attributed partly to the improved socio-economic status of the population. In contrast population-based studies from Japan using national birth data between 1979-2010 reported a decline in birth weight (from 3200g in 1979 to 3020 g in 2009) and increase in prevalence of low birth weight and preterm birth amongst singleton births [7,8]. During the same period an increase in maternal height was also reported [8]. Takemoto, et al. [8] suggested that this deceleration in birth weight may have been related to changing nutritio-nal status of Japanese women, recommendations to limit weight gain in pregnancy and an increase in preterm deliveries. da Silva, et al. [9] reported on the changes in birth weight of term singleton newborns born in Brazil from 1978 to 2010 (32,147 newborns from three population-based cohorts). Between 1978-1994 there was a reduction in birth weight which ranged from -27.7g to -89.1g. From 1994-2010 there was an increase in birth weight that ranged from +24.7g to +30.2g. The changing trends were attributable to differing reasons in each of the cohorts at different time periods, indicating lack of common pattern even within a country at similar time periods [9]. These large datasets from the more affluent nations show that there has been no consistent pattern in secular birth weight trends over the past five to six decades.

More recently declining birth weight trends have been reported from North America. The US data for 2008 as compared to 1990 indicated that there was a decline in macrosomia (>5000g) and a 17% increase in low birth weight (including small for gestation (SGA) [10]. It has been suggested that part of this could be explained by obstetric interventions terminating pregnancy earlier at lower gestation. It has also been suggested that fetal growth was declining independent of gestational age, reasons for which were not entirely clear. Using Canadian Vital Statistics - Birth database, Adam, et al. [11] observed that amongst 5,941,820 singleton live births in Canada, there was a decline in birth weight between 2000 (mean birth weight 3442 g) and 2016 (mean birth weight 3367 g), while SGA births increased from 7.2% to 8.0%. An adjusted multivariate analysis suggested that the increased odds of SGA birth could partly be explained by factors such as births to parents born outside of Canada, unmarried women, older women, nulliparous women, and women residing in low-income neighborhoods. Similar findings have been reported from LMICs too. Declining birth weight trends have also been reported from Iran [12]. A meta-analysis of births between 1971 and 2010 in Iran noted that from 2000 onwards there was a significant

negative secular trend in birth weight (approximately -8.1g/y) [12]. Similar findings have been reported from Argentina for births between 1992-2002 [13]. A study published from Vietnam using surveillance data showed no change in birth weight between 2005-2012 [14].

In contrast, there are reports that document a secular increase in birth weight. A single center data from Israel documented an increase in birth weight amongst all the 32,062 births in the health facility over the entire time span [15]. This was attributed to a decrease in the number of preterm births. However, when the data for term babies was analyzed, they showed no change in birth weight, while length and head circumference showed a significant increase. Similar trends in hospital derived data have also been reported from other countries [16], including India. Thomas, et al. [3] noted an increase of 100-200g in all live born neonates in 2009-2016 compared to those born in 1971-73 at a single center in North India. Paradoxically, this increase was observed despite an increase in the prevalence of SGA (9.8% vs 4.7%) and preterm babies (16.6% vs 8.0%), and a decrease in the proportion of larger babies (unlike the inverse association between mean birth weight and proportion of SGA/LBW/preterm reported in other large population-based studies). The authors have offered no explanation for this paradox. Similar trends of increase in birth weight spanning about 10-20 years have been reported both from hospital [17], and from population based demographic surveillance system in India [18].

However, it is important to note that even within the same geographic region ethnicity may influence the trends in birth weight. Lahmann, et al. [19] analyzed the Queensland Perinatal dataset for singleton births during 1988-2005. While the annual increment in birth weight over this period was about +1.9 g/yr, the change observed was confined to only the non-indigenous newborns.

Mere improvement in socioeconomic status of a region does not ensure an increase in birth weight over time. It would be important to be cognizant of other influencers such as demographic and ethnic character-istics, maternal nutrition and life style, environmental factors and disasters, and most importantly medical interventions especially early termination of pregnancies by the obstetricians. Combination of socio-political and economic factors coupled with demographic factors influence these trends, making predictions of change over time rather challenging. One needs to be cautious while interpreting secular trends from hospital data which are fraught with several pitfalls, most important amongst them being selection bias which could change substantially over time. Tracking secular trends from population-based data offer useful information for influencing policy, especially when adjusted for a variety of factors that are known to influence fetal growth and birth weight.

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RESEARCH PAPER

Secular Trends in Birthweights in Two Epochs Over 40 Years in a Tertiary Care Center

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Objective: To compare the average birthweights and the weight centiles of the 'new' growth charts with the 'old' (1974) charts developed in the same unit four decades ago.

Methods: Birthweight and gestation data of the eligible 12,355 singleton neonates born between 2009 and 2016 at a level-3 neonatal unit at a public sector hospital were used to develop the new growth chart. We then compared the prevalence of small for gestational age (SGA) and large for gestational age (LGA) classified by the new charts and the old charts, the incidence of short-term adverse outcomes among them, and the diagnostic performance of both the charts to identify the adverse outcomes in a separate validation cohort.

Results: The mean birthweights of boys and girls across all gestations were higher by 150-200 g and 100-150 g, respectively, in the new chart. The prevalence of SGA doubled (9.8% vs 4.7%), but LGA decreased by one-third (17.5% vs 25.9%) with the new chart. However, the proportion of SGA and LGA having one or more short-term adverse outcomes, and the diagnostic performance of both the charts to identify neonates with short-term adverse outcomes, were comparable.

Conclusion: There was an upward shift in the birthweights by about 150 g across all gestations in the new chart compared to the old chart developed 40 years ago. The findings imply the need to consider using updated growth charts to ensure accurate classification of size at birth of neonates.

Keywords: *Gestational age, Growth chart, Newborn, Small for gestational age*.

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Advances in perinatal and neonatal care in the last few decades have led to significant improvement in the survival of extreme preterm and low birthweight neonates across the globe. Concurrently, there has been an increase in the average birthweight of neonates over the years in many countries [1-3]. With the change in birthweights, the growth centiles and the proportion of small-for-gestational age (SGA) neonates are also expected to change; though, the magnitude of the change may vary across regions [2].

We planned to examine the average birthweights and the birthweight centiles (from 3rd centile to 97th centile) on two charts – generated almost 40 years apart from the same unit. We compared the cut-offs at different centiles and the prevalence of SGA and large-for-gestational age (LGA) neonates with the 'new' and 'old' charts. We also evaluated the charts' diagnostic performance to identify SGA and LGA neonates at risk of short-term adverse outcomes.

METHODS

In this study conducted at the level-3 neonatal unit of our public sector referral hospital, we enrolled two cohorts of neonates – one comprising the eligible neonates born between March, 2009 and November, 2016 for the generation of the new growth charts and the other including the neonates born between December, 2016 and August, 2017 for validation of the new chart and comparison with the old chart produced in 1974 [4]. The institute ethics committee approved the study protocol.

Invited Commentary: Pages 601-02.

For developing the new centiles, we obtained the relevant information from the unit's electronic database system for all the neonates born between 2009 and 2016. All consecutive live births during this period were eligible for inclusion in the study. We excluded neonates born to mothers with significant medical and obstetric morbidities known to affect fetal growth, including type 1 and type 2 diabetes mellitus, chronic hypertension, heart disease, renal disease, seizure, tuberculosis during pregnancy, malaria, asthma, hepatitis, syphilis, HIV infection, severe anemia (hemoglobin <7 g/dL), gestational hypertension, preeclampsia/eclampsia, and gestational diabetes mellitus. Twins or higher-order births and neonates with major

congenital malformations or immune or non-immune hydrops were also excluded.

Gestation at birth is determined in the unit from the mother's last menstrual period (LMP). If there is a discrepancy of more than seven days between the LMP and the first-trimester ultrasound (USG) dating, the gestational age is revised as per the USG dating [5]. In pregnancies with unsure dates and non-availability of first-trimester ultrasound dating, the expanded new Ballard score is used to determine the gestational age. Birthweight is documented within one hour of birth using an electronic weighing scale with 5 g calibration (ADE M10400). The designated staff of the neonatal intensive care unit calibrates the weighing machines in all the birthing areas once weekly using pre-specified weights.

Developing the new chart: The birthweight and gestational age data were entered separately in R software (ver 3.6.1) for boys and girls. Smoothening was done using the Lambda-Mu-Sigma (LMS) method [6]. After smoothe-ning, the new gender-specific charts containing the 3rd, 10th, 50th, 90th, and 97th centiles were obtained.

Extracting data from the old AIIMS growth chart: The 'old' regional growth chart – generated by Singh, et al. [4] – used the data of all consecutive singleton neonates born at the hospital between 1971 and 1973, irrespective of the maternal morbidities and neonatal conditions (*n*=3550). Neonates with uncertain gestation at birth (because of the disparity between the calculated and clinically assessed gestational age) and with no birthweight records were excluded. Birthweight at different centiles at each gestational age was derived from the 'old' growth chart using the WebPlotDigitizer developed by Rohtagi, et al. [7] (available at *https://automeris.io/WebPlotDigitizer/*).

Neonates born at 31 to 41 weeks between December, 2016 and August, 2017 (validation cohort) were used to compare the *i*) prevalence of SGA and LGA; *ii*) incidence of short-term adverse outcomes, including in-hospital morta-lity or one of 14 predefined key morbidities among SGA and LGA neonates identified by both the old and new charts; and, *iii*) diagnostic performance to detect the short-term adverse outcomes among SGA and LGA neonates. Neo-nates in the validation cohort were prospectively tracked from birth till 28 days of life – for another study (Under publication) – to detect the occurrence of one or more adverse outcomes. The following adverse outcomes, apart from neonatal mortality, were prospectively recorded in the validation cohort of neonates: need for delivery room resuscitation (BE <12 or positive pressure ventilation >30 sec), seizures (clinical), respiratory support for more than 24 hours or NICU stay for more than 48 hours, sympto-matic hypoglycemia, culture-positive or clinical sepsis, symptomatic hypocalcemia, polycythemia requiring intra-venous fluids/partial exchange transfusion, any acute life-threatening event, persistent pulmonary hypertension (PPHN) confirmed by echocardiography, bronchopul-monary dysplasia (BPD), retinopathy of prematurity (ROP) requiring laser therapy, patent ductus arteriosus requiring treatment, shock requiring inotropes, and necrotizing enterocolitis.

Statistical analysis: This was done using STATA version 15.1 (StataCorp). The diagnostic performance of both charts was determined using the '*diagt'* command in Stata. The relative risk of adverse outcomes among the additional SGA identified by the new chart and the LGA missed was computed using the '*csi'* command in Stata.

RESULTS

Of the 18,979 neonates born between March, 2009 and November, 2016, four with implausible birthweights and gestation (wrong data entry), 31 born before 24 weeks or after 41 weeks, and six neonates with ambiguous genitalia were excluded; another 6583 were excluded based on the pre-specified exclusion criteria. Gender-specific growth charts were then constructed using the data of 6583 boys and 5772 girls (**Fig. 1** and **2**). The mean birthweight and gestational age of the boys and girls were 2841 g and 37.6 weeks, and 2740 g and 37.7 weeks, respectively. About one-fourth were low birthweight, and nearly one-fifth were preterm (**Web Table I**). **Web Table II** provides the birthweights of boys and girls at the 10th, 50th, and 90th centiles. The mean birthweight of boys and girls with the new chart was nearly 150-200 g and 100-150 g more than the old chart across almost all gestational categories, respectively (except 30-31weeks in boys and 30-31 and 32-33 weeks in girls) (**Table I**).

The validation cohort included 1294 neonates born between December, 2016 and August, 2017. The proportion of neonates labeled SGA was almost twice with the new charts (9.8% vs 4.7%). In contrast, the proportion of neonates marked as LGA decreased by nearly one-third – from 25.9% with the old chart to 17.5% with the new chart (**Fig. 3**). The prevalence of AGA increased by 3.3% (72.7% vs 69.4%). The proportion of SGA and LGA having one or more short-term adverse outcomes is comparable between the charts (**Table II**).

Both the new and old charts had similar sensitivity (29% vs 30%), specificity (73% vs 69%), positive predictive value (32% vs 30%), negative predictive value (71% vs 70%), and diagnostic odds ratio (1.13 vs 0.98) for identifying short-term adverse outcomes among SGA or LGA neonates (**Web Table III**).

To determine if the observed increase of 100-200 g in

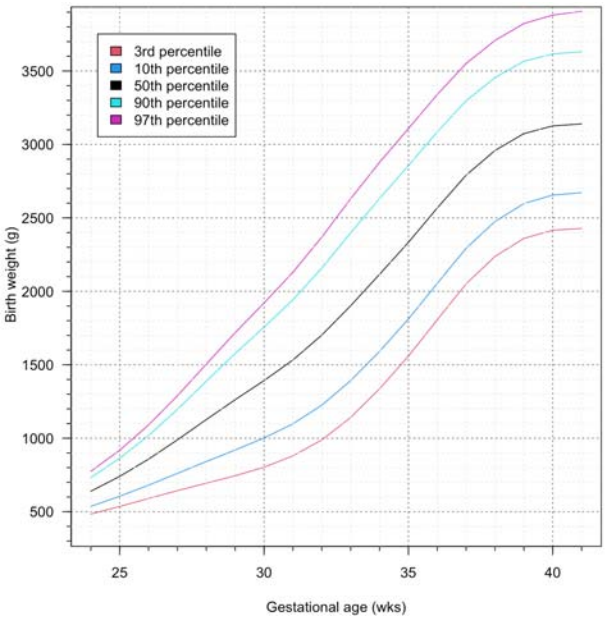

Fig. 1 New AIIMS neonatal growth chart– Boys.

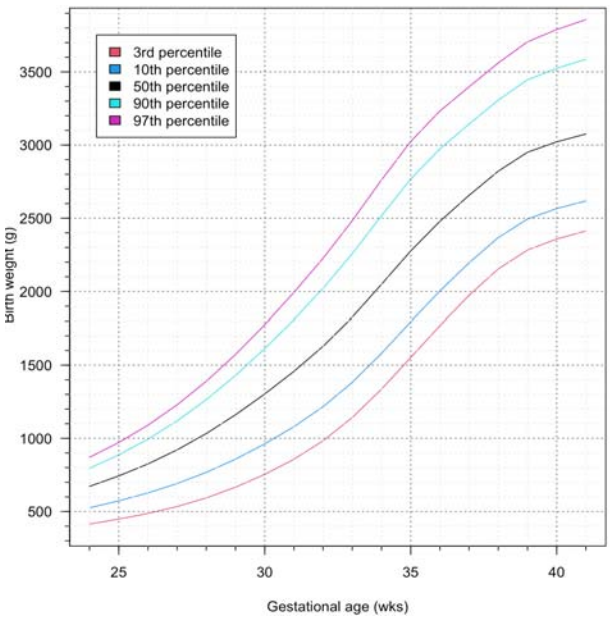

Fig. 2 New AIIMS neonatal growth chart– Girls.

mean birthweights with the new chart was purely due to the exclusion of neonates with higher-order gestation and congenital malformations and those who were born to mothers with chronic morbidities, we conducted a sensitivity analysis by including all the neonates born between March, 2009 and November, 2016, irrespective of the maternal and neonatal morbidities. Of the total 18,979 neonates, four with implausible birth weights and

Table I Birthweight at Different Gestation With the 'new' and 'old' AIIMS Neonatal Growth Charts

Gestational age (wk)	*Old chart*		*New chart*		*Mean difference*
	n	*Birthweight (g)*	*n*	*Birthweight (g)*	*(95% CI)*
Boys					
30-31	10	1580 (820)	60	1442 (306)	-138 (-419 to 143)
32-33	19	1660 (350)	127	1785 (426)	125 (-78 to 328)
34	31	1940 (280)	134	2142 (405)	202 (50 to 354)
35	24	2110 (340)	222	2324 (384)	214 (53 to 375)
36	58	2360 (410)	507	2553 (430)	193 (81 to 305)
37	114	2630 (400)	1498	2803 (389)	173 (98 to 247)
38	259	2790 (410)	1886	2957 (392)	167 (116 to 218)
39	337	2960 (410)	1400	3083 (385)	123 (76 to 169)
40	689	2960 (400)	638	3132 (386)	172 (130 to 214)
41	167	3060 (450)	38	3106 (422)	46 (-112 to 204)
Girls					
30-31	11	1470 (240)	57	1416 (291)	-54 (-241 to 133)
32-33	18	1740 (260)	90	1699 (364)	-41 (-220 to 138)
34	13	1950 (370)	119	2014 (384)	64 (-157 to 285)
35	18	2280 (510)	205	2314 (397)	34 (-163 to 231)
36	60	2340 (480)	427	2481 (394)	141 (31 to 251)
37	70	2540 (430)	1189	2663 (379)	123 (31 to 215)
38	251	2680 (390)	1605	2831 (362)	151 (102 to 199)
39	305	2830 (390)	1271	2968 (389)	138 (89 to 197)
40	680	2900 (400)	699	3028 (367)	128 (87 to 168)
41	195	3030 (400)	47	3107 (439)	77 (-53 to 207)

Values in mean (SD). AIIMS - All India Institute of Medical Sciences.

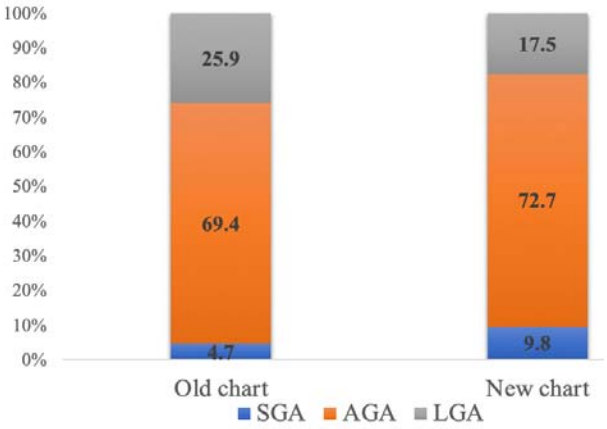

Fig. 3 Proportion of SGA, AGA, and LGA in the validation cohort using both charts.

gestation (wrong data entry), 31 born before 24 weeks or after 41 weeks, and six neonates with ambiguous genitalia were excluded. The mean birthweights and 10th, 50th, and 90th percentile of the remaining 18,938 neonates (10,073 boys) were compared to the old chart **(Web Table IV** and **V)**. Mean birthweights were nearly 100 g more even when all neonates were included.

DISCUSSION

We compared growth charts developed in 1974 and 2016 at our center, and found an upward shift in the average birth weight by about 150-200 g in boys and 100-150 g in girls at almost all the gestations over the last 40 years. Even with the inclusion of neonates born to mothers with chronic morbidities, the mean weights across all gestational categories were nearly 100 g in the new chart signifying a change over the years.

The secular trend in birthweights over four decades is probably because of the improvements in antenatal and perinatal care, and the nutritional and socioeconomic status of the population in general. However, similar secular trends of improved birthweights were not apparent in cohorts that were 15 to 20 years apart from the same institutes (viz., Safdarjung hospital [8,9], AIIMS [4,10] and CMC, Vellore [11,12]). The shorter interval between the cohorts could possibly explain the lack of trends of improved birthweights in these studies. Amongst the International charts, the updated Babson and Benda charts over 27 years (1976 to 2003) showed a statistically significant difference in weights only for neonates with term gestation [13,14].

The upward shift of the mean birthweights could explain the increase in SGA prevalence and reduction in LGA prevalence. The proportion of SGA with adverse outcomes was lower in the new chart, but the chart's performance in identifying short-term adverse outcomes among SGA or LGA neonates was comparable to that of the old chart. Moreover, the prevalence of AGA increased by 3.3% (72.7% vs 69.4%), which implies that for every 1000 neonates born in any unit, 33 fewer need to be screened for hypoglycemia/polycythemia in the immediate neonatal period.

Table II Short-Term Adverse Outcomes in Validation Cohort Using Two Growth Charts

Growth category	*Babies with adverse outcomes*	
	Old chart	*New chart*
Small-for-gestational age (SGA)	25 (40.9)	47 (37.0)
Appropriate-for-gestational age (AGA)	271 (30.2)	276 (29.3)
Large-for-gestational age (LGA)	93 (27.7)	66 (29.2)

Values in no. (%). The number of SGA, AGA and LGA babies in the old chart was 61, 898 and 335; and 127, 941 and 226 in the new chart, respectively.

Compared to 8% of preterm neonates in the 1974 AIIMS chart, the preterm neonates formed 16.6% of the cohort in the new chart, which is considerably higher than the previous regional charts by Ghosh, et al. (13%) [8] and Fenton charts (1.9%). With the improving survival rates of extreme low birth weight and extreme preterm neonates, these neonates must form a considerable proportion of the cohort used to develop the neonatal charts. Given that the new charts are created using a much larger sample size and provide gender-specific charts, it is preferable to use the new charts for accurate classi-fication of neonates at birth. The WHO MGRS growth charts are the preferred choice for monitoring the growth of term neonates [15]. However, the lack of gestation-wise data in those charts, even among term neonates, makes it challenging to classify neonates as AGA/SGA/LGA at different gestations, thereby preventing them from being used as the optimal 'size-at-birth' charts.

The strengths of the current study included large sample size, application of the LMS smoothening technique, and selective inclusion of mothers without health constraints. We used a cohort of neonates who were prospectively observed for predefined short-term adverse outcomes to validate the new chart. The study is limited by the retrospective nature of the collected data and the consequent lack of rigorous methodology followed in the construction of prescriptive charts like Intergrowth 21st [16], wherein the healthy mothers were longitudinally followed up to allow for accurate assessment of fetal growth and subsequent growth of neonates. Moreover, there was restricted recruitment of extreme preterm neonates, though the proportion is comparable with the global standard charts. The disparity in inclusion criteria of

WHAT IS ALREADY KNOWN?

- With improving antenatal and perinatal care, neonatal birthweight centiles are expected to change with time.

WHAT THIS STUDY ADDS?

- There is an upward shift in the mean birthweights by 150-200 g among boys and 100-150 g among girls across all the gestational categories compared to the regional chart developed 40 years ago.

mothers in the two charts may have implications on the interpretation of the comparative analysis. Inclusion of neonates from a single center that deals predominantly with high-risk pregnancies is also likely to affect the generalizability of the study results.

Comparing two epochs over the last 40 years shows an upward shift in the birth weights across the gestation by about 150-200 g and 100-150 g among boys and girls, respectively. The proportion of neonates classified as SGA and AGA was also higher, and the performance to identify neonates with short-term adverse outcomes was comparable to the old centiles. The findings imply the need to consider using updated growth charts to ensure accurate classification of size at birth.

Ethics clearance: IEC, AIIMS, New Delhi; No. IECPG/768/30.01.2020 dated Feb 11, 2020.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: DT: designed the study, collected the data, did the initial analyses, and drafted the initial manuscript; PA: contributed to the initial data collection & analysis and helped draft the initial manuscript; RA, AT, AD: provided critical insights into the study design, supervised the conduct of the study and critically reviewed the final manuscript; MJS: helped design the study, supervised the conduct of the study, did the final analysis, and reviewed and finalized the manuscript. All authors approved the final manuscript.
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Web Table I. Baseline characteristics

Characteristic	*Males n=6583*	*Females n=5772*
Birth weight (g)*	2841 ± 527	2740 ± 507
Low birth weight	1394 (21.2%)	1570 (27.2%)
Very low birth weight	152 (2.3%)	145 (2.5%)
Extremely low birth weight	36 (0.5%)	42 (0.7%)
Gestation (weeks)*	37.6 ± 1.9	37.7 ± 2
Late preterm	863 (13.1%)	751 (13%)
Moderate preterm	127 (1.9%)	90 (1.6%)
Very/extreme preterm	133 (2.0%)	120 (2.1%)

*Data expressed as n (%) *Data expressed as mean ± SD.*

Web Table II. The 10th, 50th and 90th percentile of male and female neonates in the 'new' chart at various gestation

GA* (weeks)	n		10th percentile (grams)		50th percentile (grams)		90th percentile (grams)	
	Male	Female	Male	Female	Male	Female	Male	Female
24	3	3	628	685	640	717	696	764
25	6	3	591	691	705	750	824	786
26	7	8	698	612	817	767	976	889
27	10	16	871	669	987	948	1207	1130
28	24	12	754	693	1151	894	1342	1217
29	23	21	1087	880	1305	1180	1687	1473
30	22	26	1067	1037	1352	1337	1604	1578
31	38	31	1045	1187	1521	1430	1859	1812
32	59	41	1191	1080	1673	1582	2049	1959
33	68	49	1285	1475	1891	1827	2491	2124
34	134	119	1586	1484	2191	2059	2636	2418
35	222	205	1841	1792	2324	2319	2812	2848
36	507	427	1948	1997	2554	2474	3108	2984
37	1498	1189	2317	2214	2803	2642	3280	3161
38	1886	1605	2466	2375	2958	2824	3434	3277
39	1400	1271	2603	2489	3072	2956	3580	3461
40	638	699	2648	2584	3114	3002	3608	3511
41	38	47	2559	2535	3117	3096	3653	3550

**GA: gestational age*

Web Table III. Diagnostic performance of 'new' vs. 'old' AIIMS chart for identifying GA/ LGA with short term adverse outcomes

Parameter	*'New' chart*	*'Old' chart*
Sensitivity	29.0% (24.6-33.8)	30.1% (27.6-32.6)
Specificity	73.5% (70.5-=76.3)	69.3% (66.2-72.3)
Positive predictive value	32.0% (27.2-37.2)	29.8% (25.3-34.6)
Negative predictive value	70.7% (67.6-73.6)	69.8% (66.7-72.8)
Positive likelihood ratio	1.10 (0.91-1.32)	0.98 (0.76-1.27)
Negative likelihood ratio	0.97 (0.90-1.04)	1.01 (0.93-1.09)
Diagnostic odds ratio	1.13 (0.87- 1.48)	0.98 (0.76-1.2)

95% confidence intervals provided in parentheses
SGA: Small for gestational age; LGA: Large for gestational age

Web Table IV. Comparison of mean birth weights and 10th, 50th and 90th percentile of 'new' chart with eligible neonates vs. all neonates (males)

GA (wks)	n		Mean weight (g)		10th percentile (g)		50th percentile (g)		90th percentile (g)	
	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates
30	22	69	1345	1336	1067	986	1352	1335	1604	1636
32	59	158	1656	1626	1191	1150	1673	1640	2049	2089
34	134	302	2142	2078	1586	1490	2191	2068	2636	2627
37	1498	2374	2803	2791	2317	2261	2803	2788	3280	3323
40	638	824	3132	3109	2648	2602	3114	3106	3608	3593
24-41 weeks	6583	10073	2841	2748						

Eligible neonates *are the neonates used to construct the 'new' male growth chart after exclusion of maternal and neonatal morbidities;* ***All neonates*** *are all the male neonates during the study period*

Web Table V. Comparison of mean birth weights and 10th, 50th and 90th percentile of 'new' chart with eligible neonates vs. all neonates (females)

GA (wks)	n		Mean weight (g)		10th percentile (g)		50th percentile (g)		90th percentile (g)	
	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates	Eligible neonates	All neonates
30	26	74	1317	1254	1037	804	1337	1250	1578	1622
32	41	109	1544	1507	1080	1078	1582	1539	1959	1876
34	119	282	2014	1944	1484	1420	2059	1934	2418	2411
37	1189	1947	2663	2659	2214	2167	2642	2642	3161	3193
40	699	853	3028	3017	2584	2562	3002	3000	3511	3505
24-41 weeks	5772	8865	2740	2644						

Eligible neonates *are the neonates used to construct the 'new' female growth chart after exclusion of maternal and neonatal morbidities;* ***All neonates*** *are all the female neonates during the study period*

RESEARCH PAPER

Manual Method vs Breast Pump for Breast Milk Expression in Mothers of Preterm Babies During First Postnatal Week: *A Randomized Controlled Trial*

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Objectives: To compare breast milk volume between manual method and breast pump expression in mothers of preterm infants at different time point of first week.

Design: Randomized controlled trial.

Setting: Postpartum ward of Obstetrics department and tertiary level neonatal intensive care unit (NICU) in a single institution in Orissa between October, 2020 and May, 2021.

Participants: Mothers who delivered before 34 completed weeks of gestation.

Interventions: Manual breastmilk expression (ME) group using Marmet technique and breast pump milk expression (PE) group using pigeon manual breast pump, initiated milk expression within one hour of delivery.

Outcome measures: Expressed breast milk (EBM) volume in mothers of preterm infants at different time point of first week, and cumulative milk volume.

Results: Out of 170 mothers (83 PE and 87 ME group), 7-days milk volume data was available for 137 (71 ME and 66 PE) mothers. In per protocol analysis for 126 mothers (63 in each group), the median (IQR) EBM volume on day 2 and day 7 of ME and PE groups were similar [10 (5,20) vs 12 (5,28), *P*=0.10] and [280 (220-356) vs 280 (220-360), *P*=0.66]. The median (IQR) cumulative EBM volume over first 7 days in ME group was not significantly different from PE group [733 (593-995) vs 848.5 (571-1009)] *P*=0.55). A similar number of mothers in the PE and ME group [56 (88.9%) vs 58 (92%); *P*=0.14] provided exclusive breast milk for their neonates during the first week. Similar results were found on intention to treat analysis.

Conclusion: EBM volume expressed was comparable between mothers expressing manually or with breast pump.

Key words: *Lactation*, *Low birthweight, Nutrition, Volume*.

Mothers own milk is always prioritized for enteral nutrition of preterm neonates [1]. However, premature delivery is associated with immature mammary gland, delayed onset of lactogenesis phase II, lack of physiologic breast suckling and presence of maternal stress, resulting in low milk yield in initial days [2]. Early initiation of milk expression within one hour of delivery is an important dimension for availability of breast milk [3,4]. Manual hand expression is a standard practice for milk availability, and breast pump is used as a rescue modality during lactation failure. Increased maternal comfortness during milk expression favors the use of breast pump [5,6].

The milk production in mothers of preterm babies is a complex physiological phenomenon, influenced by timing and type of milk expression. There is limited literature regarding utility of breast pump from early postpartum period for availability of colostrum and long term milk supply. Considering the need of mother's own milk for aggressive enteral nutrition, the objective of the present study was to determine the efficacy of exclusive pump expression in mothers of preterm babies compared to manual expression for availability of expressed breast milk (EBM) volume when initiated within one hour of delivery.

METHODS

This was a non-blinded parallel group randomized control trial conducted in the postpartum ward of the obstetrics department and tertiary level neonatal intensive care unit (NICU) of our hospital between October, 2020 and May, 2021. All mothers delivering a live baby before 34 weeks of completed gestation, except mothers with recent breast surgery or any contraindications to breastfeeding, were eligible to participate in the study. The study was conduc-ted after approval from the institutional ethics committee. Mothers with gestational age <34 week (as per last mens-trual period or first trimester antenatal ultrasound), when planned for cesarean section or proceeding for vaginal delivery, were recruited in the study after taking written informed consent. All recruited mothers were re-counselled about advantages of breastmilk and need of breast milk expression within one hour of delivery, and then randomized into the two groups in the ratio 1:1 viz., Manual breastmilk expression (ME) group and Breast pump milk expression (PE) group.

Computer generated randomization was done and group assignment was placed in serial number for the calculated sample size; allocation concealment was done through opaque sealed envelope, that were opened prior to delivery. A non-electrical (pigeon) manual breast pump was provided to all mothers allocated to the PE group, immediately after delivery, which was free of charge for the first 7 days of postpartum period. Breast pump was autoclaved after each use. The Marmet technique was demonstrated to mothers allocated to the ME group. Mothers of both groups were assisted by delivery room nursing staffs and lactation educators for breast milk expression within one hour of delivery irrespective of the feeding status of their neonate. Each mother was explained the technique for milk expression through an educational video, verbal instruction, and hands-on support during initial three to four sessions of milk expression. Pumping every 2-3 hours with no more than a 5-hour break during the night (minimum 6 cycles a day for a minimum of 15 minutes each) was the scheduled frequency of the milk expression for mothers of both groups. The evening and night shift nur-sing staffs assisting in the study had ensured compliance with assigned milk expression method by monitoring mothers twice during their duty hours.

Each session comprised of sequential single breast milk expression with the manual pump (pigeon) in PE or Marmet technique in ME after maternal self or assisted breast massage. Milk was collected in a sterilized container and milk volume was measured with the help of syringe. A written log document 'milk diary' was maintained by all mothers that contained the time of expression, method of expression, and the milk volume obtained at each session throughout the initial seven postnatal days. Those mothers who failed to express at least three sessions per 12 hours, were counseled by a lactation nurse educator in a face-to-face session or telephonically under guidance of the principal investigator. During the non-availability of breast milk as per baby needs, pasteurized donor breast milk was used for enteral nutrition. Mothers were not given galactogogues during this period, irrespective of milk output. Participants were asked to exclusively use the assigned method of expression for the first 7 days after baby birth, and thereafter mothers of each group were free to choose any one or both of the methods for milk expression. Kangaroo mother care was provided to preterm neonates who were hemodynamically stable and not requiring intensive care management. The EBM volume on different postnatal days, cumulative EBM volume over first postnatal week of ME and PE were compared.

Maternal characteristics such as age, mode of conception, parity, educational qualification, working status, socioeconomic status (Kuppuswamy scale) were documented in a structured form. Maternal health status during pregnancy including gestational diabetes, hypertension, thyroid disorders, premature rupture of membranes, antenatal steroids was collected from maternal case records. Mode of delivery, initial timing of milk expression, frequency of milk expression was strictly monitored by designated delivery room nursing staff and postnatal ward nurse educator. Neonatal demographic characters like birthweight, gender, gestational age and type of feeding were recorded. Enteral nutrition of preterm neonates including trophic feeding and feed advancement were guided by NICU preterm feeding protocol.

In a previous RCT, comparing expressed breast milk volume between breast pump vs hand expression, the mean (SD) breast milk volume over 6 days pumping in group were 631.7 (426) mL and 419.6 (290.4) mL, respectively [7]. The expected sample size with equal number of cases in both arms, with a power of 90% at 99% confidence interval, was calculated to be 176. We recruited 170 participants during the study period (time allowed for student dissertation). Total 126 (63 in ME and 63 in PE) participants remained after drop out beyond randomization, this sample size satisfies 90% power with 95% confidence interval for this study purpose.

Statistical analysis: Comparison of EBM between two groups has been performed using Mann Whitney U test. Fisher exact test/Chi-square test has been used for comparing categorical variables between the groups. Both intention to treat analysis and per protocol analysis were done. Mothers whose 7 postnatal days expressed milk volume in ME and PE group were available were included for intention to treat analysis. A P value <0.05 was considered as statistically significant, and data were analyzed by SPSS version 25.0.

RESULTS

During the study period, a total of 170 preterm mothers with gestational age <34 weeks were delivered. After antenatal counseling and randomization, 83 mothers were allocated to PE group and 87 mothers in ME group. The complete seven postnatal days expressed milk volume data available in 71 mothers in ME and 66 mothers in PE group were analyzed by intention to treat analysis. Data of 63 mothers in ME group and 63 in PE group were subjected to per protocol analysis (**Fig.1**).

Total 146 preterm neonates were delivered from 126 mothers (40 being twin pregnancy). The mean (SD) gestation age and birthweight of neonates were 31.3 (2.5) weeks and 1381.6 (314.4) grams, respectively. Among these, 78 (53.4%) were females, and 84 (57.5%) neonates were delivered vaginally. Maximum neonates delivered

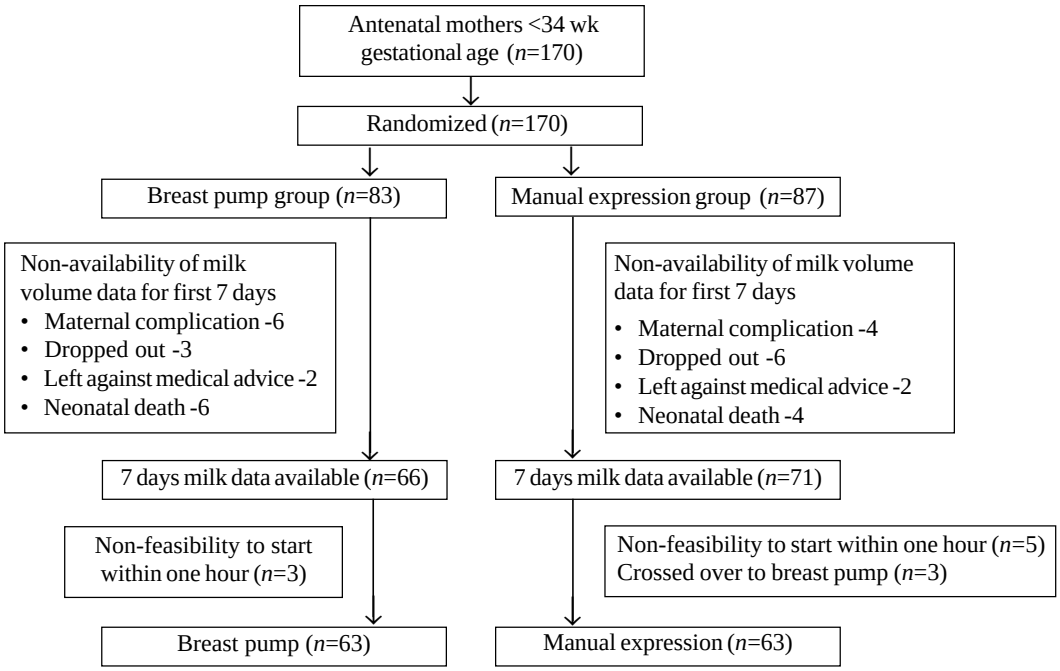

Fig. 1 Study flow diagram.

were between gestation age of 32-34 weeks (51.2%), followed by 28-32 weeks (33.7%).

The baseline maternal characteristics were comparable between the two groups (**Table I**). Both ME and PE groups were initiated with exclusively expressed breast milk on median (IQR) postnatal day 2 (1,2). The number of neonates receiving exclusive breast milk within first postnatal week in ME and PE groups were 56 (88.9%) and 58 (92%), respectively in per protocol analysis. The median EBM volume on different postnatal days and cumulative EBM of first postnatal week were comparable between ME and PE groups by both per protocol and intention to treat analysis (**Table II**).

DISCUSSION

In this study, with early initiation of milk expression using either manual or pump method, the availability of cumulative EBM volume over first postnatal week were similar. Majority of neonates (90%) in both groups were fed mother's own milk exclusively, and there were no significant difference in EBM volume on different postnatal days between the groups, for availability of colostrum and further enteral feed advancement.

The maternal demographic parameters, pregnancy related maternal morbidities, antenatal steroid exposure, frequency of milk expression per day and practice of KMC, which are known confounders towards milk production, were comparable between both groups [8,9].

Early milk expression behaves as a priming of breast tissue, increases hormonal production and influences lactogenesis [10]. The average EBM on day 2 as colostrum, day 7, and cumulative EBM during first postnatal week in this study is consistent with Parker, et al. [4] with initiation of milk expression within one hour of delivery. In comparison to a previous study from this center [11], the available EBM by seventh postnatal days was much higher, with introduction of earlier milk expression. Similarly, in a quality improvement study [12], the day 7 mothers' own milk volume in the intervention phase increased more than three-folds compared to observation period with prioritizing of early initiation of milk expression.

In a cross over study [13], higher volume of breastmilk was obtained through breast pump compared to manual expression and mothers preferred pump method in first postnatal week and manual method subsequently. Similarly, the EBM volumes in both electric and non-electric pump group were significantly higher than hand expression in a multicentric randomized controlled trial in Africa [7]. In another randomized controlled trial, where milk expression was initiated within six hours of birth, the cumulative EBM in first 7 postpartum days was significantly higher in electric pump group compared to manual expression among mothers of very low birth weight neonates [14]. However, in a randomized cross over study of preterm mothers, where milk expression was initiated after six hours of baby birth, more EBM volume was

Table I Maternal Characteristics in Manual Expression and Breast Pump Expression Groups

Maternal characteristics	*Manual expression (n=87)*	*Breast pump (n=83)*
Gestational age (wk)[a]	31.0 (2.57)	31.5 (2.45)
Pregnancy		
Singleton	67 (77)	57 (68.7)
Multiple	20 (23)	26 (31.3)
Primigravida	41 (47.1)	49 (59)
Mode of delivery		
Vaginal	57 (65.5)	50 (60.2)
Caesarean	30 (34.5)	33 (39.8)
Education		
Less than 10th grade	43 (49.4)	38 (45.8)
10th-12th grade	19 (21.9)	15(18.1)
Graduate	14 (16.1)	20 (24.1)
Postgraduate	11 (12.6)	10 (12)
Socioeconomic status (Kuppuswamy scale)		
Upper	9 (10.3)	5 (6)
Upper Middle	28 (32.2)	35 (42.2)
Lower Middle	32 (36.8)	24 (28.9)
Upper Lower	17 (19.5)	14 (16.9)
Lower	1 (1.1)	5 (6)
Occupation		
Homemaker	72 (82.8)	69 (83.1)
Working	15 (17.2)	14 (16.9)
Gestational diabetes	17 (19.5)	16 (19.3)
Thyroid disorder	19 (21.8)	12 (14.5)
PIH	25 (28.7)	28 (33.7)
Cardio-respiratory disease	2 (2.2)	3 (3.6)
PPROM	26 (29.9)	24 (28.9)
Antenatal steroids	54 (62.1)	56 (67.5)
Kangaroo mother care	14 (16.1)	16 (19.2)

Values in no. (%) or [a]mean (SD). PPROM: Preterm premature rupture of membrane; PIH: Pregnancy induced hypertension. All P>0.05.

obtained using manual expression over electric breast pump during early postpartum period [15]. The discrepancy could be explained by timing of initiation of milk expression, type of breast pump used, and the preterm maternal population characteristics. The advantage of early expression could nullify the benefit of pump, and hence timing of expression should be more prioritized towards availability of EBM.

To the best of our knowledge, this is the first randomized control trial comparing breast pump and manual expression, where sample recruitment and randomization was done prior to delivery, and milk expression was initiated within one hour of birth. The expressed milk volume is influenced by types of pump such as single or simultaneous pumping, electric versus foot-operated or manual pump, bilateral or single electric pump [16]. In this study, manual breast pump was used, and hence results may not be generalizable to other pump types. The study was conducted during the COVID-19 pandemic, so there were many mothers who were counseled virtually rather than face-to-face.

The aggressive enteral nutrition practice for preterm neonates is crucial in early postnatal days. As hand expression is as good as expression by manual pump, we advocate to initiate milk expression, using either manual or pump method at the earliest period after delivery to maximize breast milk for preterm infants. The decision regarding method for preterm milk expression during initial days may be based on maternal choices. Antenatal breast milk counselling and provision of lactation support immediately after birth is the need of the hour.

Ethics clearance: IEC, KIMS Hospital; No. KIMS/KIIT/IEC/521/2020 dated Dec 08, 2020.

Table II Expressed Breast Milk Volume (in mL) in Manual Expression and Breast Pump Expression Groups of Mothers of Preterm (<34 week) Neonates in First Postnatal Week

Postnatal days	*Intention to treat analysis*			*Per protocol analysis*		
	Manual expression (n=71)	*Breast pump expression (n=66)*	*P value*	*Manual expression (n=63)*	*Breast pump expression (n=63)*	*P value*
Day-1	2 (0.5, 5)	3.5 (1, 8.5)	0.09	2 (1, 6)	4 (1, 9)	0.06
Day-2	10 (5, 18)	11(5, 27.5)	0.32	10 (5, 20)	12 (5, 28)	0.10
Day-3	40 (30, 50)	46 (35, 64.5)	0.09	40 (34, 52)	47 (39, 65)	0.10
Day-4	80 (55, 110)	86.5 (60, 113.5)	0.28	85 (65, 110)	90 (65, 115)	0.20
Day-5	120 (86, 185)	137 (90, 185.25)	0.46	120 (90, 186)	140 (94, 186)	0.50
Day-6	185 (145, 255)	200 (141.5, 275)	0.59	190 (150, 256)	210 (150, 275)	0.70
Day-7	270 (205, 347)	275 (217.5, 352.5)	0.49	280 (220, 356)	280 (220, 360)	0.66
Milk volume[a]	703 (593, 935)	759 (571, 1002)	0.56	733 (593, 995)	848.5(571,1009)	0.55

Data in median (IQR). [a]Cummulative milk volume.

WHAT IS ALREADY KNOWN?

- Breast pump is used as a rescue modality during lactation failure with manual expression in preterm mothers.

WHAT THIS STUDY ADDS?

- With early milk expression, manual method is comparable with pump expression for availability of breast milk in preterm mothers.

Contributors: AD: data collection and methodology; SSB: manuscript editing and revising it for intellectual content; SKP: development of concept, critical input in the manuscript. All authors approved the final version of the manuscript.
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RESEARCH PAPER

Risk Factors for Catheter-Associated Urinary Tract Infections (CA-UTI) in the Pediatric Intensive Care Unit

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Objective: To describe the occurrence, microbiology, and risk factors of catheter-associated urinary tract infections (CA-UTI) in critically ill children. **Methods:** We conducted a review of hospital records for CA-UTI in the pediatric intensive care unit (PICU) over a 7-year period (2014-2020). **Results:** 62 CA-UTI cases (48% boys, median (IQR) age 36 (12,96 month) were identified during the study period with occurrence rate of 7.2/1000 catheter-days. The most common organisms were *Escherichia coli* (32.4%) and *Enterococcus faecalis* (30.6%). Using a multivariate logistic regression analysis, the significant associated variables for CA-UTI were duration of catheter drainage (a OR (95% CI) 1.14, (1.03,1.27), *P*=-0.009), PICU stay (aOR (95% CI) 1.13 (1.05,1.21) (*P*<0.001), and hospital stay (aOR (95% CI): 1.03 (1.01,1.06), *P*=0.015). **Conclusion:** CA-UTI is not an uncommon nosocomial infection in PICU. The risk increases with increasing duration of catheter drainage, and hospital or PICU stay.

Keywords: *Causes, Organisms, Outcome, Urinary catheterization*.

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Catheter-associated urinary tract infections (CA-UTI) are one of the most common nosocomial infections, accounting for 30% of healthcare-associated infections [1]. The most important predictor for CA-UTI is the duration of catheterization [2]. The acquisition of CA-UTI is associated with a three-fold increase in mortality, and with longer duration of mechanical ventilation, hospital stay and healthcare charges [3,4].

Despite multiple studies in adult literature, little is known about CA-UTI in critically ill children, especially from India. Therefore, we conducted this study to describe the occurrence, microbiology, and risk factors of CA-UTI in critically ill children admitted to the pediatric intensive care unit (PICU).

METHODS

In this case-control study, we reviewed hospital records of all patients (1month to 18 years) with CA-UTI admitted at our 12-bedded tertiary care PICU between January 1, 2014, and December 31, 2020. Clearance of the study with waiver of informed consent was obtained from the institutional review board. Patients were identified from PICU clinical database, hospital infection committee register, and electronic hospital records entered to data abstraction forms. A CA-UTI was defined as per diagnostic criteria of the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) [5]. The patients either had a urinary catheter placed for more than two consecutive days with fever (>38°C), and a quantitative culture with significant growth (≥10^5 colony forming units (CFU)/mL) of one or two micro-organisms present. Duplicate cultures and those with contaminants were eliminated from the analysis. A sample was considered contaminated if more than two types of micro-organisms were isolated [6]. Apart from demographic characteristics, details of causative pathogen, their susceptibility to commonly used antibiotics were collected from the microbiology laboratory reports. The CA-UTI rate per 1000 catheter-days was calculated by dividing the number of CA-UTI episodes by the number of catheter-days and multiplying the result by 1000.

To identify risk factors that may contribute to infection, CA-UTI patients were individually matched 1:2 by gender and age (±2 year) to those with a urinary catheter but did not experience CA-UTI (control group) within the study period. The PRISM-III score was used to match for severity of illness, and case matches were matched to within ± 10 points at admission [7].

Statistical analysis: All parameters were compared between CA-UTI and control groups by independent *t*-test/Mann-Whitney test in case of continuous variables, and chi-square/Fisher exact test in case of categorical variables. A univariate followed by multivariate logistic regression was conducted to estimate the effects of PICU stay, hospital stay and catheter days on CA-UTI adjusted for significant

factors across the groups. A *P* value <0.05 was considered as significant. The statistical software R version 4.0.3 (R Core Team, 2021) was used for data analysis.

RESULTS

Among 1488 catheterizations during the study period, 62 CA-UTI were identified after excluding five patients [duplicate cultures (*n*=3), asymptomatic colonizer (*n*=1) and contaminants (*n*=1)]. The overall CA-UTI occurrence rate was 7.2/1000 catheter-days [6.9 (2014 calendar year), 5.3 (2015 calendar year), 5.6 (2016 calendar year), 4.7 (2017 calendar year), 8.9 (2018 calendar year), 7.8 (2019 calendar year), and 4 (2020 calendar year)]. While two-third (73.3%) of CA-UTI cases had one indwelling urinary catheterization during their hospital stay, 26.7% had ≥2 indwelling urinary catheterizations.

The median (IQR) age of the study population was 36 (12, 96) month and 48% were males. Sixty-two patients with CA-UTI were then matched to 120 control patients. Demographic profile of the cases and controls are described in **Table I**. The potential risk factors like neurogenic bladder and surgical procedure did not have an influence on acquiring CA-UTI, except for patients with congenital anomalies of genitourinary tract (14.5% vs 3%, *P*=0.004). The mean (SD) length of PICU stay [7.2 (2.2) vs 4.8 (2) days; *P*<0.001] and hospital stay [15.3 (2.3) vs 10.6 (2.2) days; *P*=0.012] among children with CA-UTI was longer than control group. CA-UTI patients were more likely to have catheters in place for a longer period compared to control group [mean (SD) 5 (4.29) vs 3.3 (2.8) days; *P*= 0.01].

Both in univariate analyses and multivariate analyses, none of the potential risk factors that could increase the risk of UTI influence CA-UTI rates compared to control patients. Using a multivariate logistic regression analysis, the three variables associated with acquiring CA-UTI were duration of catheter drainage [aOR (95% CI) 1.14 (1.03,1.27); *P*=0.001], PICU stay [aOR (95% CI) 1.13 (1.05,1.21); *P*=0.001], and hospital stay [aOR (95% CI) 1.03 (1.01,1.06); *P*=0.015] (**Table II**). The odds of CA-UTI occurrence increased by 14% for each additional day the catheter remained in situ.

Table I Baseline Characteristics of Children in the Pediatric Intensive Care Unit Enrolled in the Study

Characteristic	*CA-UTI (n=62)*	*Non-CA-UTI (n=120)*
Age[a]	36 (12,96)	42 (14,84)
Male	30 (48.4)	58 (49)
PRISM III[b]	7.2 (5.5)	7 (4.2)
Potential risk factors		
CAKUT [c]	9 (14.5)	3(2.5%)
History of neurogenic bladder	3 (6.2)	2(1.7)
Surgical procedures	6 (9.8)	9(7.6)
Hemoglobin (g/dL)[b]	9.7 (2.47)	10.1 (1.43)
Total WBC ($\times10^9$/L)[a]	13.59 (6.7,18.56)	15.74 (8.76,18.7)
Platelets[a] ($\times10^9$/L)	220 (94,3.13)	272 (1.0,4.03)
Catheter days [b,c]	5 (4.29)	3.3 (2.8)
PICU length of stay (d)[b,d]	7.2 (2.2)	4.8 (2)
Hospital length of stay (d) [b,c]	15.3 (2.3)	10.6 (2.2)
Mortality	11 (17.7)	10 (8.3)

Data presented as no. (%), [a]median (IQR) or [b]mean (SD). [c]P<0.05; [d]P=0.001. CA-UTI: catheter associate urinary tract infection, CAKUT: congenital anomalies of the urinary tract; PICU: pediatric intensive care unit; PRISM: pediatric risk of mortality; WBC: white blood count.

The most common isolated organisms were *Escherichia coli* (32.4%), *Enterococcus faecalis* (30.6%), *Klebsiella pneumoniae* (9.6%), candida non-albicans (13%), *Candida albicans* (3.2%), and pseudomonas (4.8%) (**Fig.1**). Gram-negative infections were multidrug-resistant with limited sensitivity to piperacillin-tazobactam (40%) and meropenem (60%), and maximum sensitivity to aminoglycosides (70%) and colistin (90%) (**Web Fig 1a** and **1b**).

DISCUSSION

In this study conducted in critically ill children, the occurrence rate of CA-UTI was 7.2/1000 catheter days, slightly higher than other studies [8,9]. The occurrence of CA-UTI varied from 4 to 8.9/1000 catheter days from 2014-2019, dropping again to 4/1000 catheter days in 2020. The

Table II Risk Factors for Catheter-Associated Urinary Tract Infection

Variable	*OR (95% CI)*	*P value*	*aOR (95% CI)*	*P value*
CAKUT	6.2 (1.53, 25.14)	0.004	0.66 (0.08,5.23)	0.696
Catheter days	1.13 (1.02,1.26)	0.013	1.14 (1.03,1.27)	0.009
PICU stay[a]	1.1 (1.04,1.17)	<0.001	1.13 (1.05,1.21)	<0.001
Hospital stay[a]	1.03 (1.01,1.06)	0.016	1.03 (1.01,1.06)	0.015

CAKUT: congenital anomalies of kidney and urinary tract; PICU: pediatric intensive care unit. [a]Length of stay.

WHAT THIS STUDY ADDS?

- Longer duration of catheter drainage, longer pediatric intensive care unit (PICU) stay, and longer hospital stay were the three major risk factors for catheter-associated urinary tract infections in children admitted to a tertiary level PICU.

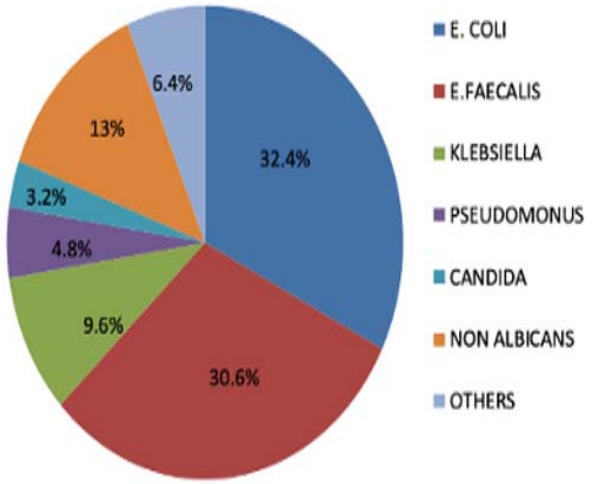

Fig. 1 Various pathogens isolated causing CA-UTI among children in the pediatric intensive care unit (*n*=62).

lower rate of CA-UTI in the last year of the study is likely due to the introduction of quality-improvement initiative to reduce hospital-acquired infections in that year.

Previous studies have also reported male preponderance in their cohort [10,11]. However, Goudie, et al. [12] published a study with a similar demographic profile as our group with females experiencing CA-UTI and a high incidence among children between 1- 4 years of age. Similar to our results, other authors have also shown strains of MDR Gram negative bacteria causing CAUTI [13,].

Factors associated with CA-UTI, identified in our study, have also been previously reported [12,14]. The duration of catheterization appeared to be contributing additively to the odds of the occurrence of CA-UTI, with an 14% increase in odds for each consecutive day that the catheter was left in place. The data is consistent with the adult study by Lo, et al. [2], which showed a 3-7% risk of bacteriuria for every additional day the catheter is left in place [2]. The relationship between length of stay and duration of catheterization with risk for CA-UTI has also been described in previous adult study [15].

Our study has inherent limitation of case-control design. Due to this limitation, we were unable to evaluate for potential confounding risk factors for CA-UTI, including antibiotic exposure, prior hospitalizations, and urinary tract infections, especially if patients sought their care at other institutions. Although these patients were found to have longer PICU stay and hospital stay, with presumed CA-UTI, it was difficult to determine whether these effects were due to the primary disease or the UTI.

CA-UTI is not an uncommon hospital acquired infection with common pathogens being *E. coli* and *E. faecalis.* The three most common risk factors for acquiring CA-UTI were duration of catheter drainage, length of PICU stay and hospital stay. Further research is needed to elucidate the factors associated with CAUTIs among critically ill children.

Ethics clearance: IEC, St John's Medical College; No. 94/2019 dated March 14, 2019.
Note: Additional material related to the study is available with the online version at *www.indianpediatrics.net*
Contributors: LAV: contributed to data collection, analysis of the data and writing of the manuscript. MP: contributed to study design, analysis of data and writing of the manuscript; SV: contributed to critical review of the manuscript; and SG: contributed to statistical analysis and review of the manuscript. All authors approved the final version of manuscript and are accountable for all aspects related to the study.
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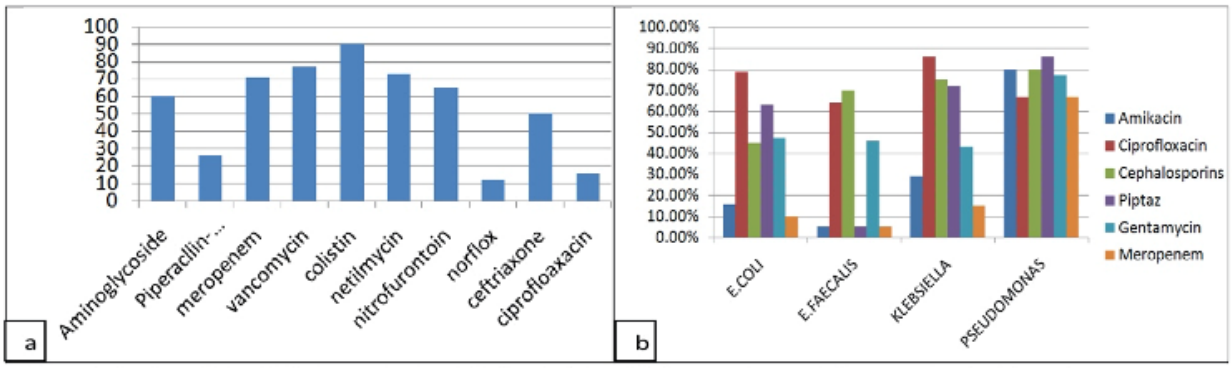

Web Fig. 1 *a)* Antibiotic sensitivity and *b)* resistance pattern among different microbes isolated from children with catheter-associated urinary tract infections in the pediatric intensive care unit.

RESEARCH PAPER

Outcome of COVID-19 in Children With Tuberculosis: Single-Center Experience

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Objective: To evaluate the outcome of Coronavirus disease 2019 (COVID-19) infection in children and adolescents with tuberculosis. **Methods**: We analyzed hospital records for the period May, 2020 to September, 2021 for children who were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase-polymerase chain reaction (RT-PCR) positive or SARS-CoV-2 antibody positive. They were divided into two groups viz., those with tuberculosis (tuberculosis group) and those without tuberculosis (non-TB group). Demographic information, symptoms, and outcomes of COVID-19 were compared between the two groups. **Results**: Median (IQR) age of participants was 11 (8,14) and 4.5 (2,9) year for the tuberculosis and non-TB groups, respectively. 93.5% and 36.1% of children were asymptomatic in the tuberculosis and non-TB group, respectively. No variable in the study was significantly associated with COVID-19 positivity in children with tuberculosis. No difference was found in the outcomes of COVID-19 infection in children having tuberculosis. **Conclusions**: No differences were noted in the outcomes of COVID-19 infection in children having tuberculosis.

Keywords: *Co-infection, Diagosis, Presentation, Severity*.

Coronavirus disease 2019 (COVID-19) is a contagious disease with varied presentations, ranging from asymptomatic or mild features to acute respiratory distress syndrome leading to death. Co-infection of severe acute coronavirus 2 (SARS-CoV-2) with other micro-organisms appears to pose a significant challenge for the management and prognosis of COVID-19 infected patients, one such association being with *Mycobacterium tuberculosis* [1]. In 2020, tuberculosis was the commonest cause of death caused by a single infectious pathogen, and India accounted for 26% of the global tuberculosis cases [2]. Of the worldwide tuberculosis, 16% cases were accounted for by children <15 years of age [2].

Only a few studies have highlighted the association between tuberculosis and COVID-19. Having a reliable estimate of the association between tuberculosis and COVID-19 severity, and outcomes is crucial to ensure appropriate strategies for these patients. In this study, we have evaluated outcomes of COVID-19 infection in children and adolescents with tuberculosis.

METHODS

We extracted hospital records of children with tuberculosis (both new and those on treatment) and those without a tuberculosis diagnosis, attending the outpatient and inpatient department between May, 2020 and September, 2021. All the patients were tested with reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 detection at presentation. Those negative on RT-PCR were tested for SARS-CoV-2 nucleocapsid antibody levels in serum, which in the absence of a vaccination mandate for children up to 18 years of age, was considered to indicate a sub-clinical exposure to SARS-CoV-2. As per the directives from the National tuberculosis Elimination Programme (NTEP) [3], all patients with tuberculosis had to be mandatorily screened for COVID-19 and vice versa.

After approval from the institutional ethics committee, the demographics, anthropometry, history, symptomatology, vaccination status, investigations, and outcomes were recorded on a pre-designed proforma, along with a history of close contact with a confirmed SARS-CoV-2 positive index case. Complete blood counts, liver and renal profile, chest *X*-ray, and sputum/gastric aspirate for cartridge-based nucleic acid amplification test (CBNAAT) were done for all tuberculosis patients (as per NTEP guidelines). Additionally, MGIT cultures along with line probe assay (LPA) for drug resistance testing and phenotypic drug sensitivity testing (DST) were done, wherever applicable. The antibody test was done by ECLIA (enhanced chemiluminescence immunoassay).

Statistical analysis: Data were compiled in a Microsoft office excel sheet and analyzed with IBM SPSS 26.0. Chi-square test was used to test the association between categorical variables. Kolmogorov-Smirnov test was used to test the normality of the data. If the normality was rejected, then non-parametric tests for significance were used. For factors associated with SARS-CoV-2 positive status in children with tuberculosis, bivariate logistic regression analysis was applied while adjusting for potential confounders. A *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 137 (35% males) and 154 (59.1% males) children were enrolled in the TB and non-TB groups, respectively. The baseline characteristics of the participants in the two groups are shown in **Table I**.

Out of 137 patients with tuberculosis, 108 had either a positive RT-PCR or COVID-19 antibodies. Of these 108 children, the majority (93.5%) were asymptomatic. Out of seven symptomatic children, five had a fever, one had a cough, six had increased respiratory activity, two had lethargy, and one had vomiting with abdominal pain. In the non-TB group, 111 children were RT-PCR positive, and 11 were antibody positive, with fever being the most common symptom in 78 children, followed by cough in 65; 36.1% children were asymptomatic. A history of close contact with the SARS-CoV-2 positive index case was found in 10 (9.3%) children in the TB group and 15 (12.3%) children in the non-TB group.

In the TB group, 106 patients with evidence of COVID-19 recovered completely, whereas two patients died. In the Non-TB group, 118 patients recovered completely, and four died. The two deaths in the TB group were patients with disseminated multi-drug resistant tuberculosis. Upon comparing the outcomes of COVID-19 in both groups, there was no difference in mortality risk of COVID-19 infection in children having tuberculosis as compared to those without tuberculosis [RR (95% CI) 0.56 (0.09 – 3.10); *P*=0.50].

Table I Characteristics of Children With COVID-19 With or Without Tuberculosis Enrolled in the Study

	TB group (n=137)	*Non-TB group (n=154)*
Age[a] (y)	11 (8,14)	4.5 (2,9)
Females gender	89 (65)	63 (40.9)
RT-PCR Positive	6 (4.3)	111 (79.3)
COVID-19 Antibody positive	102 (74.4)	11 (7.69)
Neither Antibody nor RT-PCR Positive	29 (21.2)	32 (12.9)

Data in no. (%) or [a]median (IQR). Mortality rate was 1.85% in children with tuberculosis (TB) as compared to 3.27% in non-TB group (P>0.05).

DISCUSSION

Majority of children with tuberculosis were asymptomatic for COVID-19, as also reported previously. Amongst those with symptomatic COVID-19 and tuberculosis, cough and fever were the predominant symptoms. Several studies have shown that the most common presentation of COVID-19 infection is fever and cough [4,5].

Similar to a previous Indian study [6], we also found <5% of children with tuberculosis infected with SARS-CoV-2. A study on mouse models [7], where activation of a stem cell defence mechanism accelerated the activation of dormant tuberculosis, indicates a poten-tial increase in active tuberculosis post-COVID-19 infection.

A meta-analysis reported a 2.1-fold increase in severity of COVID-19 in those with tuberculosis, although it was not statistically significant [8]. Liu, et al [9]. studied the severity of COVID-19 in 36 patients with tuberculosis in which 78% patients were in the severe/critical category, while mild/moderate cases were just 22% of the total, which was in contrast with our study. However, all these studies have focused only on adult population, in whom the incidence of other co-morbidities is also high.

In both groups, the majority of the mild cases recovered only with symptomatic treatment. The use of immunosuppressive drugs for COVID-19 remains an area of concern, as it can potentially increase the risk of reactivation of latent tuberculosis. In our study, amongst those children who died, only two children were treated with remdesivir and steroids were used in nine children.

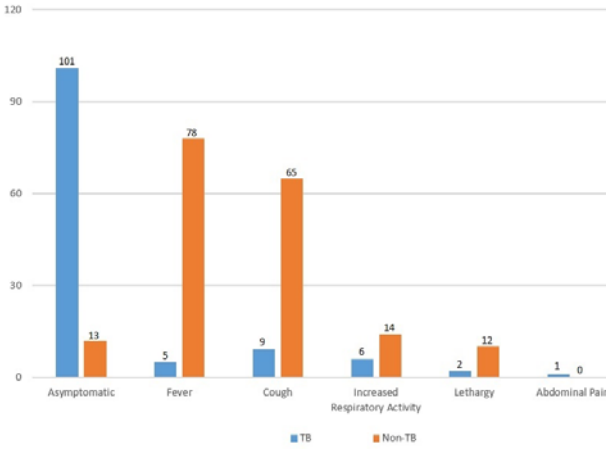

Fig. 1 Symptoms of COVID-19 in children with (TB) and without TB (non-TB).

WHAT THIS STUDY ADDS?

- No difference was noted in the outcome of SARS-CoV-2 infection in children with and without tuberculosis.

No difference was noted in the outcome of SARS-CoV-2 infection in children with or without tuberculosis in this study, as also seen in other studies around the world.

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Contributors: All authors were involved in concept and designed the study, collected and analyzed data, and drafted, revised the manuscript the manuscript. All authors approve the present version for publication, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Comparison of Continuous Real Time Blood Glucose Measurement With Venous Laboratory Blood Glucose Level in Neonates During Perioperative Period

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Objective: To compare the continuous real time blood glucose (CG) measurement with venous laboratory blood glucose (LG) level in neonates during perioperative period.

Methods: Glucose levels were measured simultaneously by CG, glucometer glucose (GG) and LG at 40 time points in ten neonates during perioperative period. Intraclass correlation coefficient (ICC) and Bland Altman analysis were used for comparison.

Result: Correlation between CG and LG was excellent (ICC= 0.953; *P*<0.001), and average difference was 23.8 (95%CI 52.9 to -5.3) mg/dL, showed better reliability than at hyperglycemic state (ICC=0.653; *P*=0.006). The GG-LG showed excellent reliability with ICC = 0.985; *P*<0.001 and average difference of 15.4 (95% CI 30.7 to 0.1) mg/dL. CG at euglycemic state (ICC= 0.880; *P*<0.001).

Conclusion: CG measurement is reliable for blood sugar estimation in neonates; but has lower reliability for hyperglycemia. The continuous trend of glucose measurement by CG is helpful for timely diagnosis of hyperglycemia during perioperative period in neonates.

Keywords: *Hyperglycemia, Hypoglycemia, Surgery*.

Both hypoglycemia and hyperglycemia are dangerous to the neonatal brain [1,2]. Neonates undergoing surgery are at high risk for hyperglycemia during post-operative period and it increases the length of hospital stay [3]. Continuous glucose (CG) monitoring has the advantage of providing continuous instantaneous blood glucose level, avoiding multiple blood sampling [4]. Till date CG monitoring is not approved for blood glucose testing in routine neonatal practice. In this context, we planned to compare the blood glucose level by CG monitoring with laboratory blood glucose (LG) testing in neonates during perioperative period.

METHODS

This was a single center prospective observational study conducted over four months period in a tertiary level neonatal intensive care unit between January, 2022 and April, 2022. The study was started after approval of the institutional ethical committee, and written informed parental consent was taken prior to enrollment.

CG monitoring is a newer invasive method for blood glucose estimation in neonates with possible risk of infection and pain at insertion site. As neonates undergoing operative procedures are at high risk of hyperglycemia and remain under coverage of antibiotics and analgesics, the accuracy of this device has been tested in them.

Neonates born at term gestation (≥ 37 weeks) within 28 days postnatal age, and neonates born at < 37 weeks till discharge from hospital, were eligible for enrolment. Neonates undergoing any operative procedure under anesthesia were enrolled, and neonates with dysglycemic states (blood glucose level >150 mg/dl or < 40 mg/dL) before surgery were excluded.

Continuous glucose (CG) monitoring was measured by Free Style Libre System (Abbott), consisting of a reader and sensor kit. This device does not need repeated calibration (factory calibrated) and reading accuracy persists for two weeks [5]. The glucose value was obtained from subcutaneous tissue by an enzymatic amperometric three-electrode sensor system. After skin disinfection with ethanol swabs, the sensor was placed into the subcutaneous tissue on the lateral part of thigh or arm of the newborn, at least 2 hours prior to shifting to the operation theatre and kept for 72 hours of post-operative period. Continuous blood glucose measurement in CG reader was started one hour after the insertion of sensor. The reader was placed in a bag near the patient side and blood glucose level was recorded on hourly basis by bedside staff nurse. The sensor insertion site was frequently monitored for skin infection, and thrombophlebitis by bedside nurses and residential doctors.

The blood glucose values by bedside intermittent glucometer glucose (GG), (ACCU –CHEK Roche Diabetes Care India Pvt. Ltd.) were measured from capillary blood

samples by pricking lateral part of heel by 26G needle after proper disinfection with ethanol swabs. For laboratory estimation of blood glucose (LG), 2 mL venous blood was taken in a Sodium Fluoride container and analyzed by hexokinase method in the institutional central laboratory. GG was measured one hour prior to surgery and every six hourly during the three post-operative days as routine care. The venous sampling was done at four time points (one hour prior to surgery; at 0-2,24-26,48-50 hours of post-operative period). For the comparison, simultaneous blood glucose level measured by CG vs GG vs LG were taken for analysis. Bedside GG testing was done immediately prior to venous sampling and maximum care was taken for laboratory blood glucose estimation within 30 minutes of phlebotomy. Neonates were managed as per the blood glucose level in GG readings. The blood glucose values were mentioned as mg/dL and laboratory blood glucose (LG) is considered as reference test. Laboratory blood glucose level >150 mg/dl was considered as hyperglycemia and <40 mg/dL as hypoglycemia [6].

Assuming the minimum acceptable reliability of CG monitor Intraclass correlation coefficient (ICC)=0.8, with expected reliability ICC=0.9 and number of repetition per subjects =4; with significance level 95% and power 80%, the calculated sample size was 36. Assuming 10% drop out rate, the final sample size was 40 [7].

Statistical analysis: Continuous variables were expressed as mean (SD) and categorical variables as frequency (%). The reliability index between two different methods (CG-LG, GG-LG, CG-GG) for glucose measurement was analyzed by Intraclass correlation coefficient (ICC) [8] ICC values <0.5,0.5-0.75,0.75-0.9 and >0.9 were considered as poor, moderate, good and excellent reliability respectively. The agreement between glucose level by two different methods was also analyzed by Bland Altman analysis plot [9]. Data were analyzed by software IBM SPSS version 20.0 (IBM Corp). A *P* value <0.05 was considered to be statistically significant.

RESULT

The study included 10 consecutive neonates undergoing surgery (6 gastrointestinal surgeries, 2 neural tube defect repairs, 1 palliative surgery for complex congenital heart disease and 1 urological disorder). Simultaneous blood glucose level by CG monitoring, GG and LG were measured at 40 time points. The detail baseline characteristics of neonates are presented in **Table I**.

CG monitoring showed excellent reliability with LG (ICC= 0.953; *P*<0.001). The average difference between CG-LG was 23.8 (95% CI 52.9, -5.3) mg/dL, and 92% of the data points remained within both arms of Bland Altman analysis.

During euglycemia (27 paired observations), CG monitoring showed good reliability with LG (ICC=0.880; *P*<0.001) and the average difference between CG-LG was 19.2 (42.8, 4.4) mg/dL. However, during periods of hyperglycemia (*n*=13 paired observations), CG monitoring showed moderate reliability with LG (ICC=0.653; *P*=0.006) and average difference between CG-LG was 33.4 (64.7, 2.1) mg/dL. None of the neonates had local infection or thrombophlebitis at CG monitoring device insertion site.

The intraclass correlation coefficient between GG and LG was 0.985; *P*<0.001, the average difference between GG-LG was 15.4 (95% CI 30.7, 0.1) mg/dL in Bland Altman analysis. The average difference between CG and GG was 8.4 (95% CI 37.8, 25) mg/dL and the ICC was 0.956; *P*<0.001.

DISCUSSION

This study showed excellent reliability between CG monitoring and laboratory testing for glucose measurement in neonates. Bedside glucometer monitoring is more reliable over CG monitoring for blood sugar estimation, however CG could provide the continuous trend information.

Previous studies have demonstrated a good agreement between CG and bedside glucometer recordings in preterm neonates and more time spent in euglycemia with CG monitoring [10,11]. In another study, closed loop automated insulin delivery with CG monitor device helped in reducing dysglycemic state in preterm infants [12]. Recently the safety and feasibility of CG monitoring for detection of hypoglycemia in neonates of diabetic mothers has also been studied [13]. Historically, laboratory blood glucose has been considered as the gold standard, and bedside intermittent glucometer is used as point of care in patient management [6]. The accuracy of CG monitoring device is in congruence

Table I Baseline Characteristics of the Study Population

Characteristics	*Value*
Birth weight (g)	2228 (755)
Gestational age (wk)	34.3 (3.46)
Cesarean section[a]	6 (60)
Preterm neonates[a]	7 (70)
Male[a]	5 (50)
Age at surgery (d)[b]	19 (3,26)
Neonatal temperature (°C)	36.6 (0.2)
Time in operation theater, h	3.25 (0.75)
Blood glucose CG monitoring, mg/dL	138.55 (53.23)
GG, mg/dL	130.15 (47.89)
LG, mg/dL	114.7 (43.73)
Time gap between CG-LG, min[b]	27.5 (16, 30)

Mean values (SD), [a]no. (%) or [b]median (Q1, Q3). CG- continuous glucose; GG- glucometer glucose; LG- laboratory glucose.

WHAT THIS STUDY ADDS?

- The reliability between continuous real time glucose monitoring device and laboratory testing is excellent for glucose measurement; however, this may or may not be applicable for identifying hyperglycemia.

with previous studies, and the variation in bias level among different studies could be explained by differences in the sensor and the different glycemic ranges [14,15]. The CG monitoring device used in previous study needs frequent sensor calibration on daily basis [14]. The advanced technology in the instrument used by us provides sensor stability and eliminates repeated calibrations [5,15].

The differences between CG and LG were more during hyperglycemic states as compared to periods of euglycemia. Hence, accurate diagnosis of hyperglycemia may not be concluded from a single reading of CG monitoring device, rather trend of glucose reading may direct point of care testing or response to treatment of hyperglycemia. However, the bias in Bland Altman analysis could help in interpretation of blood glucose level from CG monitor device readings.

In perioperative neonates, the adverse effect of subcutaneous invasive electrodes of CG monitoring may be masked by co-administration of analgesics and antibiotics. The accuracy of CG monitoring during periods of hypoglycemia not evaluated in this study. Further randomized control studies are needed to explore the clinical benefit of CG monitoring for timely addressing the hyperglycemic events in neonates in postoperative period, and other high risk neonates during intensive care treatment.

The study results have applicability for neonatal population particularly extreme preterm, neonates in peri-operative period and those at risk of hyperglycemia. Our study validated the utility of CG monitoring device for glucose measurement in neonates and can be used for identification of dysglycemia during perioperative periods. Further studies and innovations in CG monitoring devices may be useful in neonatal intensive care unit in the near future.

Ethics clearance: IEC, KIMS; No. KIMS/KIIT/IEC/799/2022 dated Jan 13, 2022.
Contributors: SKP: conceptualization, critical inputs to manuscript writing and supervision. MAW: principal investigator, data collection and writing manuscript. SSB: analysis and vital inputs to manuscript writing. SS: data collection and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Serum Magnesium Levels in Children With and Without Migraine: A Cross-Sectional Study

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Objective: To study the association between serum magnesium level and migraine in children. **Methods:** This cross-sectional study enrolled children aged 5–18 years diagnosed with migraine, and age- and sex-matched controls without a headache disorder. International Classification of Headache Disorders 3 **(**ICHD-3) was used for the diagnosis of migraine. The association between serum magnesium level and migraine headache was analyzed. **Results**: A total of 35 children with migraine were enrolled with 35 control subjects. The median (IQR) serum magnesium levels were comparable among children with migraine and controls [2.0 (2.0,2.1) vs 2.2 (1.9, 2.2) mg/dL; *P*=0.23], respectively. In adolescent subgroup, median (IQR) serum magnesium levels were significantly low among the children with migraine as compared to those without migraine [2.0 (1.9, 2.1) vs 2.2 (2.0, 2.2 mg/dL); *P*<0.045]. **Conclusion:** We found a statistically significant association between low serum magnesium levels and the occurrence of migraine in adolescents, which may have treatment implications.

Keywords: *Adolescents, Diagnosis, Headache, Supplementation.*

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Migraine is a common cause of headache in children, particularly during adolescence [1]. The International Classification of Headache Disorders beta 3 version (ICHD-3) is currently used for the diagnosis of migraine [2]. Magnesium plays a key role in the active transport of ions across neuronal membranes [3]. Low serum magnesium can increase neuronal irritability. Reduced magnesium levels can lead to opening of calcium channels, increased intracellular calcium with release of glutamate, and increased extracellular potassium, which cause cortical spreading depression (CSD) leading to migraine [4].

Serum magnesium levels have been shown to be significantly lower among adults with migraine as compared to controls [5]. Although, there are similarities in the clinical presentation among children and adults, the treatment approaches differ [6,7]. There is limited information on serum magnesium levels among children with migraine, as it may have treatment implications. [8]. Hence, we studied the association between serum magnesium levels and occurrence of migraine among children and adolescents.

METHODS

This cross-sectional study with controls was done between 1 July, 2018 and 31 March, 2020, in the pediatric department of a tertiary care hospital, after permission from the institutional ethics committee. Children aged 5 to 18 year with headache were screened and those diagnosed with migraine were enrolled after getting informed consent from the parents, and assent from the adolescents aged 12 years and above. Based on the previous adult study with the mean (SD) serum level of magnesium of 1.86 (0.41) mg / dL in cases and 2.10 (0.23) mg/dL in controls, the sample size calculated was 29 rounded up to 35, with power of 80%, alpha error of 5%, and with effect size of 0.76 [5].

A detailed history and physical examination of children with headache was performed as part of the routine evaluation, with ophthalmological, ear, nose and throat examinations to exclude secondary headaches as per the standard of care [9]. The diagnosis of migraine was made as per ICHD Beta-3 classification, which was independently confirmed by a pediatric neurologist. Weight was measured using digital weighing scale with minimal clothing and barefoot. Height was measured using a stadiometer. Body mass index (BMI) was calculated as per standard formula. The interpretation of the nutritional status was done using revised IAP growth charts, 2015 for both genders [10]. Blood pressure was measured in the left upper arm with a sphygmomanometer, in sitting position, using the appropriate cuff size. Those with chronic illnesses (renal, cardiac, respiratory, and gastrointestinal disorders), malnourishment in the form of underweight or overweight/ obesity, and on magnesium supplements, were excluded.

A venous blood sample of 3 mL was collected from each participant, during the period of normalcy (without an acute headache episode), and serum magnesium level was measured using Xylidyl blue method by automatic analyzer (Beckman Coulter - AU5800). Age- and sex-matched controls were selected from the pediatric outpatient department on the same day, and blood samples for serum magnesium levels were collected after informed consent, and assent, if appropriate. These children were not on any magnesium supplements and had normal BMI. Age was matched with an accepted maximum of 3 months difference between the cases and controls. The serum magnesium levels were informed to the participants, and management was planned for those with hypomagnesemia. Hypomagnesemia was defined as serum magnesium concentration <1.8 mg/dL.

Statistical analysis: The association between serum magnesium level in children with migraine and controls was analyzed and a sub-group analysis for adolescents (10-18 years) was performed. We used SPSS version 20.0 for analysis. Shapiro-Wilk test was performed for testing the normality of the data. Non parametric statistical analysis using Mann-Whitney test was done for those variables that were not normally distributed.

RESULTS

A total of 122 children with headache were screened and 35 with migraine were finally enrolled (**Fig. 1**). Another 35 age- and sex-matched control subjects were also enrolled. None of the patients with migraine had any aura, and 29% had a positive family history. All had normal blood pressure with no difference in the baseline values between the cases and controls.

The median (IQR) serum magnesium level among adolescents (10-18 years) was 2.0 (1.9, 2.1) mg/dL in cases, while among controls it was 2.2 (2.0, 2.2) mg/dL, with a *P* value of 0.045. In children (5-18 years), the median serum magnesium level of cases was 2.0 (2.0, 2.1) mg/dL and it was 2.2 (1.9, 2.2) mg/dL in control group, which was comparable (*P*=0.23). None of the patients or controls had hypomagnesemia requiring supplementation. The differences were also comparable among preadolescents (5-9 years) and across gender (**Table I**).

DISCUSSION

In this cross-sectional study, the association between serum magnesium level and the occurrence of migraine in children was not found; although, the association in the adolescent (10-18 year) sub-group was statistically significant. None of our participants with migraine had serum magnesium level below 1.8 mg/dL.

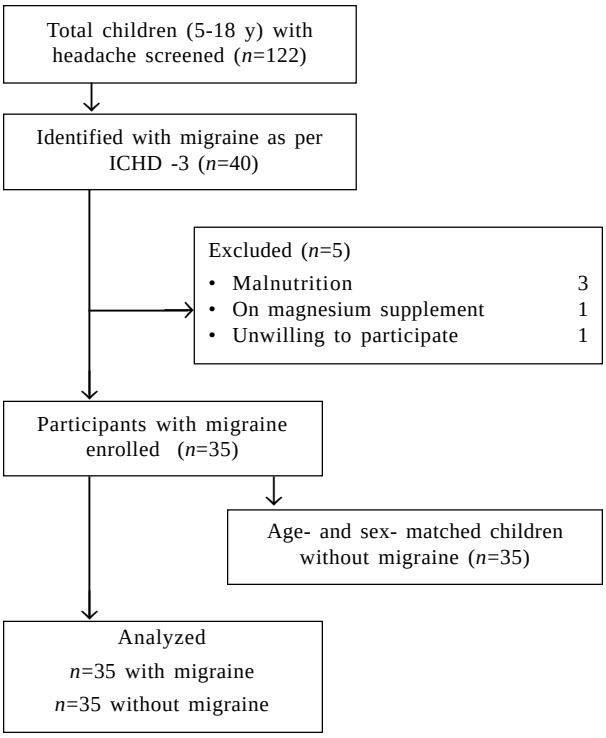

Fig. 1 Study flow chart.

In adult studies, serum magnesium levels have been reported to be low in migraine patients when compared to controls, and it was similar within and between acute episodes [5]. Adult studies have shown that women with menstrual migraine had low levels of magnesium [11]. Moreover, there is an increased frequency of migraine attacks post-puberty [11]. The increasing frequency of migraine during adolescence may develop into adult pattern [12]. The rationale for the lower magnesium levels observed among the adolescent sub-group in this study, akin to that of adult studies, may be explained by the similar pathogenetic mechanisms of adolescent and adult migraine.

In previous studies, magnesium has been used in migraine prophylaxis [13], and magnesium oxide was found to be effective. A randomized trial done in adults with migraine showed the combination therapy of magnesium

Table I Serum Magnesium Levels in Children With and Without Migraine

	Serum magnesium levels (mg/dL)		*P value*
	with migraine (n=35)	*without migraine (n=35)*	
Overall	2.0 (2.0,2.1)	2.2 (1.9, 2.2)	0.23
Male, *n*=40	2.1 (1.9, 2.2)	2.2 (1.9, 2.2)	0.5
Female, *n*=30	2.0 (2.0, 2.1)	2.1 (1.9-2.2)	0.3

WHAT THIS STUDY ADDS?

- We found a significant association between low serum magnesium levels and the occurrence of migraine in adolescents.

with sodium valproate can reduce the dosage of valproate for prophylaxis [14]. Research in the area of treatment of migraine in different age groups is quite limited [9]. There is a need for more investigations to prove safety and effectiveness of magnesium prior to use in pediatric migraine [6]. A double-blind placebo-controlled, randomized trial of patients aged 3-17 years found a statistically significant decline in headache frequency in those treated with magnesium oxide, but the difference between the placebo group and magnesium oxide group was not statistically significant [15]. It could therefore not be concluded by the authors if oral magnesium was superior to placebo in preventing frequent migraine episodes in children [15].

The major limitation of our study was its small sample size, especially among the adolescent sub-group. The post hoc power of the study was 90.7%. It is desirable to study the serum magnesium level during an acute migraine attack, rather than the period of normalcy, to further study this association.

To conclude, serum magnesium levels were comparable among children with migraine and their age- and sex-matched controls, except for low levels in adolescents with migraine. The role of magnesium supplements as either prophylaxis or treatment in children with migraine headache needs to be further explored.

Ethics clearance: IEC Sri Ramachandra Institute of Higher Education and Research; No. CSP-MED/18 JUN/44/104 dated June 23, 2018.

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

Contributors: RB: study design, acquisition, analysis, drafting; SP: study design, analysis, interpretation and drafting; RKM: study design, interpretation, revising it critically. Final approval of the version and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved by all the contributing authors.

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Surveillance for Developmental Dysplasia of the Hip in India: Consensus Guidelines From the Pediatric Orthopaedic Society of India, Indian Academy of Pediatrics, National Neonatology Forum of India, Indian Radiological and Imaging Association, Indian Federation of Ultrasound in Medicine and Biology, Federation of Obstetric and Gynaecological Societies of India, and Indian Orthopaedic Association

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Justification: When developmental dysplasia of the hip (DDH) is diagnosed during infancy, conservative management is often successful, with good long-term outcomes. In India, DDH is often not diagnosed until walking age and there are limited guidelines for its screening.

Process: A multidisciplinary Expert Group consisting of members of the Paediatric Orthopaedic Society of India, Indian Academy of Pediatrics, National Neonatology Forum of India, Indian Radiological and Imaging Association, Indian Federation of Ultrasound in Medicine and Biology, Federation of Obstetric and Gynaecological Societies of India, and Indian Orthopaedic Association worked collaboratively to develop surveillance guidelines for DDH.

Objectives: To enhance the early detection rate of DDH in India through development and implementation of a standardized surveillance care pathway, thus reducing the burden of late-presenting DDH.

Recommendations: Routine clinical hip examinations must be performed on all infants at birth and during immunization visits at these approximate time points: 6, 10, and 14 weeks; 6, 9, 12, 15, and 18 months of age. Assessments include Ortolani and Barlow tests for infants <14 weeks; limited hip abduction and leg length discrepancy for infants >14 weeks; and evaluation of limp in walking children. If clinical examination is abnormal or inconclusive, referral to orthopedics for further evaluation and management is recommended. In infants younger than 6 weeks with positive Barlow test but negative Ortolani test, hip ultrasound is recommended at 6 weeks of age. Infants must also be screened for DDH risk factors: breech presentation, family history of DDH, unsafe hip swaddling, and hip instability at any previous clinical examination. In infants with risk factors but normal clinical examination, further evaluation should include ultrasound taken no earlier than 6 weeks of age for infants younger than 14 weeks, ultrasound or *X*-ray for infants 14 weeks to 6 months of age, and *X*-ray for infants older than 6 months. Referral to an orthopedic surgeon is recommended if radiological tests are abnormal.

Keywords: *Care pathway, Early detection, Hip dislocation, Screening*.

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Developmental dysplasia of the hip (DDH) represents a wide spectrum of hip abnormalities, present at birth or developed during infancy, that ranges from sub-clinical dysplasia to complete hip dislocation [1]. When DDH is diagnosed and treated during infancy, conservative management is often successful at achieving a safe and effective reduction with good long-term outcomes [2-5]. In contrast, DDH that is diagnosed after the child starts walking often results in the need for more complex surgical reconstructive procedures and can lead to significant morbidity [4-7]. A recent scoping review [8] estimated the incidence of DDH in India to be between 0-75 per 1000 live births when considering the entire spectrum of hip dysplasia, but the incidence of true DDH to be between 0- 2.6 per 1000 live births. Until now, only limited guidelines have been available for DDH screening in India and DDH is often not diagnosed until the child starts walking [8-10]. The aim of this guideline is to enhance the early

detection of DDH through the development of a standardized surveillance care pathway, thus reducing the burden of late-presenting DDH. This guideline has been developed specifically for the Indian context, with the goal of identifying all cases of hip dislocation, instability and dysplasia before the child starts walking, but ideally before six months of age.

OBJECTIVES

To devise consensus guidelines for surveillance and diagnosis of DDH in India, so as to help healthcare providers detect most cases of DDH before walking age, and ideally before six months of age.

PROCESS

A multidisciplinary Expert Group consisting of members of the Paediatric Orthopaedic Society of India (POSI), Indian Academy of Pediatrics (IAP), National Neonatology Forum of India (NNFI), Indian Radiological and Imaging Association (IRIA), Indian Federation of Ultrasound in Medicine and Biology (IFUMB), Federation of Obstetric and Gynaecological Societies of India (FOGSI), and Indian Orthopaedic Association (IOA) was convened. The Executive Committee of each organization nominated representatives from various regions of the country to join the group, based on their expertise in DDH and leadership within their respective organizations. Care was taken to include representatives from all five zones of India and a wide range of experts working in the Government public healthcare sector, private sector and university teaching hospitals. Two representatives (one from IAP and one from IOA) represented the rural population. The resulting expert group, designated as the DDH India Care Pathway Working Group, worked collaboratively to develop a list of consensus statements that were used to frame sur-veillance guidelines for DDH screening in India, as outlined in this document.

The guidelines were developed by the Expert Group, with technical support from the Department of Orthopaedics at the University of British Columbia, Canada. A three-phased process was used, consisting of a preparatory phase, a consensus-building phase, and a writing phase. The study methodology used in developing the guidelines was reported and published earlier [11]. In the initial phase, members reviewed the existing evidence during a series of virtual meetings beginning on 31 May, 2020 and concluding on 2 August, 2020. Group members participated in an informal literature review process in which presenters synthesized relevant high-quality articles on designated topics, including the incidence of DDH in India, clinical examination, the role of imaging, and comparisons of existing screening programs. A repository of literature was created and stored on a cloud-based server for group members to access at their convenience. In addition to the articles selected for group discussion, the repository included publications cited in a recent systematic review of DDH in children younger than 6 month [12], on the Delphi consensus process, and other articles selected by group members. Key topics included clinical examination, risk factors, the role of ultrasound and *X*-ray, and management of DDH. A preliminary survey of NNFI and IAP membership was designed and circulated to understand their knowledge and practices regarding DDH.

Delphi process: During the second phase, which began on 15 October, 2020, group members participated in the Delphi process to reach consensus on a list of statements about DDH screening that were used to frame the guideline. The Delphi approach employed two online rounds of surveys along with virtual meetings between each round until consensus was achieved [11,13].

Upon the conclusion of the consensus-building phase on 10 February, 2021, the final guidelines were drafted by a core writing group and then distributed to the Expert Group for feedback. During a final consensus meeting on 14 March, 2021, the group reviewed the guidelines prior to finalization and endorsement by the participating organi-zations. While no formal external review was performed, DDH experts from Canada (who were part of the American Academy of Orthopaedic Surgeons Clinical Practice Guidelines development) were integrated into the process to bring perspective from outside of the Indian context.

GUIDELINES

The Rashtriya Bal Swasthya Karyakram (RBSK) program under the National Health Mission (NHM) aims at providing child health screening and early intervention services for a number of pediatric conditions, including DDH. This current guideline aims to expand and elaborate upon the RBSK program, improving practicability, feasibility and effectiveness. The guidelines (**Fig. 1**) are broad in order to remain applicable to India's diverse public and private healthcare settings. The guidelines have been developed for use by a wide cadre of clinical healthcare providers, especially pediatricians, neonatolo-gists, primary care physicians and other trained healthcare providers who care for children, so as to maximize uptake across the country.

The focus of this guideline is on 'surveillance' rather than 'screening' – emphasizing the concept of periodic physical examinations as part of regular well baby checks/ immunization visits until the child is of walking age. For the Indian context, we have recommended regular clinical examination of the hips at every well-baby check/ immunization visit in addition to selective imaging using ultrasound or *X*-ray for any baby with abnormal clinical

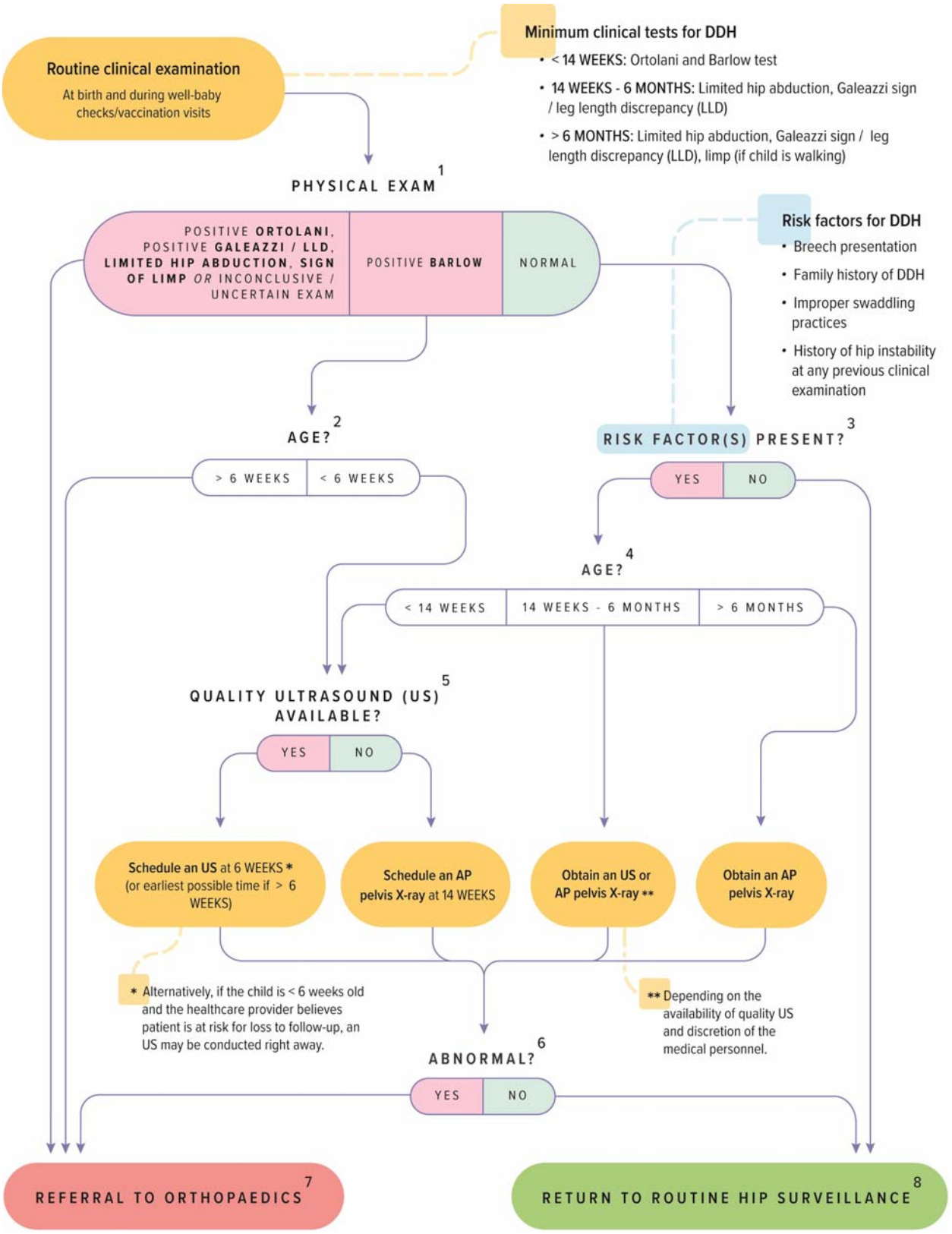

Fig. 1 Flowchart showing clinico-radiological surveillance protocol for screening infants for developmental dysplasia of the hip (copyrighted to the Paediatric Orthopaedic Society of India (POSI) and reproduced with permission).

finding(s) and/or risk factor(s) present. These recommendations are in alignment with those of the Pediatric Orthopedic Society of North America (POSNA), the American Academy of Pediatrics (AAP), the American Academy of Orthopaedic Surgeons (AAOS), and the Canadian Task Force on DDH.

To create ease of use, the recommended periodic hip examinations have been aligned with the immunization schedule recommended under the Universal Immunization Programme (UIP) and Government of India.

Terminology

Quality ultrasound: Refers to both accessibility of ultrasound and expertise in interpretation of its results in the area of practice, at the discretion of the screener. While ultrasound facilities are widely available in urban areas and even in rural regions of India, diagnostic ultrasound is tightly controlled under the restrictive Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) Act, 1994. Furthermore, expertise in performing and interpreting pediatric musculoskeletal ultrasound is often lacking in the country, and this must be considered by the healthcare provider while choosing the appropriate imaging tool for screening.

Routine hip surveillance: Refers to regular clinical hip examinations using age-appropriate tests that occur at birth and during well-baby checks/immunization visits.

Referral to Orthopedics: Referral should be to a pediatric orthopedic/orthopedic surgeon. While a pediatric orthopedic surgeon is preferable, whenever possible, an orthopedic surgeon is sufficient if a pediatric orthopedic surgeon is not available in the area of practice.

Inconclusive Exam: Refers to instances where the healthcare provider performing the clinical examination suspects hip instability or dysplasia but is uncertain of the clinical finding, or the examination lacks a definitive posi-tive or negative result. If the examiner is unsure of the clini-cal examination or has reason for heightened suspicion of DDH, referral to a pediatric orthopedic/orthopedic surgeon is prudent so as not to miss a potential case.

Clinical Examination Schedule

All babies should undergo routine clinical examinations of the hip to check for hip dysplasia. A newborn clinical examination is universally accepted to screen for DDH [14-16]. Clinical hip examinations will primarily be performed by pediatricians, neonatologists, and primary care physi-cians, but can be performed by any trained clinical healthcare provider involved in the care of children, including paramedical personnel. These examinations should occur at birth, before the baby and mother are discharged, and also during well-baby checks/immuni-zation visits. To align with the national immunization schedule as much as possible, these examinations should occur at these approximate time points: at birth, 6 weeks, 10 weeks, 14 weeks, 6 months, 9 months, 12 months, 15 months, and 18 months of age.

Minimum Clinical Tests

There are many clinical tests that can be used to screen for DDH. The minimum clinical tests that are required for each age group are outlined in **Table I** and **Fig. 2**.

The Barlow and Ortolani tests (**Fig. 2a** and **b**) were established in the 1960s as critical clinical tests to determine instability and reducibility in the infant hip [14,17,21]. Both these tests are most effective in early infancy (up to 3 month of age), since they tend to become negative as the baby grows [3,15,21]. Consequently, other clinical tests such as leg length discrepancy (Galeazzi sign) (**Fig. 2c**) and limited hip abduction (LHA) (**Fig. 2d**) become more valuable over time [5,18-20]. Unilateral limitation of hip abduction beyond eight weeks of age is an important clinical indicator of pathologic DDH, with high specificity (>90%) and moderate sensitivity (>70%) [18,19]. A limp in the walking child can also indicate DDH. Bilateral hip dislocations can lead to hyperlordosis of the lumbar spine (exaggerated C-shaped lumbar curve) and a waddling gait. Unilateral dislocations may cause a short limb gait and a Trendelenburg lurch, in which the pelvis fails to remain in the neutral position but tilts downwards to the unaffected side.

Imaging Guidelines

Ultrasound: An ultrasound can be used as a screening tool anytime from birth to six months of age, provided that quality ultrasound imaging and interpretation is available. Beyond six months of age, the appearance and growth of the ossification centre of the femoral head begins to obscure key sonographic landmarks including the ilium [22,23]. Expertise in performing and correctly interpreting musculoskeletal ultrasound, especially in an infant, may not be uniformly available, and thus, these guidelines provide practical alternatives if ultrasound accessibility and expertise is an issue.

Table I Clinical Tests for Screening for Developmental Dysplasia of the Hip As Per Age of the Baby

<14 wk of age	*14 wk – 6 mo*	*> 6 mo*
Ortolani test [17]	Limited hip abduction [5,18-20]	Limited hip abduction [5,18-20]
Barlow test [14]	Galeazzi sign /leg length discrepancy (LLD) [5,20]	Galeazzi sign/leg length discrepancy (LLD) [5,20]
		Limp (if child is walking) [5,20]

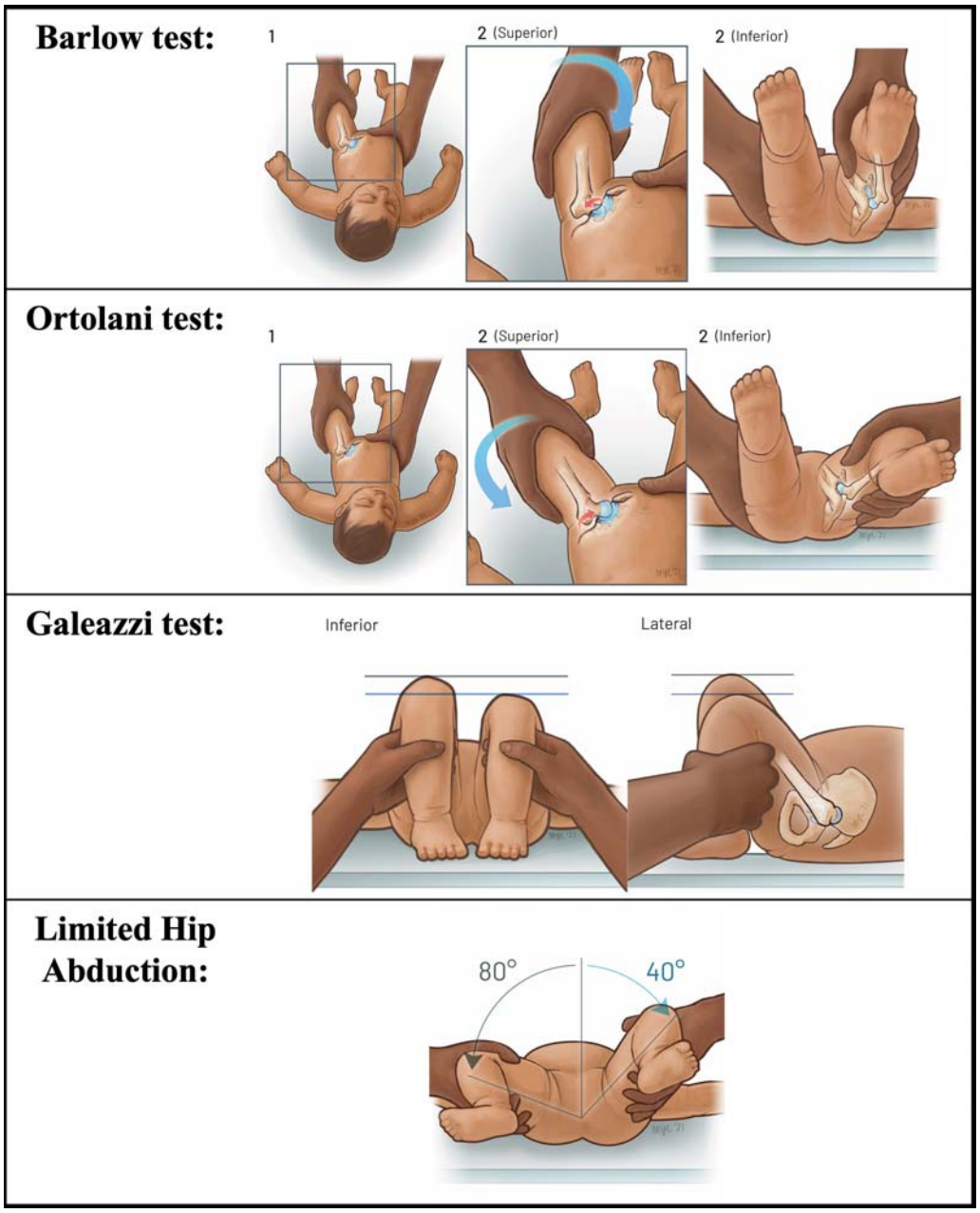

Fig. 2 Pictorial representation of various clinical tests used for screening of developmental dysplasia of the hip in infants (copyrighted to the International Hip Dysplasia Registry (IHDR) and reproduced with permission); *a*) The Barlow provocative test is performed with the newborn positioned supine and the hips flexed to 90^0. The leg is then gently adducted while posteriorly directed pressure is placed on the knee. A palpable clunk or sensation of movement is felt as the femoral head exits the acetabulum posteriorly – this is a positive Barlow sign, which indicates hip instability; *b*)The Ortolani maneuver is performed with the newborn in the supine position and the examiner's index and middle fingers placed along the greater trochanter with the thumb placed along the inner thigh. The hip is flexed to 90^0, and the leg is held in neutral rotation. The pelvis is stabilized with the other hand and the hip is gently abducted while lifting the leg anteriorly. With this maneuver, a "clunk" is felt as the dislocated femoral head reduces into the acetabulum; *c*) The Galeazzi test is conducted with the infant supine, on a firm, flat surface with the pelvis stabilized and level. The hips are flexed to 90^0 and placed in neutral adduction/abduction, with knees in flexion. In this position, the vertical level of the knees can be assessed for asymmetry; and *d*) The clinical assessment of limited hip abduction (LHA) is made with the child supine with both hips flexed to 90^0 and full abduction of both hip joints is attempted. Any block to full abduction is noted from the horizontal, and the sign is considered positive if there is a limitation of $>20^0$ as compared to the opposite hip in unilateral cases or if $<60^0$ of hip abduction is possible on each side in bilateral cases [18-20].

X-ray: The earliest that an *X*-ray can be used as a screening tool is at 14 weeks of age. The recommended time to transition from ultrasound to *X*-ray imaging screening is between 4-6 months of age, as this is when the femoral head ossific nucleus typically becomes visible radio-graphically [5,24,25]. However, the working group reached consensus to give healthcare providers the option to perform an *X*-ray slightly earlier (14 weeks), as this aligns with the national immunization schedule and ensures that infants requiring imaging can still be screened if quality ultrasound is not available. The International Hip Dysplasia Institute (IHDI) classification [26] is a reliable radiographic system to quantify DDH severity using the midpoint of the proximal femoral metaphysis, rather than the femoral head utilized in the commonly used Tonnis criteria [26]. Consequently, the IHDI classification holds value even prior to ossification of the femoral head, enabling the use of *X*-ray when needed in these younger infants. Use of *X*-ray in this younger age group is only recommended if quality ultrasound is not available; in order to prevent potential missed cases that may arise if left without surveillance until after four months of age. A single antero-posterior (AP) pelvis radiograph is required for DDH screening, without the need of a frog-leg lateral radiograph [27].

Key imaging recommendations are outlined in **Box I**.

Guidelines As Per the Age of the Child

1. Baby younger than six weeks

*Clinical tests***:** The minimum clinical tests for babies less than six weeks of age include both Ortolani and Barlow tests.

Positive clinical examination: If the Ortolani test is positive, the baby should immediately be referred to a pediatric orthopedic/orthopedic surgeon for further management. This recommendation is consistent with the AAOS Appropriate Use Criteria (AUC) and AAP Guidelines [15,28].

Box I Imaging Recommendations for Developmental Dysplasia of the Hip

Younger than 6 weeks

Recommendation: Ultrasound at 6 weeks of age.

Alternative approach: Ultrasound immediately, if potential for loss to follow-up. *X*-ray at 14 weeks of age, if quality ultrasound unavailable.

6 to <14 weeks

Recommendation: Ultrasound at earliest possible time.

Alternative approach: *X*-ray at 14 weeks of age, if quality ultrasound unavailable.

14 weeks to 6 months

Recommendation: Ultrasound or AP pelvis *X*-ray, depending on availability.

Older than 6 month

Recommendation: Antero-posterior pelvis *X*-ray.

Positive Barlow test: If the Barlow test is positive, the baby does not require immediate referral to orthopedics, as these hips may spontaneously resolve [29]. Ideally, babies with a positive Barlow test should wait to obtain an ultrasound at six weeks of age, consistent with the AAOS AUC [28]. Prior to six weeks of age, most hip instability and morphologic abnormalities detected on ultrasound are due to immaturity of the hip joint. Most of these abnormalities spontaneously resolve during normal maturation and development of the hip joint in infancy [30,31]. Thus, ultrasound performed before six weeks of age is prone to detecting morphologic abnormalities that will self-resolve over time. However, if the examiner believes the baby is at risk for loss to follow-up, an ultrasound can be obtained right away. If quality ultrasound is not easily available, an AP pelvis *X*-ray should be scheduled at 14 weeks of age. Any abnormal imaging findings on ultrasound at 6 weeks or *X*-ray at 14 weeks should prompt a referral to orthopedics, again consistent with the AAOS AUC [28]. If imaging is normal, the baby can return to routine hip surveillance. Alternatively, if the first imaging is normal, an examiner can choose to schedule an additional follow-up X-ray at six months. This additional follow-up imaging for a baby with an initial positive Barlow test is recommended, particularly if there are also risk factor(s) present.

Normal clinical examination: If clinical examination is normal, babies must undergo risk factor screening, as the AAOS clinical practice guideline (CPG) found that there is moderate evidence to support additional imaging before six months of age for infants with breech presentation, family history of DDH or history of clinical hip instability [32].

Inconclusive exam: If the clinical exam is inconclusive or uncertain, the baby should be referred to a pediatric orthopedic/orthopedic surgeon for further assessment.

2. Age between 6 to 14 weeks

Clinical tests: The minimum clinical tests for babies in this age range include both Ortolani and Barlow tests.

Positive Ortolani and/or positive Barlow test: If the Ortolani and/or Barlow tests are positive, the baby should be referred to a pediatric orthopedic/orthopedic surgeon. This recommendation is consistent with the AAOS AUC [28].

Normal clinical examination: If clinical examination is normal, the baby must undergo risk factor screening.

Inconclusive examination: If the clinical exam is inconclusive or uncertain, the baby should be referred to a pediatric orthopedic/orthopedic surgeon.

3. Age between 14 weeks and 6 months

Clinical tests: The minimum clinical tests for babies in this age range include both limited hip abduction and Galeazzi

sign/leg length discrepancy (LLD).

Limited hip abduction and/or positive Galeazzi sign/ LLD: If the baby has limited hip abduction and/or a positive Galeazzi sign/LLD, the baby should be referred to a pediatric orthopedic/orthopedic surgeon, consistent with the AAOS AUC [28].

Normal clinical examination: If clinical examination is normal, the baby must undergo risk factor screening [32].

Inconclusive examination: If the examination is inconclusive or uncertain, the baby should be referred to a pediatric orthopedic/orthopedic surgeon.

4. Baby older than 6 month

Clinical tests: The minimum clinical tests for babies >6 months who are younger than the age of walking include limited hip abduction and Galeazzi sign/leg length discrepancy (LLD). If the baby is walking, the minimum tests include limited hip abduction, Galeazzi sign/LLD, and limp.

Limited hip abduction and/or Positive Galeazzi sign / LLD and/or Sign of limp: If the baby has one or more positive clinical tests (limited hip abduction, positive Galeazzi sign/ LLD, sign of limp), they should be referred to a pediatric orthopedic/orthopedic surgeon.

Normal clinical examination: If clinical examination is normal, the baby must undergo risk factor screening.

Inconclusive examination: If the examination is inconclusive or uncertain, the baby should be referred to a pediatric orthopedic/orthopedic surgeon.

Risk Factor Screening

All babies should be assessed for the presence of risk factors along with their clinical examination. With a normal clinical examination, the baby's risk factor status becomes important, since defined risk factors warrant additional screening regardless of clinical examination status. While girls are approximately 4-5 times more likely than boys to have DDH, with girls born breech having the highest risk [33], female sex alone will not be used as an indication for risk factor screening in this surveillance guideline. The risk factors are listed in **Box II**.

No risk factor(s) present: If no risk factors are present, the baby can return to routine hip surveillance.

One or more risk factors present: If one or more risk factors are present, the baby will require further imaging. The recommended imaging (ultrasound vs *X*-ray) will depend on the age of the child and the availability of the imaging tool (**Box I**). The AAOS clinical practice guideline described two moderate strength studies that suggested a significant role for further imaging in infants with risk factors of family history, breech presentation or history of clinical instability in order to prevent late detection of dysplasia or dislocation [39,43].

Any abnormal imaging findings should prompt a referral to orthopedics. If imaging findings are normal, the baby can return to routine hip surveillance.

Guidelines in the context of RBSK Program

The RBSK program provides valuable screening, examination and care recommendations for the detection and treatment of DDH in the government and public healthcare sector in India. The RBSK recommends that screening for DDH occur at the public health facility level at birth by Auxiliary Nurse Midwives (ANMs), Medical officers (MOs) or gynecologists, and by the mobile health team at anganwadi centers at six weeks and beyond. Children with positive clinical findings and/or risk factors are referred to the District Early Intervention Centre (DEIC) or District Hospital (DH) for further examination, imaging and treatment. Under the RBSK program, screening/examination is recommended to occur at birth, 6 weeks, and at 3, 6 and 12 months. The intent of the current guideline is to integrate, where applicable, with the existing RBSK guidelines and improve practicality and feasibility of its successful implementation. Endorsement by national professional organizations, whose members provide healthcare to children, will encourage adoption of these guidelines especially for infants who do not access public healthcare and hence do not come under the ambit of the RBSK

Box II Risk Factors For DDH Screening

Breech presentation at any point after 36 weeks of pregnancy, irrespective of presentation at birth or mode of delivery.

Family history of DDH, defined as first-degree (parents, siblings) or second-degree (grandparents, aunts, uncles) relatives diagnosed with DDH.

Improper swaddling practices. Swaddling is the traditional practice of wrapping a baby in cloths or blankets that can tightly restrict limb movements. While swaddling has been shown to have several beneficial effects for the newborn, tight swaddling of the legs with the hips in extension and adduction can tighten the muscles around the hip joint and predispose to hip dislocation. 'Hip-safe swaddling' permits the lower limbs of the infant to be positioned loosely in a frog-leg attitude within the swaddle and allows space for the legs to have unrestricted flexion-abduction movements, facilitating normal hip development.

Presence of hip instability at any previous clinical examination.

Prepared from references 34-42. Other risk factors historically associated with DDH, such as, oligohydramnios, multiple pregnancy, foot deformities, torticollis, asymmetric thigh or gluteal skin creases, and hip clicks, have not been included among risk factors warranting screening due to the lack of strong evidence of association.DDH - developmental dysplasia of the hip.

program. A key difference this guideline presents from the RBSK program is a more structured surveillance schedule that links hip examinations with immunization visits. While the recommended clinical examinations are similar between the two guidelines (Ortolani/Barlow tests, limited hip abduction, Galeazzi sign/leg length discre-pancy), the current guideline elaborates more on age-appropriate clinical tests and provides clear guidelines for referral. Additionally, the RBSK does not address availability of quality ultrasound, and consequently, does not discuss the important role of *X*-rays when ultrasound access is lacking.

Limitations

There are a few limitations to these guidelines. First, patients/families were not included as stakeholders in the care pathway development process. To facilitate timely completion and practicability of the project, a decision was made to develop the pathway with relevant medical experts and stakeholders, and instead include patients/families in the implementation and knowledge translation phases. Second, the expert group lacked sufficient representation from rural areas, a limitation that will be addressed by recruiting involvement and input from rural practitioners in the implementation process. Third, discussion of the management of DDH was not within the purview of these guidelines. The aim was to develop screening and surveillance guidelines to ensure a timely referral to a pediatric orthopedic/orthopedic surgeon, who would offer appropriate management using established treatment protocols.

We provide consensus guidelines for screening and surveillance of DDH in India (**Table II**), targeting the practicing pediatricians and trained healthcare workers in the country. We feel that widespread adoption of these will improve the outcomes of children with DDH with early diagnosis and timely initiation of treatment.

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Contributors: AA, ES, JL: conceptualised and designed the study; AA,RPA,ES,JL: wrote the first draft of the manuscript. All authors commented on and edited initial versions of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

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Table II Summary of Guidelines for Screening for Developmental Dysplasia of the Hip

Clinical workup	*Imaging recommendations*	*Timing for referral to orthopedics*
Risk factors	*Indications for imaging*	*Urgent*
Breech presentation	One or more risk factor(s) present	Abnormal imaging findings
Family history of DDH	Positive Barlow in baby <6 wk	Abnormal clinical exam:
Improper swaddling practices	Inconclusive/uncertain clinical exam	- Positive Ortolani
History of hip instability in any previous clinical exam	*Age-dependent imaging recommendations*	- Positive Barlow in baby >6 wk - Limited hip abduction
Clinical tests	6 wk ultrasound for babies <6 wk of age	- Positive Galeazzi test/leg length discrepancy
Ortolani test (<14 wk)	Immediate ultrasound for babies 6-14 wk of age-	Limp in walking age child
Barlow test (<14 wk)	Immediate ultrasound or AP pelvis *X*-ray for babies between 14 wk-6 mo of age	
Limited hip abduction (>14 wk)	Immediate AP pelvis *X*-ray for babies >6 mo of age	*Not urgent*
Galeazzi test/leg length discrepancy (>14 wk)		Positive Barlow in baby <6 wk[a]
Sign of limp (walking age)	*Imaging alternatives*:	*Referral not required*
	Ultrasound before 6 wk of age if baby is at risk for loss to follow-up	Normal physical exam and no risk factors present
	AP pelvis *X*-ray not earlier than 14 wk of age if quality ultrasound is not available	Normal imaging findings

[a]*May spontaneously resolve. Only refer if first imaging is abnormal.*

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ANNEXURE

National DDH Expert Group

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REVIEW ARTICLE

Monkeypox Disease Outbreak (2022): Epidemiology, Challenges, and the Way Forward

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The biggest-ever outbreak of monkeypox disease in non-endemic countries started in May, 2022. Though no monkeypox case has been reported from India, till mid-June, 2022, yet, considering the rate of spread to the non-endemic countries, there is an urgent need of better understanding of the monkeypox virus and disease epidemiology to help clinicians, public health specialists, and policymakers to be prepared for any eventuality. This review summarises the monkeypox disease epidemiology, clinical features, therapies, vaccines and outlines the measures for preparedness and response for a possible outbreak. The disease is known to cause severe outcome in children, pregnant women, and immunocompromised hosts and this group need to be given special attention. The monkeypox disease outbreak (2022) in non-endemic countries should be used as an opportunity by India and other low and middle income countries to strengthen public health surveillance and health system capacity for outbreak and epidemic preparedness and response.

Keywords: *COVID-19, Smallpox, Vaccines, Zoonoses*.

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Monkeypox has been endemic in 11 countries in Western and Central Africa since the 1970s [1,2]. In May, 2022, the biggest-ever monkeypox disease outbreak in non-endemic countries had started and by June 15, 2022, around 36 non-endemic countries had reported the disease in their territories [3,4]. Though a mild and self-limiting disease for most of the people affected, the disease is known for having comparatively severe outcomes in pregnant women, children and immuno-suppressed individuals. In this review, the authors describe the epidemiology, clinical features, and preventive measures and clinical case management of monkeypox. The article also analyzes the epidemic and pandemic potential, and possible steps for preparedness and response for India and other non-endemic countries.

METHODS

A desk review of literature was conducted to collect, collate, synthesize and analyze information on the epidemiology, and impact of the monkeypox virus (MPXV) and disease. The information from credible and reliable sources such as websites of the World Health Organization (WHO), the Centre for Disease Control and Prevention (CDC), and the publications in peer-reviewed journals were reviewed. Recommendations and updates from international and national scientific and government bodies were searched for relevant information.

EPIDEMIOLOGY

Monkeypox is an infectious zoonotic disease caused by the monkeypox virus (MPXV), which belongs to the Orthopoxvirus genus of the Poxviridae family, the same genus as that of the smallpox virus [4-7]. It is a double stranded deoxy ribonucleic acid (dsDNA) virus. The MPXV was first detected in 1958, in a group of monkeys in a laboratory in Denmark [8,9]. The first human case was identified in a 9 month-old child, during the intensive search for smallpox cases, in the Democratic Republic of the Congo (then known as Zaire) in 1970 [10]. Ever since, the disease has been endemic in nearly 11 countries of the Central and Western African regions with thousands of cases being reported annually [11-13]. Though various animal species have been identified as susceptible to the monkeypox virus, uncertainty remains on the natural host of the monkeypox virus and further studies are needed to identify the reservoir(s) and how virus circulation is maintained in nature [13,14].

The case fatality rate of monkeypox ranges from 0-11% [4,15], slightly lower at around 0 to 3% for the West African clade and 0 to 11% for the Central African (Congo basin) clade, in comparison to the high fatality of 30% for smallpox virus [16]. To date, deaths in the endemic countries have mainly been reported mostly in young children and people with human immuno-deficiency virus and Acquired Immunodeficiency syndrome (HIV/AIDS) or other immunocompromised hosts [17].

Cases in non-endemic countries and ongoing outbreak

In 2003, there was first-ever MPXV outbreak outside the endemic countries, in the USA with around 70 confirmed or suspected cases [18-20]. This outbreak was linked to the importation of Gambian giant rats, squirrels from Ghana, which had transmitted the virus to prairie dogs that were then sold and transported to the USA as pets [18]. There were no confirmed cases of person-to-person transmission [19]. Imported monkeypox infections in humans following travel have been reported in the United Kingdom, Israel, and Singapore in 2018-19 and then in the US again in 2021 [3,4, 20].

In the ongoing outbreak, the West African clade is responsible for the unprecedented rise of cases [3]. As per the latest WHO update, till June 15, 2022, around 2,039 laboratory confirmed cases of Monkeypox disease have been notified from 36 non-endemic countries worldwide [3,4]. Majority of the cases (84%) have been reported from WHO European region. However, cases have been reported from WHO Region of the Americas; Eastern Mediterranean and Western Pacific Region. Amongst the endemic countries, an outbreak of monkeypox disease is ongoing in Nigeria since 2017. [21].

Transmission and pathogenesis

The incubation period, the period from the exposure to development of first symptoms, of MPXV is usually from 6 to 13 days (range from 5 to 21 days) [4]. A person is not contagious during the incubation period. The MPXV, primarily infects animals [4,14]. Human-to-human transmission occurs primarily through direct skin-to-skin contact with lesions (skin and mucocutaneous) and bodily fluids (such as pus, fluid, or blood from skin lesions) [3,20,21]. Transmission can also occur via the placenta from mother to foetus (which can lead to congenital monkeypox) or during close contact during and after birth [4,20,21]. During the ongoing multi-country outbreak, most of the cases have been reported among men who have sex with men (MSM); though, there is variable evidence of its sexual transmission [3,4]. The virus multiplies at the site of inoculation before entering the bloodstream [22]. Lesions usually start in the oropharynx then appear on the skin. Serum antibodies are often detectable by the time lesions appear [16].

LABORATORY AND DIFFERENTIAL DIAGNOSIS

Polymerase chain reaction (PCR) by testing of samples from skin lesions, is the preferred diagnostic test due to its higher sensitivity even in presence of bacterial contami-nation of patient's specimen. PCR in blood is usually inconclusive [10,20,23].

An important differential diagnosis is illnesses which manifest with rashes i.e., chicken pox, measles, bacterial skin infections, scabies, syphilis, and medication-asso-ciated allergies [4,13,20]. The differences in the clinical features of monkeypox with chickenpox and measles are shown in **Table I.** Monkeypox has a typical rash pattern and lymphadenopathy during the prodromal stage of illness [3,4,20,21].

CLINICAL FEATURES

The clinical presentation can be divided into two phases. First, the invasion period or the febrile stage that lasts between 0-5 days and is characterized by fever, intense headache, lymphadenopathy, back pain, and myalgia or muscle pain. Lymphadenopathy is a distinctive feature of monkeypox compared to other diseases that may initially appear similar (chickenpox, measles, smallpox) [3,4]. Second, the skin eruption phase, which usually begins within 1-3 days of the appearance of fever. The rash tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face (95%), palms of the hands and soles of the feet [3,4]. Other areas that may be affected are oral mucous membranes, genitalia and conjunctivae as well as the cornea. The rash evolves sequentially from macules to papules to vesicles, pustules, and then forms crusts which dry up and fall off [3,4,13,16]. The number of lesions may vary from a few to several thousand. The complications commonly observed are conjunctivitis and corneal scarring, vomiting and diarrhea, encephalitis, sepsis, and broncho-pneumonia [13]. Full recovery may take days to weeks after the rashes subside **(Box I)** [3,4,23,24].

Outcome of infection and risk in children

Monkeypox is usually a self-limiting disease and remains mild but severe cases occur among children, pregnant

Table I Differentiation of Monkeypox From Other Illnesses With Rash

Symptoms	*Monkeypox*	*Chickenpox*	*Measles*
Fever	1-3 d before rash	1-2 d before rash	3-5 d before rash
Rash/lesions	Single stage	Often in multi-ple stage	Often in multi-ple stages
Rash develop-ment	Slow	Rapid	Rapid
Distribution of rash	More dense on face, present on the palms and soles	More dense on trunk; Not present on the palms and soles	Starts on face, then to hands and feet.
Lympha-denopathy	Yes	No	Rarely
Death	Upto 10%	Rare	Variable

Adapted from references [3,4,20,21].

Box I Risk Factors and Clinical Findings Associated With Monkeypox Severity

Higher risk of severe disease or complications

Children, pregnant women, persons who are immunosuppressed i.e., living with HIV

Signs and symptoms of complications

Nausea and vomiting, painful cervical lymphadenopathy causing dysphagia, poor oral intake, eye pain, vision abnormalities, hepatomegaly, sepsis, dehydration, respiratory distress/pneu-monia, and/or confusion.

Laboratory abnormalities

Elevated hepatic transaminases (AST and/or ALT), low blood urea nitrogen (BUN), low albumin, elevated white blood count (WBC), or low platelet count.

Skin lesion severity score from smallpox experience

- Mild (<25 skin lesions)
- Moderate (25-99 skin lesions)
- Severe (100-250 skin lesions)
- Very severe (>250 skin lesions)

Adapted from reference [3,4,20,24]. HIV: human immunodeficiency virus, ALT: alanine aminotransforse, AST: aspartate aminotransferase.

Box II Complications and Sequelae of Monkeypox

Complications

- Bacterial skin and soft tissue infections such as cellulitis, abscesses, necrotizing soft tissue infections
- Subcutaneous fluid accumulation in the crusting phase leading to intravascular depletion and shock
- Skin exfoliation
- Severe pneumonia and respiratory distress
- Corneal infection and vision loss
- Loss of appetite, vomiting and diarrhoea which may lead to severe dehydration, electrolyte abnormalities and shock
- Cervical lymphadenopathy which may lead to retropharyngeal abscess or respiratory compromise, sepsis, septic shock, and, encephalitis
- Death

Sequelae

- Complications during pregnancy (miscarriage, bleeding, still birth)
- Congenital disease in newborn born to affected mother.

Adapted from Reference [3,4,20,24].

women, comorbid and immunocompromised hosts [4,13,10,25,26]. The transplacental transmission of monkeypox has resulted in miscarriages and fetal deaths. However the association between severity of maternal illness and these outcomes is unclear [27,28]. Over the years, there has been a shift in the median age of monkeypox disease in Africa, which was 4 and 5 years old children in the 1970s and 1980s to 10 and 21 years old in the 2000s and 2010s [19]. In an outbreak in the US in the past, among the confirmed cases 10 out of 34 (29%) were in younger than 18 years of age [29]. However, during the first year of the ongoing outbreak in Nigeria, in 2017-2018, children formed around 8% of the 91 cases [29,30].

A recent longitudinal study from the Democratic Republic of Congo showed that among 216 admitted patients of monkeypox from the year 2007 till 2021, half were in the age group of 0-12 years [31]. Available data shows that the risk of children developing disease may have gone down over the years; however, they continue to be more vulnerable group given the possibility of adverse outcomes in this population. The prognosis is related to the extent of virus exposure, infection with Congo Basin clade of virus, patient's health status and nature of complications [32,33]. The complications and long term sequelae of the disease are listed in **Box II** [4,34].

THERAPEUTICS

Treatment of monkeypox disease is mostly symptomatic with management of complications and prevention of long-term sequelae. Fluids and adequate nutrition are necessary to improve overall recovery [4,20]. A drug named Tecovirimat, originally researched and developed for smallpox, was approved for MPXV in a few countries in early 2022; however, it is not yet widely available [4,20]. Two other antiviral drugs Cidofovir and Brinci-dofovir, also developed to treat smallpox and working by inhibiting the viral DNA polymerase, have shown efficacy in animal studies [3,22,24]. However, data is insufficient on their effectiveness for treatment of monkeypox disease in humans [23, 24]. Research is also in progress on monoclonal antibody combinations. Vaccinia Immunoglobulins (VIG) shown some efficacy against other Orthopoxviruses and is licensed by the US Food and Drug Administration [35]. VIG plays a role in post exposure prophylaxis and reducing the severity of the disease, but further studies are needed [3,24].

Vaccination

In observational studies, the vaccination against smallpox had shown upto 85% cross protection and reduced severity of monkeypox disease [19]. However, in the current outbreak, immunity from the past smallpox vaccination may not be useful as firstly, it is limited to those who were administered the vaccine by or before the 1980s and secondly, there is every possibility of further waning of the protective effect in that population, over last four decades [4,20]. Smallpox vaccines have not been available to the public since its eradication in 1980. It is also believed that vaccination, upto 14 days after exposure and four days before appearance of symptoms, may also prevent from disease or reduce it's severity, as monkeypox disease has long incubation period [20].

A third-generation smallpox vaccine, MVA-BN (Modified vaccinia Ankara-Bavarian Nordic strain) was approved against monkeypox in 2019. This vaccine is based on a strain of vaccinia virus and is considered protective

against MPXV [3,4,15]. As of June 11, 2022 MVA-BN smallpox vaccine is available in many European countries, USA and Nigeria, mostly for 'off-label' use [36]. An interim guideline from WHO has recommended that local authorities may consider the use of approved smallpox and/or monkeypox vaccines in response to ongoing outbreak [36]. Only second and third generation smallpox vaccines can be used for the ring vaccination in monkeypox outbreak, guided and determined at local level [24,36] A summary of key features of approved smallpox /monkeypox vaccines is provided in **Web Table I** [36].

These vaccines may be used for pre-exposure and post-exposure prophylaxis for specific groups; however, vaccination of general population is not recommended. The guidelines suggest that safety and reactogenicity data on the available vaccines should be considered by the technical experts to assess the 'need-risks-benefits' before arriving on a decision and choice of the vaccine [36].

For pregnant and breastfeeding women, non-replicating (MVN-BN) and minimally replicating (LC16) are preferred. For children, MVA-BN and LC-16 are preferred. Only approved vaccine for infants and children is LC 16; however, MVA-BN, which is approved for adults, can also be administered as off-label use in children in different settings [3,36].

PREPAREDNESS AND RESPONSE

The monkeypox disease cases have not yet been reported from India; however, considering the pattern of spread of MPXV in the ongoing outbreak, there is need for every country to be prepared. The outbreak readiness measures such as the designated isolation facilities and dedicated beds, equipment's and reagents for laboratory diagnosis, and training of group of health care workers as members of rapid response team (RRT) in standard elements of care should be prioritized. The Infection and prevention control measures at the designated facilities should be reviewed and strengthened. Early case identification, contact tracing, and as and where possible, the ring vaccination (of close contacts and family members), remains to be mainstay of response. It also needs to be remembered that while laboratory confirmation of suspected cases is needed, it should not delay the public health measures. Similarly, while awaiting the laboratory confirmation, patients and contacts in community need to be traced and further investigated (backward contact tracing).

Risk Communication is another essential but under-used public health intervention for any disease with an outbreak and epidemic potential, as we have witnessed in the coronavirus disease 2019 (COVID-19) pandemic. The concerned health staff needs to be trained in risk communication. once one or more MPXV cases are reported, special efforts should be made to raise awareness about clinical symptoms and prevention of spread. However, it should not be overdone, which may result in panic.

In end May 2022, the Ministry of Health and Family Welfare (MoHFW), Government of India released guidelines on the detection and management of Monkeypox disease [37]. There is emphasis on intensified surveillance and early case identification, using standard case definitions [37]. A laboratory at National Institute of Virology (NIV) in Pune has been designated as nodal laboratory for monkeypox virus testing in India.

An interim response guideline by the WHO for monkeypox outbreak control, has provided recommendations on preventing the spread and managing monkeypox disease [24]. Key features are summarized in **Box III.**

DISCUSSION

In the ongoing Monkeypox disease outbreak, other than the index case in the UK, there were no substantial travel links of the cases to the endemic areas in Africa, indicating that community transmission may have already begun in some

Box III Key Recommendations for Monkeypox

Management case management

- Mild (suspected or confirmed) cases can be isolated at home with adequate infection control measures and supportive and symptomatic care.

  Antipyretics, adequate nutrition and rehydration form the mainstay of treatment.
- Skin lesions, need to be monitored for secondary bacterial infections and treated accordingly.
- Patients with high risk for complications, including children and pregnant women should be admitted to the hospital for closer monitoring and clinical care.

Pregnant women and children

- Any pregnant women if presents with mild and uncomplicated case, immediate hospital care is not recommended.

  Complicated cases need to be admitted immediately.

  MPX disease is not a direct indication for caesarean section.
- Children at risk should be completely vaccinated according to routine National immunization schedule.

  Newborn baby born to affected mother should be closely monitored for possible congenital infections.
- Breastfeeding of baby born to affected mother should be decided based on general physical status and severity of disease.

Post exposure prophylaxis of health workers

- There should be an assessment and management plan for staff with occupational exposure to MPXV.

Prepared from reference 3,36.

settings. A majority of population in the non-endemic countries, including those affected in the ongoing outbreak, as well as people in India, do not have natural or acquired immunity to MPXV. Though smallpox vaccine is known to have provided protection against monkeypox disease; after the eradication of smallpox virus from India in 1978, immunization against smallpox was stopped which makes the people younger than 42 years relatively more susceptible. However, people older than 42 years may not much protection because of waning immunity.

In the monkeypox outbreak, a majority of cases have been detected in men who have sex with men (MSM)[3]. However, this might be linked to early care seeking by MSM, and the route of sexual transmission further needs further careful assessment [4]. Experts have argued that sexual contact is just a context which has provided close physical contact and thus opportunity to spread.

Due to the COVID-19 pandemic, the capacity in many countries for conducting genomic sequencing has been strengthened. In case of MPXV, genomic sequencing would be useful to identify the clade and the chain of infection. However, considering that MPXV is a DNA virus which has a slow rate of mutation, the repeated genomic sequencing has limited value. Then, MPXV genome has around 200,000 nucleotide bases, six times larger than the severe acute respiratory syndrome corona-virus 2 (SARS CoV-2) and thus genomic sequencing is a bit harder, more time consuming and expensive, with limited benefits.

A key question is whether the MPXV is capable of causing a pandemic? There are several points which make MPXV disease unlikely to become a pandemic. First, it is not a new virus and has been present globally for five decades. There is a reasonable understanding of the viral structure, transmission and pathogenicity. Second, the virus causes mostly mild illness, as evident from zero deaths occurring since the onset of the ongoing outbreak. Third, it is less contagious and requires close personal contact in contrast to SARS-CoV-2 that had a respiratory spread and a high proportion of asymptomatic cases. In Monkeypox disease, person is contagious only when symptoms start appearing, therefore, chances of transmission going undetected are negligible. Fourth, a few smallpox vaccines are readily available and their off-label use can be recommended, and production can be ramped across the globe, if required. Fifth, it is relatively stable virus with very slow rate of mutations. It is in this backdrop, most experts on infectious disease believe that monkeypox outbreak would not turn into the pandemic. There is every reason, as of now, to believe that a Monkeypox outbreak can effectively be tackled and virus contained by isolation of confirmed cases, quaran-tine of contacts and the use of authorised smallpox vaccines as off-label for ring vaccination [24,36,37]. The vaccination of general population is not currently recommended.

The ongoing monkeypox outbreak also raises questions about broader global public health response and collaboration. Despite the existence monkeypox disease in 11 countries in Africa for more than five decades, the disease is getting global attention now only when high and upper-middle income countries have been affected. This reflects the inherent bias in global public health, where diseases of low and middle income countries do not get commensurate priority for research and policy interventions [38].

There is a need for technical discussion amongst experts, at all levels, regarding possible use of smallpox vaccines for monkeypox outbreak situation. The national technical advisory group on immunization (NTAGI) in India and the immunization working groups and expert committees of the professional associations should discuss possible target groups as well as come up with technical guidance on possible target groups and to plan, procure, stockpile and if needed deployment of such vaccines.

In India, many viral and zoonotic diseases have emerged and re-emerged in the last two decades [39,40]. With change in the climate across the world, there are estimates of increased risks of cross-species viral trans-mission and zoonotic diseases [41]. The interventions to tackle those diseases are mostly similar. A stronger primary healthcare system, well-functioning disease surveillance systems, trained public health workforce and focus upon 'One-health' approach where interventions are coordinated to protect the health of humans, animals and ecosystem [42] are essential for any such eventuality. In the last one year, the Indian government has launched Pradhan Mantri-Ayushman Bharat Health Infrastructure mission (PM-ABHIM) [43] to strengthen the block public health laboratories and workforce. Then, in April 2022, a guidance document on public health and management cadre (PHMC) was released [44]. An accelerated and timely implementation of PM-ABHIM and PHMC by Indian states will prepare Indian states for epidemic and pandemic preparedness and response including for responding to zoonotic diseases [45].

CONCLUSION

The emergence of monkeypox disease in non-endemic areas is a reminder that infectious diseases and pathogens are not restricted by the geographical borders. No case of monkeypox virus and disease has been reported from India in the ongoing outbreak; however, there is a need for better preparedness. Strict surveillance at port of entry and early identification, isolation, and case management are the key to response. Disease surveillance, contact tracing and ring vaccination with available smallpox vaccines, authorized for off-label use for monkeypox, for prioritized affected

population are the key strategies. The outbreak in non-endemic countries should be used as an opportunity by India and other countries to strengthen public health surveillance and health system capacity for outbreak and epidemic preparedness and response.

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

Contributors: CL: conceptualized the review, prepared the outline of the paper, conducted initial literature review and prepared the first draft; AT,ND: conducted additional literature review, contributed to the writing of the first draft and analysis. All authors read, reviewed, and approved the final draft.

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Web Table I Key Characteristic of Smallpox and Monkeypox Vaccines

Name and type	*manufacture and country*	*Licensing status*	*Recommended for*	*Remarks*
MVA-BN Third generation; Non-replicating vaccine	Bavarian-Nordic in Denmark	**For Smallpox:** In US and Canada Full market authorization (2019) In EU: exceptional circumstances (2013) **For Monkeypox:** approved and full authorization in US and Canada since 2019	adult population	Very limited supply. Supplied as Imvanex in EU; Ivmamune in Canada) and Jynneos in US (all TM) Empirical data indicate safety in this group and can be used. Off-label use for children can be considered
LC-16 Third generation; Minimally replicating vaccine	KM Biologics, Japan	For smallpox: Fully approved in Japan (1975) and special approval in USA 2014 Not approved for monkeypox in any country	Approved for all ages including infants, children and adults	Only vaccine approved for infants and children. Can be given to pregnant and lactating women.
ACAM2000 Second generation. Standard Replicating vaccinia-based vaccine developed by cell culture technique.	Developed in France and USA,	Smallpox: Approved in USA **For monkeypox;** special circumstances approval in USA	Adults in 18-64 years	Contraindicated in immunodeficient; atopic dermatitis and HIV/AIDS etc. Not recommended for use in pregnant women, infants and children.
Vaccinia/Smallpox vaccines First generation	Multiple countries	Not approved for monkeypox in any country.	Wider age groups.	Not recommended for monkeypox. Ensure strategic reserve for health security and preparedness.

Reference [3,20,36].

Nasal High-Flow Therapy vs Standard Care During Neonatal Endotracheal Intubation

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SUMMARY

In this randomized controlled trial, nasal high-flow therapy was compared with standard care (no nasal high-flow therapy or supplemental oxygen) in neonates undergoing oral endotracheal intubation at two neonatal intensive care units. The primary outcome was successful intubation on the first attempt without physiological instability (defined as an absolute decrease in the peripheral oxygen saturation of >20% from the pre intubation, baseline level or bradycardia with a heart rate of <100 beats per minute) in the infant. At the time of intubation, infants had a median postmenstrual age of 27.9 weeks and a median weight of 920 g. The primary intention-to-treat analysis included the outcomes of 251 intubations in 202 infants; 124 intubations were assigned to the high-flow group and 127 to the standard-care group. A successful intubation on the first attempt without physiological instability was achieved in 62 of 124 intubations (50%) in the high-flow group and in 40 of 127 intubations (31.5%) in the standard-care group (adjusted risk difference, 17.6 percentage points; 95% CI, 6.0 to 29.2), for a number needed to treat of 6 (95% CI, 4 to 17) for 1 infant to benefit. Successful intubation on the first attempt regardless of physiological stability was accomplished in 68.5% of the intubations in the high-flow group and in 54.3% of the intubations in the standard-care group (adjusted risk difference, 15.8 percentage points; 95% CI, 4.3 to 27.3). The authors concluded that among infants undergoing endotracheal intubation at two Australian tertiary neo-natal intensive care units, nasal high-flow therapy during the procedure improved the likelihood of successful intubation on the first attempt without physiological instability in the infant.

COMMENTARIES

Evidence-based Medicine Viewpoint

A recent randomized controlled trial (RCT) compared the success of endotracheal intubation (*Outcome*) in preterm neonates requiring intubation (*Population/Problem*) using either high-flow oxygen delivered through the nose (*Intervention*), or usual care i.e., no high flow or supplemental oxygen (*Comparison*) [1]. The RCT was conducted in two tertiary-level neonatal intensive care units (NICU) in Australia, over a period of 30 months.

Briefly, neonates requiring oral endotracheal intubation were eligible for inclusion in the trial. Those with life-threatening situations (necessitating emergency intubation, or having bradycardia) were excluded, as were those requiring nasal endotracheal intubation, those having contraindications to nasal high-flow oxygen, cyanotic congenital cardiac defects, or maternal/neonatal COVID-19 infection. The informed consent procedure allowed prospective (even antenatal) consent where possible, although retrospective consent was also permitted. The precise method for screening potentially eligible participants was not described.

Following randomization, neonates allocated to high-flow oxygen underwent removal of any pre-existing respiratory support interface, and insertion of nasal cannulae. They received oxygen at 8 L/min, targeting the pre-procedure fractional oxygen concentration (FiO_2), with the provision to increase it to 100% if transcutaneous saturation fell below 90%. High flow oxygen was delivered throughout the intubation process and terminated when the 'intubation attempt' ceased. Neonates in the comparison group did not receive high-flow or supplemental oxygen. In both groups, transcutaneous oxygen saturation was monitored using a pulse oximeter set to its highest sensitivity.

The sample size was calculated to detect an increase in intubation success from the baseline 30% to 50%, with alpha error 0.05 and beta error 0.10. To achieve this, a total of 246 intubations were planned.

At randomization, the neonates were comparable with respect to post-menstrual age, gestational age, birth weight, mode of delivery, proportion with twin deliveries, gender ratio, place of delivery, and 5-minute Apgar score. Neonates in the intervention group had a median age of 7 hours at intubation, whereas it was 13 hours among those in the comparison group. However, the confidence intervals were wide and overlapping. The FiO_2, respiratory support,

oxygen saturation, and indication for intubation, were all comparable between the groups. About half the intubating personnel in each group had performed >20 similar procedures previously.

The primary outcome was 'intubation success,' defined as intubation at the first attempt without physiological destabilization. The definition included correct insertion of the endotracheal tube (confirmed by detecting exhaled CO_2 with a detector device), without fall in oxygen saturation >20% from the baseline, or heart rate <100/minute. The time interval between insertion of the laryngoscope beyond the lips, to its removal, was counted as the duration of the intubation attempt.

Secondary outcomes were oxygen saturation during intubation, time to desaturation, duration of desaturation, duration of intubation attempt, number of intubation attempts, serious adverse events (defined as need for chest compressions, epinephrine within an hour, pneumo-thorax, or mortality within 72 hours). The results of the RCT are summarized in **Table I**.

CRITICAL APPRAISAL

The trial randomized eligible neonates using a computer-generated, block randomization method (with variable block sizes), stratified by trial site, post-menstrual age, and pre-medication use for intubation. However, the unit of randomization was 'intubation episode' and not 'infant', in the sense that infants undergoing multiple intubations could be re-enrolled if the repeat episode was >7 days after the preceding attempt, or the use of premedication differed from the preceding attempt. Allocation concealment was achieved by randomizing at the bedside, using a secure, password-protected internet based system. These procedures and baseline similarity of the groups suggested a low risk of bias.

There was no blinding of those performing the intubations, or those recording the outcomes. This could be

Table I Summary of the Results

Intervention vs Comparison

Primary outcome

- Intubation success (without destabilization)[a]: 62/124 vs 40/127
  - Intubation success (irrespective of destabilization)[a]: 85/124 vs 69/127
  - Proportion without destabilization[a]: 79/124 vs 64/127
  - Proportion without desaturation >20% from baseline: 89/124 vs 77/127
  - Proportion without bradycardia (<100/min): 113/124 vs 111/127

  Subgroup analysis
  - Post-menstrual age: neonates ≤28wk[a]: 34/64 vs 23/66; >28 wk[a]: 28/60 vs 17/61
  - Use of premedication Yes[a]: 50/92 vs 30/93; No: 12/32 vs 10/34
  - Intubator's experience: <20 previous intubations[a]: 30/61 vs 8/51; ≥20 previous intubations: 32/63 vs 32/76

Secondary outcomes

- Median (IQR) oxygen saturation during intubation[a]: 94 (83,98), *n*=120 vs 89 (79,95), *n*=126
- Proportion with desaturation: 35/124 vs 50/127
- Mean (SD) time to desaturation (sec)[a]: 44.3 (19.5), *n*=34 vs 35.5 (19.5), *n*=50
- Mean (SD) duration of desaturation (sec): 65.0 (35.1), *n*=34 vs 63.6 (38.9), *n*=47
- Median (IQR) duration of intubation attempt (seconds):
  - First attempt: 50.5 (33.5, 69.0), *n*=124 vs 46.0 (33.0, 66.0), *n*=127
  - All attempts: 58.0 (36.0, 95.0), *n*=123 vs 68.0 (35.0, 125.0), *n*=127
- Median (IQR) number of intubation attempts: 1 (1,2), *n*=124 vs 1 (1,2), *n*=127
- Proportion with bradycardia: 11/124 vs 16/127
- Mean (SD) time to bradycardia (sec): 39.4 (22.9), *n*=11 vs 39.9 (19.9), *n*=15
- Mean (SD) duration of bradycardia (sec): 26.6 (20.7), *n*=11 vs 31.3 (23.3), *n*=15
- Serious adverse events
  - Need for chest compressions or epinephrine: 0/124 vs 2/125
  - Pneumothorax within 72 h: 2/124 vs 6/127
  - Mortality within 72 h: 1/124 vs 3/125

[a]*Statistically significant.*

a source of bias in this RCT, as the impact of foreknowledge of the allocation, on the measurement of the outcome cannot be judged. However, there were no major protocol deviations reported, and the investigators used intention-to-treat analysis. For most outcomes, almost all the randomized participants were included in the analysis, and the results do not appear to be biased by missing data. The methods used for measuring the outcomes appear to be appropriate, and ascertainment of outcomes did not differ in the two groups. The data were reported as specified a priori, and there is no suggestion that data presentation was influenced by the results obtained. Overall, the RCT may be classified as having low to moderate risk-of-bias, fostering reasonably high confidence in the reported results.

The RCT included several noteworthy methodological refinements. Strict definitions were used for the various outcomes recorded. Sensitive measurements such as oxygen saturation recording and confirmation of place-ment of the nasal cannulae, were done using sophisticated instruments. In addition to recording of outcomes by personnel present at the site, the entire procedure was videographed, and reviewed independently. Discrepancies between on-site versus observations based on video-recording were resolved by a different assessor. An independent data and safety monitoring board (DSMB) evaluated patient safety after each quartile of the population sample was enrolled, and an independent interim data analysis was planned midway through the trial.

Despite these, there are a few issues raising concern. It appears that the comparison group did not receive any oxygen during the intubation procedure. The rationale for this is unclear, especially because the indication for intubation itself was hypoxia in nearly 60% of the neonates, and apnea in another 20%. In such a population, omission of oxygen during intubation appears to put the com-parison group neonates at a disadvantage. As the study was designed to evaluate the efficacy of high-flow oxygen therapy, it would seem reasonable to provide the comparison group neonates at least (low-flow) blow-by oxygen delivered close to the nose.

The intervention group neonates required approximately 10 seconds for securing the high-flow nasal cannulae, during which time, they would have received high-flow oxygen for part or the entire duration. However, this duration of time was not factored into the total duration of delivering high-flow oxygen, which could tilt the results is favor of the intervention.

Further, 90% neonates in both groups were receiving continuous positive airway pressure (CPAP) at randomization. Presumably CPAP was delivered using oxygen; this is borne out by the high baseline FiO_2 in both groups. As supplemental oxygen was discontinued in the comparison group, most likely CPAP also had to be discontinued in them. In contrast, high-flow oxygen delivered at 8.0 L/min through nasal cannulae in the intervention group could have had some positive airway pressure effect, which was denied to the comparison group. These factors suggest that the comparison group neonates were at a disadvantage from the time of randomization to intubation. The influence of this on the overall results is unclear.

As in the real-word scenario, considerable leeway was provided to the intubating personnel with regards to pre-oxygenating the neonates, use of video laryngoscopy, and most important, the duration of each intubation attempt. This flexibility within a RCT is likely to have resulted in a scenario, wherein intubation attempts in individual neonates continued until desaturation occurred, rather than being ceased after a pre-specified time had elapsed. Thus, intubation time exceeded the suggested limit of 30 seconds [2] in both groups by more than 15 seconds. It can be argued that in a RCT, the duration of each intubation attempt should have been capped by a prespecified time limit. As statistically significant differences in successful intubation were observed only among less-experienced intubators, but not among more experienced personnel, this methodological aspect should not have been overlooked. However, to be fair, there was no difference in the actual duration of intubation (first attempt or overall) in the two groups.

In this RCT, although 462 neonates were eligible for inclusion, 161 (34.8%) were not enrolled because either the "researcher was unavailable" or "not notified." The reasons for (and impact of) these exclusions are unclear. If these occurred due to being out of routine working hours, it could have created a selection bias.

CONCLUSION

This well-designed RCT suggested that high-flow oxygen therapy delivered through nasal cannulae resulted in greater success in oral intubation, better oxygen saturation during the procedure, and longer time-to-desaturation, in preterm neonates requiring endotra-cheal intubation, compared to those who did not receive supplemental oxygen. However, some methodological issues, and the diversity of the study setting (compared to the usual settings in India) suggest that these apparently impressive results are insufficient for a blanket change in local clinical practice.

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Neonatologist's Viewpoint

Endotracheal intubation is one of the common procedures in neonatal intensive care units (NICUs) and is often realized as an emergency procedure. Hypoxemia, bradycardia, and cardiac arrest are serious adverse events, and the reported incidence in NICUs varies between 5-36% [1,2]. Neonates, especially preterms, are particularly predisposed due to their low functional residual capacity. Several strategies like use of video laryngoscope, premedication, selection of experienced operators, and use of checklists have been evaluated to ensure safe intubations [3-5]. Pre-oxygenation before intubation has been a standard of care in many adult ICUs [6], and in earlier recommendations of neonatal resuscitation.

High flow oxygen (HFO) is a device to provide heated and humidified high flow oxygen with very soft nasal cannula at titratable oxygen concentration (FiO2). In the current study done in Australia on preterm babies, the investigators report greater success in intubation rate in first intubation with the use of high flow oxygen (50%), using Vapotherm, immediately after removing the pre-exiting respiratory support (CPAP) interface, compared to standard intubation procedure with no supplemental oxygen (31.5%). The study describes outcomes from an innovative strategy to ensure successful intubation with-out any adverse outcomes. It was an unblinded randomized controlled trial, where video reviews of all the intubations were done, to assess the primary outcome. Per protocol analysis was not performed. The consent was taken antenatally; however, retrospective consent was also approved.

It was a well-planned and well executed study, and presents some thought provoking issues. Out of the 462 eligible neonates, nearly 50% (204) were not included in randomization, thus raising concerns of selection bias at enrolment. The characteristics and sickness scores of non-enrolled neonates would be interesting to look at. Use of video laryngoscopy is known to facilitate intubations and this factor in both groups was based on clinicians' discretion. It would be of interest to know the proportion of intubations that were performed using video laryngo-scope in the two groups.

Considering the current evidence, tight control of oxygenation for preterm neonates in the delivery room is prudent; the authors state that 25% of enrolled intubations were performed in delivery room, in the immediate period after birth. Use of high flow at 8L/min even for brief period during intubation, can be a potential source of harm due to hyperoxygenation, in the real world scenario of delivery room intubation. Of note, 90% of neonates before intubation were on CPAP in the study cohort, which raises a logistic concern of using or even just keeping both the high flow equipment as well as CPAP equipment and tubing in most of the resource-limited settings, like India.

Intubation by indication is one factor which can determine the success or failure of the procedure, and in this study 15% indications for intubations were non-specific. This may have implications on generalizability of this intervention in dissimilar settings. The authors state that mechanical failure of the nasal high flow device and dislodgment of nasal cannula were documented but not deemed to be protocol violation; however, such mecha-nical failures could be expected in settings where a skilled person may be the only person responsible for the management of the neonate. The use of premedication was 50.3% in high flow group compared to 34.8% in standard group; many neonatal units in developing world may still not be proficient with the use of premedication before intubation. The contribution of premedication to success of intubations remains to be explored in this context. Lastly, peripheral oxygen saturation can be sometimes misleading and use of EtO2 would be a better guide as a marker of saturation as outcome measure and efficacy of intubation [7,8].

HFO can also be delivered by use of the CPAP used for respiratory distress pre-intubation, but with increased FiO2 only for pre-oxygenation instead of removing CPAP and trying a new device like Vapotherm for pre-oxygenation for intubation. It would be worthwhile conducting another trial comparing successful intubation while continuing CPAP with higher FiO2 to HFO after removing CPAP interface and evaluate similar outcomes again. One should also be cognizant that Vapotherm, which is the device used in this study, is still not available universally in many neonatal care units. Other high flow oxygen devices that are very commonly used in India also need to be evaluated for aiding pre-oxygenation in success of intubation. We also need to evaluate how free flow oxygen with varying oxygen concentration through blender compares to Vapotherm or other HFO devices in reducing adverse events during neonatal intubations.

The study has raised the important question of devising a strategy for improving successful neonatal intubations. The external validity and generalizability of this intervention in other dissimilar settings remains to be evaluated. Whether improving the skills in existing standard operating procedure using simulators and/or video laryngoscopes for intu-bation is cost effective in resource limited settings is also to be deliberated upon. Till we have these questions answered, as

per results of this study, neonatal units may consider initiating Vapotherm as HFO for pre-oxygenation for successful intubation without physiological instability.

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Pediatrician's Viewpoint

Endotracheal intubation is a common procedure in a neonatal intensive care unit (NICU). Though, over the years, neonatal care has become more noninvasive and endotracheal intubations are more often preferred to be avoided. Nonetheless, intubations become essential when a sick neonate deteriorates on a noninvasive mode of ventilation or during delivery room care. This randomized control trial, which was conducted at two tertiary centers of Australia, compared the efficacy of nasal high flow therapy for successful attempts at oral intubation. The control group was given standard care during intubation without nasal high flow therapy. The randomization done in the study is robust and safety was monitored regularly during the trial. The trial results are encouraging as physiological instability (desaturation and/or bradycardia) during intubation is the major reason behind failed intubation attempts [1,2]. The intubations at delivery room were also included in the trial, which are done without premedication. The mean postmenstrual age of study population was 27.9 week and weight was 920 gram. The use of video recording during intubations has added to the objectivity of the outcomes studied.

The use of high flow therapy is common in Indian NICUs, nowadays. The neonates are primarily managed on noninvasive ventilation (nCPAP or High flow therapy). The need of intubation itself suggests that the neonate is critically sick and therefore successful intubation in a smaller number of attempts is what is aimed at by the treating pediatrician/neonatologist. This study is encouraging in Indian context as study population is relatively mature, which is the neonatal population mainly managed at district SNCUs (special care neonatal units). The availability of high flow nasal cannula may not be universal in district level SNCUs or government teaching institutes. The limitation of this study is treatment assigned was not concealed, and the number of intubations was taken into consideration and not individual neonates. Though this was minimized considering reintubations, which had an interval of one week.

Various studies have proven that experience of successful intubations further increases the confidence level of healthcare professional attempting intubation [3,4]. Thus, use of a simple equipment during intubation in order to improve efficacy should be attempted in Indian settings as well.

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Antiseizure Medication Withdrawal in Seizure-Free Patients: What is New for the Pediatrician?

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The American Academy of Neurology (AAN) has recently updated its practise advisory on antiseizure medication withdrawal. The recommendations have been formulated for pediatric as well as adult epilepsy, with emphasis on the risk factors for seizure relapse, occurrence of status epilepticus or death on drug withdrawal, and effect on quality of life in both age groups. We herein list the important aspects of the updated recommendations in pediatric epilepsy for the benefit of the general pediatricians. The full update is available at the AAN website.

Keywords: *American Academy of Neurology, Epilepsy, International League Against Epilepsy, Italian League Against Epilepsy.*

After a patient with epilepsy has initiated an anti-seizure medication (ASM) and achieved a sustained period of seizure freedom, the decision regarding continuation of therapy indeterminately, can be perplexing. Stopping ASMs is routinely practiced in patients who have epilepsy in remission. However, in literature there are no established guidelines that can lead to the constant application of a universally accepted withdrawal protocol in adults as well as children.

With obvious reason of drug associated side effects (behavioral, cognitive and chronic side effects) and the possibility of achieving 65-85 % of remission with ASM therapy, it is prudent to consider for ASM withdrawal. However, as the risk of relapse is around 23.7%, the decision of ASM withdrawal becomes controversial even in individuals with well controlled epilepsy [1,2]. The Akershus study done to assess effect of ASM withdrawal on cognitive function, seizure relapse and health related quality of life in adults, showed significant improvement in neuropsychological performance at 12 months of stopping ASM with relative risk of seizure relapse of 2.46, compared to those continuing the therapy [3].

The physician contemplating ASM withdrawal is faced with two important considerations i.e., time of withdrawal and mode of withdrawal. American Academy of Neurology (AAN), in 1996, recommended two to five years of seizure-free period before stopping ASMs [4]; however, the minimum period of seizure freedom has been indicated to be two years according to the recent literature [5]. There is no consensus on the mode of withdrawal, and the drug tapering can range from slow (spread over up to 2 years) to rapid withdrawal (within 3 to 6 months). Slow tapering has also been defined as drug withdrawn over more than three months, and rapid tapering as, drug withdrawn within three months [6]. A recent Cochrane review [6] did not find a reliable agreement on the optimal rate of drug tapering based on the results of two randomized control trials done in pediatric population.

Another important point of contemplation in drug withdrawal is monotherapy versus polytherapy. Studies have revealed a higher relapse rate in patients receiving polytherapy as compared to those receiving mono-therapy after stopping ASMs [7]. However, the interplay with other factors in patients with polytherapy e.g., higher age at seizure onset and longer duration of epilepsy before treatment, may contribute to recurrence. Therefore, a practical approach would be slow and steady withdrawal in patients receiving polytherapy.

In order to decide suitability for ASMs withdrawal, it is necessary to consider factors related to patients' profile, epilepsy characteristics and specific pharma-cological treatments, which may predict the chances for seizure recurrence after stopping ASMs [7-10] **(Table I)**.

Majority of the published guidelines lack a universal protocol on ASM withdrawal after a period of seizure remission. It has been mentioned in various guidelines that neuroimaging and electroencephalogram play an important role in identifying the seizure etiology and aid in prognostication for future relapse. Access to these

Table I Prognostic Factors Associated With Risk of Seizure Reccurrence

Increased risk	*No increased risk*
Patient-related factors (neuropsychiatric conditions) [8-10]	–
Abnormal neurological examination Global developmental delay Intellectual disability History of neonatal seizures Late childhood/adolescent onset of seizure	
Factors related to epilepsy [5,8,10]	
Symptomatic generalized and partial epilepsies Juvenile myoclonic epilepsies Juvenile absence epilepsies Presence of status epilepticus Epileptiform EEG pattern before or after drug withdrawal EEG changes: Focal slow abnormalities or paroxysmal abnormalities	Symptomatic, cryptogenic or idiopathic epilepsy, Benign childhood epilepsy with centrotemporal spikes, Benign infantile seizures etc.
Factors related to therapy [7,10]	
Polytherapy needed for seizure control	–

modalities may modify the clinician's decision regarding the ASM withdrawal, even in a well-controlled epilepsy.

American Academy of Neurology (AAN) has recently updated its recommendations on ASM withdrawal [11]. The recommendations are listed separately for children and adults (≥18 years), and focal seizures are distinguished from generalized seizures. The outcome measures considered in formulation of recommendations in patients who withdrew ASM after 12 months or more of seizure remission vs those who did not, included *i*) seizure relapse among those with electroclinical syndromes, epilepsy surgeries; *ii*) Risk factors for seizure recurrence in terms of Odds Ratio; *iii*) Quality of life data; *iv*) Occurrence of status epilepticus; and *v*) Mortality.

We, herein, list the major recommendations on ASM withdrawal and discuss some of the important changes of the revised AAN practice advisory [11] along with the recommendations from Italian League against Epilepsy (LICE), 2013 [5] (**Table II**).

AAN, 2021 RECOMMENDATIONS

The recommendations applicable to pediatric population are discussed here.

Risk of Seizure Recurrence

The new practice advisory states that there is no significant difference in seizure recurrence rate in children who taper ASMs at 2 years vs 4 years (Level B); however, there is insufficient evidence to comment on risk of seizure recurrence in children who taper ASMs at 18 vs 24 months. Moreover, different electroclinical syndrome have different set of characteristics (specific age of onset, semiology, EEG changes) that would influence seizure relapse rate. Thus, natural course of a specific electroclinical syndrome must be known to the pediatrician as it may influence the seizure reoccurrence rate in individual syndromes (Level A). Insufficient evidence was found to support or refute that a variety of risk factors (age, sex, type of seizure, intellectual disability, perinatal insult etc.) may predict the possibility of recurrence. Abnormal EEG before ASM withdrawal and EEG with interictal epileptiform discharges is associated with likely increased rate of seizure recurrence. There is insufficient evidence to suggest the type of EEG required (sleep deprived), or length of EEG needed to predict seizure recurrence risk.

Risk of Status Epilepticus

The advisory states that ASM withdrawal possibly may not increase the risk of status epilepticus in adults; however, there is insufficient data on children. Though the evidence is low, recurrent seizures may put children at risk of status epilepticus and death, and this aspect of ASM withdrawal should always be discussed with the patient's family. (Level B**)**

Effect on Quality of Life

There is scarcity of data on quality of life (QOL) in children with ASM usage, and therefore, it is suggested that the other contributors to QOL should be taken into consideration while making a decision regarding ASM withdrawal in children. (Level B)

Speed of Medication Withdrawal

According to the new practice advisory, children who are seizure free for at least 18-24 months, withdrawal of ASMs at

Table II Summary of Recommendation for Antiseizure Medication (ASM) Withdrawal in Pediatric Patients

Italian league Against Epilepsy, 2013 [5]	*American Academy of Neurology, 2021 [11]*
Duration of seizure free period	
At least 2 years of seizure freedom (Level B).	2 years of seizure freedom (Level B).
Risk factors for seizure recurrence in epilepsy type	
Benign epilepsy with centrotemporal spikes and most idiopathic generalized epilepsies are associated with favorable prognosis.	
The presence of partial seizures should not be considered per se a risk factor for relapse, in absence of other relevant seizure predictors (abnormal EEG and/or documented etiology) (Level B).	
Female sex, family history of epilepsy, history of febrile seizures, disease length/severity, and number and type of drugs taken should not influence the decision to stop treatment (level C)	
Prolonged duration of active disease before and during treatment and high seizure frequency per say should not stop ASM withdrawal (Level C).	-
Electro-clinical syndrome	
Specific epileptiform EEG should preclude the decision of ASM withdrawal (Level B).	Clinicians must know about the natural history of the specific electroclinical syndrome when counselling about ASM withdrawal (Level A).
Abnormal EEG at ASM withdrawal	
A patient with abnormal EEG (with or without epileptiform activity) at the time of ASM withdrawal should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if abnormal EEG is the only negative prognostic predictor (Level B).	In children seizure-free for at least 18–24 mo, an EEG should be ordered before attempting ASM withdrawal (Level B). Interictal epileptiform activity on EEG possibly increases the risk of seizure recurrence in children (low confidence). There is insufficient evidence to suggest the type and length of EEG required to predict the seizure recurrence risk.
Documented seizure etiology including mental retardation and perinatal insult	
A patient with a documented seizure etiology should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if this is the only negative prognostic predictor. (Level B).	Insufficient evidence to refute or support.
Risk of status epilepticus/SUDEP after ASM withdrawal	
No recommendation	Clinicians should counsel that recurrent seizures may put children at risk for status epilepticus and death; although, existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal (Level B).
Rate of ASM withdrawal	
Slow discontinuation of AEDs should be encouraged and the duration of the tapering period should be tailored to the patient's needs and preferences (Level B).	ASM withdrawal should be offered, at a rate no faster than 25% every 10–14 d (Level B). There is a small risk to treatment non-responsiveness if seizure reoccurs during or after ASM withdrawal (Level B).
Follow up after ASM withdrawal	
A patient discontinuing treatment for seizure freedom should be followed for no less than 2 y (Level B).	No recommendation

SUDEP: sudden unexpected death in epilepsy.

a rate of 25% every 10 days to 2 weeks is not significantly different in increasing the risk of seizure recurrence than withdrawal at a rate of 25% every 2 months. Therefore, ASM may be withdrawn rapidly at the rate of 25% every 10-14 days (Level B).

These new guidelines lacks specific recommen-dations on commonly seen pediatric epileptic conditions (meningitis, neurocysticercosis, post trauma epilepsy etc.) in developing countries like India.

CONCLUSION

The decision to withdraw ASM in seizure-free patients is a difficult aspect of pediatric epilepsy management as parental anxiety and presence of other risk factors make it more challenging. The new AAN practice advisory is likely to aid in making a decision regarding the ASM withdrawal in seizure-free patients. High-quality studies are required to further investigate the unexplored parameters and address the following questions: *i*) should different seizure free period be considered for ASM withdrawal? *ii*) should epilepsy syndrome with specific character and seizure morphology preclude or favor ASM withdrawal? *iii*) should any of specific EEG or MRI brain findings and genetic testing add to the prognosis for seizure recurrence?

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Clinical Features and Adverse Prognostic Indicators in *Datura* Poisoning in Children

We describe the clinical features and adverse prognostic indicators of *Datura* intoxication in 47 children. 15 (31.9%) children required intensive care and 1 (2.1%) died. Time elapsed >3.15 hour between ingestion and starting treatment [RR (95% CI): 9.4 (3.1-28.3)], age <9.5 year [RR (95% CI): 3.5 (1.5-8.0)], and seizure [RR (95% CI): 2.8 (1.4-5.8)] were the most important adverse prognostic features.

Keywords: *Atropine, Anticholinergic, Physostigmine, Toxidrome.*

Datura stramonium, an annual herb found universally in India, and is a frequently encountered cause of plant poisoning in children [1]. All the parts of the plant are toxic, particularly the fruits and seeds [2]. Intoxication results in anticholinergic symptoms and signs, due to presence of alkaloids (predominantly atropine, hyoscyamine, and scopolamine) [3]. Majority of available literatures is descriptive in nature, and focuses primarily in the Western population [4,5]. Hence, this study was conducted to identify the clinical features and adverse prognostic indicators of *Datura* intoxication in Indian children and adolescents.

This observational study was conducted in the Pediatric ward of a tertiary care center of West Bengal between 1 January, 2016 and 31 December, 2021, after taking approval from the Institutional ethics committee. Informed consents/assents were obtained from parent/ legal guardians/participants prior to enrolment. Datura poisoning was confirmed by identification of plant parts (by doctors/nurses/relatives), suggestive clinical features and, pilocarpine test [2]. A pre-designed, pre-tested schedule was used for data collection. Age- and sex-specific charts were used for identifying tachycardia and hypertension. Treatment included gastric lavage, supportive measures, physostigmine, and sedatives (diazepam). Paediatric intensive care unit (PICU) admission was decided by on-duty residents, guided by PRISM III score [6]. Blood investigations were performed if fever persisted for more than 12 hours, and according to clinical indications.

Shapiro-Wilk test was used to check nature of distribution. Chi-square test and Student *t*-test were used for checking statistical significance of difference between proportions and means, respectively. Relative risk (RR) for PICU admission was calculated. For continuous variables, cut-off values were calculated from the Receiver Operator Characteristic curve with the help of Youden's index. Binary logistic regression analysis was used to identify contribution of individual factors. P<0.05 was taken as statistically significant. SPSS version 19.0 was used for data analysis.

Forty-nine children were admitted with datura poisoning during the study period; data for two children were not available (1-refused consent, 1-left against medical advice). Of the 47 children [57.4% boys, mean (SD) age 12.0 year (4.0)], majority were Hindu (31, 66%), Bengali (45, 95.7%), belonged to lower socioeconomic status (26, 55.3%) and from rural area (43, 91.5%). Accidental poisoning was most common (30, 63.8%), followed by suicidal (16, 34%). All cases (47, 100%) were admitted following acute datura ingestion. Fifteen children (31.9%) required PICU admission, and one child (2.1%) could not be saved. Clinical features are presented in **Table I,** and the factors associated with PICU are summarised in **Table II**. Time elapsed between ingestion of *Datura* and starting treatment (>3.15 hour) [RR (95% CI): 9.4 (3.1-28.3); *P*=0.0001], age <9.5 year [RR (95% CI): 3.5 (1.5-8.0); *P*= 0.003] and seizure [RR (95% CI): 2.8 (1.4-5.8); *P*=0.004] were the independent risk factors of PICU admission following datura ingestion. Our model could correctly predict 56.9%-79.7% variance of independent variables, out of which 47.3%-66.2% variance was due to 'time elapsed between ingestion of *Datura* and starting treatment' alone.

In this study, the need for PICU admission and mortality were higher than previous reports [7,8] probably due to variability in amount of consumed datura and variable age distribution. Poisoning was mainly accidental, contrary to western countries (intentional), probably due to difference in culture, and under-reporting. Homicidal poisoning, though reported both in India and abroad [2,9], was not documented in this study. Clinical features of datura intoxication were similar to previous observations [2,4,5,7-9]. However, unlike previous report, neither rhabdomyolysis nor acute liver failure was noted in the current study [2]. Minute variations could be due to variation of species of *Datura* in different geographic areas, and intra-species and inter-species variation of alkaloid concentration [3]. Higher time elapsed before starting treatment and seizure, were important adverse prognostic indicators, probably both lead to higher concentration of atropine in central nervous system. Better systemic absorption of alkaloids might predispose younger children to more toxicity [10].

Table I Clinical Features of Datura Ingestion Among Children (*N*=47)

Clinical feature	*No (%)*
Mydriasis	46 (97.9)
Tachycardia	42 (89.4)
Delirium	39 (83.0)
Dry mouth	37 (78.7)
Fever	34 (72.3)
Behavioral abnormalities	24 (51.1)
Urinary retention	23 (48.9)
Hypertension	18 (38.3)
Seizure	7 (14.9)

Table II Factors Associated With Need for Pediatric Intensive Care Unit (PICU) Care.

Variables	*PICU required (n=15)*	*PICU not required (n=32)*
Age (y) [a,b]	9.4 (4.0)	13.3 (3.3)
Male sex	8 (53.3)	19 (59.4)
Lower socioeconomic status	8 (53.3)	18 (56.2)
Time since ingestion (h)[a,b]	4.2 (1.3)	2.2 (0.7)
Mydriasis	15 (100)	31 (96.9)
Tachycardia	13 (86.7)	29 (90.6)
Delirium	13 (86.7)	26 (81.3)
Dry mouth	12 (80.0)	25 (78.1)
Fever	11 (73.3)	23 (71.9)
Behavioral abnormalities	10 (66.7)	14 (43.8)
Urinary retention	8 (53.3)	15 (46.9)
Hypertension	5 (33.3)	13 (40.6)
Seizure [c]	5 (33.3)	2 (6.2)

Values in no. (%) or [a]mean (SD). *[b]P<0.001; [c]P<0.05.*

Chemical analysis of seeds could not be performed and serum level of alkaloids could not be estimated, and some information was solely based on self-report. To conclude, age of patients, and time elapsed between ingestion of *Datura* and starting treatment were two important factors associated with outcome of Datura ingestion in children. Further research in this under-reported entity is warranted for more generalizable data.

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Revisiting MIS-C: Extending the Exclusions

Following coronavirus disease 2019 (COVID-19) or asymptomatic severe acute respiratory system corornavirus 2 (SARS-CoV-2) infection, multisystem inflammatory syndrome following COVID-19 in children (MIS-C), is a relatively new entity with diagnosis based on preliminary case definition criteria, formulated to assist management of this potential life-threatening condition [1]. In the absence of standardized guidelines, there is a possibility of not only missing milder cases but also over diagnosing diseases with overlapping presentations, as MIS-C.

We report 11 children, initially treated as MIS-C, who got a different final diagnosis. Out of them four were diagnosed at our center and seven were referred from outside after MIS-C treatment. **Table I** illustrates the clinical and laboratory profile of these patients. Ten (91%) patients met the World Health Organization (WHO) case definition criteria at initial presentation. One referred patient was treated as MIS-C without meeting the criteria. Median age and male:female ratio were 8 (2-15) years and 1:2.66, respectively. Median time to arrive at final diagnosis was 2 (1-5) months. All had fever and raised inflammatory markers on re-admission.

The definitive diagnosis were hematolymphoid diseases in 4 (36%), collagen vascular diseases in 4 (36%), and infections in 2 (18%) children. One child had an inflammatory myo-fibroblastic tumor. Hematolymphoid diseases were diagnosed on bone marrow and tissue examination. Diagnosis of collagen vascular diseases was as per standard rheumatological guidelines and serological reports. Imaging aided diagnosis of inflammatory myo-fibroblastic tumor, Takayasu arteritis, Hodgkin lymphoma and lymphoproliferative disorder.

During initial admission, all received antibiotics and steroids. 18% (*n*=2) received IVIg and steroids, and 36 % (*n*=4) patients needed PICU care during their treatment. Five patients (45%) were discharged on aspirin. After definitive diagnosis, nine patients (82%) responded to the specific treatment, but two patients (18%) succumbed to their illness (Hodgkin lymphoma stage 4 and lymphoproliferative disorder). The collagen vascular disease group had high serum ferritin level [median (IQR) 1909 (1208) ng/mL]; whereas, hematolymphoid group had low neutrophil: lymphocyte ratio of 2.2 and low platelet count.

Case definition criteria for MIS-C were intentionally kept wide enough to include all possible cases and were open for revision with availability of more information. Broad, et al. [2] reported that 70 patients were diagnosed as MIS-C by pediatric multi-disciplinary team based on clinical features and evidence of inflammation. After investigations, treatment was discontinued in 13 (18.5%) patients as alternative diagnosis became available. Finally, only 57 (81%) patients were truly confirmed as MIS-C [2]. They did not report any significant difference in clinical and biochemical parameters between those who met and did not meet the diagnostic criteria in this study [2].

WHO mentions 'absence of other causes of inflammation' as one of the essential case-defining criteria but has emphasized upon infections as main mimicker of MIS-C. However; our cohort had mainly hematolymphoid and collagen vascular diseases masquerading as MIS-C. Recently, American College of Rheumatology guidelines recommend ruling out malignancy and autoimmune disorders before making a diagnosis of MIS-C [3].

Inflammation being a known hallmark in collagen vascular diseases, the criteria for case definition of MIS-C are met by many children with these disorders [4]. We observed that the median serum ferritin (1208 ng/mL) of these patients were higher than that of MIS-C patients at presentation [5]. Hematolymphoid diseases may be associated with secondary hemophagocytic-lymphohistiocytosis (HLH), which has inflammatory features similar to MIS-C [6]. However, the neutrophil to lymphocyte ratio in these patients was lower than that in MIS-C patients, and platelet count was less than 1 lakh in the majority (*n*=3, 75%) [5].

At the peak of the COVID pandemic, steroids were utilized extensively as a life-saving measure to treat MIS-C. However, two patients with hematolymphoid malignancies in our cohort succumbed, as steroids induced partial remission leading to delayed diagnosis and initiation of specific treatment. Additionally, positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) antibody titers led to bias in diagnosing MIS-C. At our institute, out of 87 patients treated as MIS-C, 4 (4.6%) had different final diagnosis on follow up viz., collagen vascular disease (2 patients) and CVID with septic shock and Hodgkin lymphoma stage 4 (1 each) (Unpublished data). However, this should not discourage timely diagnosis and treatment of MIS-C, a life threatening condition.

Collagen vascular disorders, hematolymphoid diseases and atypical infections can initially present as MIS-C, and meticulous evaluation to rule out these is needed. Patients diagnosed and treated as MIS-C need to be followed-up to ensure absence of an alternate diagnosis and complete relief of symptoms.

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Table I Clinical and Laboratory Profile of Children Misdiagnosed as MIS-C

Age/ sex	*Initial presentation*[a]	*D-dimer (µg/mL)*	*ESR (mm/h)*	*CRP (mg/L)*	*Ferritin (ng/mL)*	*Re-admission*[b]	*Final diagnosis*	*Time to diagnosis (mo)*
Hematolymphoid								
6y/F	Cheilosis, abdominal pain	587	28	42	37	Inguinal lympha deno-pathy, abdominal pain	Acute leukemia	5 m
4y/F	Hypotension, pulmonary bleeding, regurgitation, abdominal pain,	5000	58	26	58	Ascites, pleural effusion	Lympho-proliferative disorder	1m
15y/M	Red tongue, oral ulcers, abdominal pain	2626	80	160	600	Jaundice splenomegaly	Hodgkins lymphoma stage 4	5 m
14y/M	Lower limb edema, rash, abdominal pain, vomiting	Not done	24	14	176	Pancytopenia	Aplastic anemia	1 m
Collagen vascular disease								
13y/F	Skin rash, ankle pain	11770	61	160	11326	Cervical lympha-denopathy, ankle and knee joint arthritis	SOJIA	3 m
14y/F	Abdominal pain, hypotension	319	70	85	445	Abdominal pain, feeble pulses	Takayasus arteritis	1 m
8y/F	Rash, Hypotension, abdominal pain, vomiting	1001	60	72	62	Cervical dystonia, lymphadenopathy, rash, wrist synovitis	Undifferentiated connective tissue disorder	5 m
9y/F	Rash, lower limb swelling, abdominal pain	2043	90	74	1971	Rash, arthritis	SOJIA	2 m
Infections								
2y/F	Rash, Hypotension, coronary dilatation, abdominal pain	10488	43	20	2550	Rash Shock	CVID septic shock	4m
2y/F	Red eyes, oral ulcer, abdominal pain	830	24	69	505	Abdominal pain	Brucellosis	1m
Other								
3y/M	Rash, conjunctivitis, dilated coronaries, abdominal pain	485	81	66	380	Abdominal pain, abdominal mass on USG	Inflammatory myofibroblastic tumor	1m

MIS-C: multisystem inflammatory syndrome following COVID-19 in children. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SOJIA: systemic onset juvenile rheumatoid arthritis; CVID: common variable immunodeficiency. [a]Along with fever >3 d; [b]along with fever and raised inflammatory markers.

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Concurrent Coxsackie Virus A6 Infection and Kawasaki Disease

Hand-foot-mouth disease (HFMD), a highly contagious viral infection commonly affecting children younger than five years, usually shows maculopapular or vesicular eruptions on the hands, feet, and the oral mucosa. Coxsackievirus A16 and Enterovirus 71 are the predominant HFMD pathogens. Of them, Coxsackievirus A6 (CVA6) manifests the more severe or atypical variant of HFMD, characterized by high fever with vesiculobullous exanthema often spreading more widely on the trunk and extremities, with perioral zone involvement [1]. Kawasaki disease (KD), the most common childhood vasculitis, preferentially involves coronary arteries. The KD etiology remains obscure despite extensive research undertaken to elucidate it. Infections may be the potential trigger for KD, especially in genetically susceptible children [2]. Our patient presented with concurrent occurrence of HFMD and KD. We therefore attempt to address comorbidity between CVA6-associated HFMD and KD.

A previously healthy Japanese 3-year-old boy was hospitalized for fever, left cervical swelling, and rash, which began 3 days before admission. His temperature was 39.4°C. Left cervical lymph nodes were tender and enlarged. Oral examination revealed 1-2 mm fine petechiae on the soft palate and erosions on the buccal mucosa. There were diffuse 1-3 mm discrete, monomorphic, erythematous papules concentrated primarily on the face in the perioral region and forehead, palms and soles, dorsal hands, fingers, and buttocks. Cardiac, respiratory, and abdominal examinations were normal at admission. The patient's elder sister had a past history of KD.

Laboratory findings included hemoglobin of 11.1 g/dL, white blood cell count of 18.1×10^9/L (neutrophils 84.4%, lymphocytes 15.6%), platelet count of 347×10^9/L, C-reactive protein of 8.74 mg/dL, and procalcitonin of 0.68 ng/mL. Coronavirus disease 2019 (COVID-19) antigen determined by the automated immunoassay system HISCL-800 (Sysmex Corp.) using nasopharyngeal swab was negative. Other laboratory tests to examine electrolytes, liver function, and kidney function yielded normal results. Intravenous ceftriaxone (100 mg/kg/day for 3 consecutive days) failed to reduce fever. Periungual hemorrhagic bullae became evident on several digits of the hands and feet.

On the 5th hospital day, an additional diffuse erythematous maculopapular rash, bilateral non-purulent conjunctival hyperemia, injected, dried and fissured lips, and strawberry tongue were found. Echocardiography showed a hyperechogenous aspect of both coronary arteries with mild dilatation. A diagnosis of KD was made. The patient was treated with intravenous immunoglobulins (IVIG, 2 g/kg over 24 hours of infusion) along with oral acetylsalicylic acid (33 mg/kg/day) [3]. Fever improved promptly on the following day. On the 7th hospital day, cutaneous desquamation of fingers and toes developed. C-reactive protein became normal. Acetylsalicylic acid was decreased to a single dose of 3.3 mg/kg/day. The patient was discharged on the 9th hospital day, after which the clinical course was uneventful. Echocardiography findings were completely normal after 35 days. Neutralizing antibody levels for CVA6 measured at admission were 512-fold higher than normal.

This case underscored two clinical issues: concomitant HFMD and KD, and provocation of KD by CVA6-associated HFMD. Concurrent occurrence of HFMD and KD is uncommon. A severe outbreak of HFMD associated with CVA6 in Japan occurred in the autumn of 2021. During that HFMD outbreak, none of the other affected individuals developed KD. Rigante, et al. [2] first reported KD with concurrent Coxsackievirus B3 infection. Widespread papulovesicular eruptions, the ongoing pandemic of CVA6, and markedly increased viral antibody titers all indicated CVA6-associated HFMD. All six diagnostic signs of KD with hyperechogenicity of coronary arteries were well consistent with KD. It is possible that CVA6-associated HFMD might trigger KD development. The associations among approximately 15 viruses and KD were investigated using serological and polymerase chain rection (PCR) assay [4]. Coxsackieviruses interact with components of the innate immune system, which can destroy peripheral tolerance and can ultimately induce autoimmune diseases including myocarditis and diabetes following infection [5]. The elder sister had KD at three years of age, and progressed well with IVIG and oral acetylsalicylic acid without any concurrent disease. Siblings of affected patients with KD tended to be more susceptible to developing KD than those without a sibling history [6]. Although the etiology of KD remains unknown, it presumably results from abnormal immunologic response to various infections in genetically susceptible individuals [2,4,7]. Reportedly, CVA6-associated HFMD that is severer than ordinary HFMD might elect excessive systemic inflammation or dysregulate innate immune response. Along with the sibling history of KD, it might eventually have predisposed this patient to develop KD [1, 7].

A four-fold or greater increase in antibody titer is inferred as serologically significant when the acute and convalescent phases are measured simultaneously, but antibody titer of CVA6 was assessed only once at the acute phase in this case. Secondly, PCR analysis to evaluate the association between CVA6 infection and KD were not performed. Third, cytokine profiles to monitor immunomodulation during the acute phase of HFMD and KD were not obtained.

In conclusion, although cases of concurrent HFMD and KD are uncommon, they are expected to be likely. Further investigations must be conducted to ascertain true immunomodulation to various inciting infections and/or genetic factors in KD. Knowledge in those areas would be appreciated to establish promotion of innovative treatments and precautionary measures against KD.

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Gardner-Diamond Syndrome in an Adolescent Girl

Most cases of functional or behavioral disorders in children are often the diagnoses of exclusion. Likewise, Gardner–Diamond syndrome (GDS) is a label applied for spontaneously appearing ecchymoses or purpuric lesions, with no identifiable cause. It is often a diagnosis of exclusion after other causes of bleeding are ruled out by doing relevant investigations. Only a few hundred cases of GDS are reported worldwide. Treatment for the underlying psychological disorder is the key to the remission of the illness.

An 18-year-old girl presented with pain and warmth over her right forearm with a diffuse swelling followed by erythema. Two days later, it turned into an ecchymosis associated with pain and burning sensation and difficulty in writing, which lasted approximately 2 weeks. No constitutional symptoms like fever, headache, nausea, pain in the abdomen, vomiting, etc. were noticed. She had attained menarche with no overt menstrual bleeds, and had no history of bleeding diathesis in the past [2]. She complained of bruises over her right forearm two year back. There was no history suggestive of self-abuse of her writing hand. On inquiry, she narrated her experience with a stressful situation at home. She had a performance anxiety related to her school examination. There was neither a mention of any other stressful situations nor any conflicts at home. She was given medications in the form of oral antihistamines, steroids, and NSAIDs for a short course and did not have any recurrence. The family history was inconclusive of easy bruising or bleeding episodes in other family members. There was no history of any recent drug intake or drug reactions.

On evaluation, she appeared to be a nervous and anxious adolescent, with normal vital signs and a normal systemic examination. A local examination of the right forearm showed a tender, diffuse ecchymosis over the lower one-third on the ventral side. Pediatric gait, arms, legs, and spine examinations (pGALS) were normal. Her investigations showed mild anemia, a normal white blood cell count, platelet count, coagulation profile, a negative rheumatoid factor, weakly positive antinuclear antibody by immunofluorescence, and a normal thyroid function test. Magnetic resonance imaging of her right forearm done two year back had shown ill-defined altered echogenicity, suggestive of cellulitis with a normal arterial doppler study. An ultrasound and color doppler during this episode showed fat panniculitis with superficial thrombophlebitis.

Her family was briefed on how the search for an organic cause was made which was inconclusive. The importance of underlying psychosocial factor (pressure from her parents in this case) was conveyed to them, and psychiatry referral was sought and was well accepted by the family [3]. Treatment was given for her anxiety-depression disorder and she was called for regular counseling sessions. She suffered from anxiety neurosis later, whenever she skipped the treatment and follow up visits for counseling.

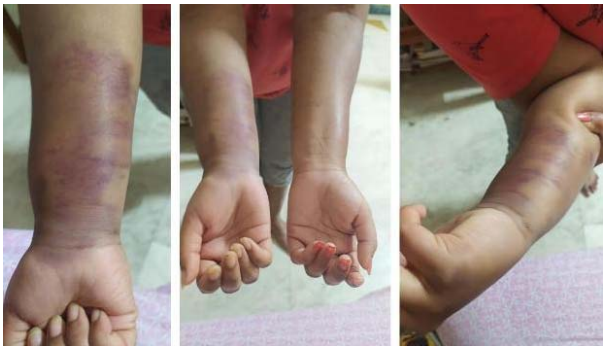

Fig. The forearm purpura appeared two days post-bruising, and remained for two weeks.

As purpura appeared every time at the same site, which suggested the possibility of self-abuse as the trigger and purpura occurring as the late manifestation, precipitated by psychological stress. The self-injury might have led to red blood cells inoculums and there was auto erythrocyte sensitization [4]. On a number of occasions later, the purpura appeared without any trivial trauma, which signifies the importance of psychological factors as the precipitating factor.

The purpura subsided in due course without any specific treatment and treatment was directed at the underlying psychological cause to prevent a recurrence. Pediatricians need to be aware of this uncommon and intriguing disorder, to ensure prompt diagnosis and appropriate management.

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Drowning in Home Environment: A Little Recognized Mode of Fatal Injury in Indian Infants and Toddlers

Bucket-associated drowning in unattended infants and toddlers is not an uncommon occurrence; although, it remains largely unrecognized and under-reported [1-3]. There is a scarcity of published reports in medical journals on these largely preventable deaths in India [4,5].

We performed a descriptive analysis by internet search of news reports in well- known Indian newspapers to gather information on such deaths by using different combinations of keywords. National crime record bureau (NCRB) of Indian Police, and Ministry of Health and Family Welfare, Government of India Websites were also assessed for available data [6].

From April, 2016 to March, 2022, there were 18 drowning reports at home that resulted in fatalities across India. On Pubmed search, we found a population based study, where two babies both aged 1.5 years under care of mothers drowned in water storage vessels and a 1-year-old boy who nearly drowned in concentrated sugar syrup (*chashni*) made at marriage home [4,5]. Thus, data on a total of 20 drowning deaths at home were extracted. We excluded drowning deaths occurring anywhere except buckets/water storage vessels occurring in home environments.

Majority (65%) of victims were boys aged 12-18 months, and most (85%) were playing unattended. Two babies were fetching water from a storage vessel to drink and, remaining one case involved bathing by a toddler sibling not supervised by elders. Studies from other countries have also reported bucket-associated drowning death [1,2] being a common problem, wherever buckets are used for water storage at home.

Due to the inherent limitations, it is assumed that our data is gross underestimation of actual data as drowning may happen in cases who did not got media coverage, rural/peripheries news not getting coverage in electronic media and news not getting media space. Duplication of data was avoided based on victims and geographical/temporal details. This analysis identifies one of the little recognized sources of drowning in infants and toddlers in home environment associated with buckets, which are used for water storage in almost every Indian household. Even if partially filled, it may pose significant drowning hazard to unattended children. This report raised an important issue of this health threat due to its ubiquitous use, and also reminds pediatricians for counselling for injury prevention at home.

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Bolus Dose of Vitamin D to Lactating Mother and Calcium Transfer in Human Breastmilk

We read with interest the article by Ramot, et al. [1]. We compliment the authors for this study on bolus vitamin D supplementation to lactating mothers in improving maternal and infant vitamin D status. We would like to highlight certain aspects in the study, and request clarifications from the authors.

The use of bolus dose of vitamin D compared to daily dose may not be physiological. The Infant receives vitamin D in its parent form (vitamin D3) from breastmilk. Vitamin D3 is rapidly converted to 25(OH)vitamin-D, which cannot be secreted in the breast milk; therefore, daily dose of vitamin D to the mother is required to achieve sufficient transfer in breastmilk [2]. References cited by authors to substantiate bolus dose showed the levels of vitamin D in maternal blood and breastmilk dropped significantly after day 1 of bolus dose; however, these were uniform when mothers were supplemented daily [3,4]. One of these studies was done in non-lactating mothers, where the physiology of vitamin D is significantly different [3]. The authors did not mention the time frame of collection of blood sample for vitamin D estimation after bolus dose. Non-availability of vitamin D levels in breastmilk further dilutes the conclusions of study.

The serum vitamin D levels were estimated using automated chemiluminescent immunoassay, which cannot differentiate between the two forms of vitamin D, 25(OH)vitamin-D2 and 25(OH)vitamin-D3, and has a cross reactivity with other vitamin D metabolites [5].

Lactating mothers increase calcium content of breastmilk by increasing the dietary intake, gut absorption, and bone resorption by parathyroid-related protein (PTHrP) [2]. Relation between maternal vitamin D and serum calcium is linear during vitamin D deficiency. In Table II and III of the study, maternal and infant serum calcium levels are significantly low at 1 year post-bolus of vitamin D supplementation compared to baseline,

which normally should have been more. This finding needs some deliberation. The study does not reveal the details of calcium supplementation to lactating mothers and infants. Vitamin D replenishment without calcium supplementation may be counter-productive due to progressive bone-resorption by activated PTHrP [2].

The study likely deprived the infants of recommended vitamin D supplementations as per IAP recommendations [5]. The details of exclusive and total breast feed duration, and complementary feeding are also missing.

The primary concern with bolus doses of vitamin D is toxicity. Though the authors have defined the exclusion for toxicity; criteria of stopping the trial in case excessive vitamin D toxicity is encountered is unclear. Monitoring for toxicity twice only at 6 months and at 1 year seems too less for an intervention, which has been postulated to have no additional skeletal benefit apart from raising vitamin D levels [5].

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AUTHOR'S REPLY

We thank the editor of the esteemed journal Indian Pediatrics and fellow readers for showing interest in our study and appreciate their concerns.

We have already mentioned that daily dosing of vitamin D supplement is more physiological than bolus dose; however, efficacy may be affected by poor compliance and acceptability. The maternal serum vitamin D estimation was done at baseline i.e., before starting of vitamin D supplementation and after 12 months of supplementation. We agree, that study results would have been more robust with estimation of breast milk vitamin D levels. Estimation of breast milk vitamin D is a tedious job and our lab has not standardized the breast milk vitamin D assay so it was not planned in the present study.

Chemiluminescent immunoassay certainly does not differentiate between 25(OH) vitD2 and 25(OH) vitD3 forms. Vitamin D2 supplementation was not given at any time point during the study. Therefore, differentiating between vitamin D2 and D3 does not seems to be essential.

The concern of lower serum calcium after vitamin D supplementation in both, mother as well as infants as compared to baseline level is valid. However, all values were within normal range. Measurement of serum iPTH could have answered this differential response, since long standing deficiency of vitamin D might have led to secondary hyperparathyroidism thereby maintaining serum calcium levels and with supplementation of vitamin D one year, serum iPTH must have reached normal limits. Also, measurement of ionized calcium could have helped to answer this differential response. Due to logistic issues with collection, storage and transportation of samples, serum iPTH levels were not planned to be measured in the present study.

No additional calcium supplementation was provided to mothers and infants other than 1g calcium supplementation, which is prescribed to lactating mothers as a part of routine clinical care. This supplementation was uniform for both the groups so differential effect of calcium supplementation would have been neutralized between the groups.

The concern about not using recommended vitamin D supplementation is well accepted; however, its practical applicability is reported to be affected by poor compliance (<20%; reference 9 in manuscript). There is published evidence for high dose vitamin D supplementation to lactating mothers to address the dual problem of vitamin D deficiency in mother-infants duo. This aspect has already been discussed in the manuscript. Moreover, since both groups received vitamin D and not the placebo, there was no concern of vitamin D deprivation in either groups.

The issue of monitoring for toxicity seems theoretical. We have used validated and standard criteria for monitoring, which have been used by others and us previously also [1].

There is sufficient literature on safety of high doses of maternal vitamin D supplementation. Endocrine society recommends 4000-6400 IU/day to lactating mothers to maintain serum 25OHD levels >30 ng/mL in exclusively breast fed infants [2]. Therefore very low risk of toxicity is anticipated with such doses of vitamin D supplementation.

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NEWS IN BRIEF

Reducing adolescent stress

A 30 minute online intervention in school and college students in the United States was found to be effective in reducing adolescent stress when tested on many fronts. Adolescent stress is at an all-time high, so this study is especially valuable today. A blinded randomized controlled trial was conducted on 5000 students. The study participants underwent either an online 'synergistic mindset intervention' or a control intervention.

The synergistic mindset intervention includes training students to relook at stress. Instead of identifying stress as unhelpful and uncontrollable, they were taught to look at it as helpful for their growth and amenable to control. It teaches them that this shift in perspective results in a change in the body's physiological response from the threat response with increase in cortisol and peripheral vasoconstriction; to a challenge response which mobilizes energy to the body and blood to the brain. Further it trains them in the growth mindset. It emphasizes that ability is not fixed or innate. Ability can be developed with effort, strategy and support.

The effect of this online training was tested using various stressors such as timed quizzes, mental mathematics, impromptu speeches etc. The effect of the training in study and control groups was compared across a range of outcomes. Outcomes included both immediate responses such as threat or stress perception, physiological responses in the form of blood pressure, total peripheral resistance, cardiac output; anxiety level questionnaires and long term effects like final school performance. Across a range of outcomes and timescales, significant positive results were noted after a single session of online training in the synergistic mindset intervention.

Scaling it up to a national level is likely change the way young adults handle stress.
(*Nature, July 2022*)

Submicroscopic malaria infections

India has seen a 71.8% fall in malarial infections between 2000 and 2019 and a 73.9% drop in mortality in the same period. However, one major reason for continued malarial transmission in various regions is submicroscopic malarial infections. What does this mean? Microscopy which is the main tool for diagnosis of malaria in all the national programs has a limit of detection of upto 10-100 parasites/µL.

A recent study from ICMR found that submicroscopic infection burden ranges from 0.4-38.4% in various districts of India. They also found that the sensitivity for detection for *Plasmodium falciparum* was lower than for *P. vivax* whereas the prevalence of *P. falciparum* is 63.8% compared to the 36.2% for vivax. They have suggested the use of molecular tests like PCR to monitor hotspots identified in their study. Point of care tests like the Truenat Malaria, which has been developed as a chip-based microPCR test with a level of detection of 5 parasites/uL, may also prove to be valuable.
(*The Lancet Regional Health, July 2022*)

Sleep duration predicts kindergarten adjustment

Regular 10 plus hours of sleep has been demonstrated to be vital in good emotional and cognitive outcomes in very young children. This study analyzed sleep durations in 221 kindergarten children using a smart watch. Mean duration of sleep over 24 hours were measured for several days in a year. Outcomes measured included tests for social competence, learning behaviors, digit span test for working memory and academic outcomes in school. Children with more nights of 10-plus hours of sleep were rated more favorably by teachers on aggression, classroom learning behaviors, school readiness, and ADHD behavior.

Sleeping for 10 hours daily was especially useful if the habit was inculcated in the pre-kindergarten years. Since parental and child sleep patterns are closely aligned, parents need to reflect on their sleep routines as well. Good sleep hygiene includes limiting screen time and regular sleep time rituals. Benefits are likely to accrue for both children and adults.
(*Pediatrics* 2022; e2021054362)

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CLIPPINGS

Intranasal midazolam for pediatric sedation during the suturing of traumatic lacerations: a systematic review *(Children (Basel). 2022;9:644)*

Sedation is always challenging in children; to decrease the adverse effects, non-parenteral routes are increasingly being investigated. This systemic review has evaluated the efficacy of intranasal sedation for suturing of traumatic laceration in children. Authors reviewed 9 randomized trials including 746 children out of which 377 received intranasal midazolam in emergency settings. No significant differences in the initiation of sedation and the suture procedure were found between the intranasal route and the parenteral route. The use of intranasal midazolam in healthy children is effective for sedation in pediatric emergency departments for laceration repairing.

Sonographic optic nerve sheath diameter measurements in pediatric head trauma *(J Ultrasound. 2022, April 8. Epub ahead of print)*

Optic nerve sheath diameter (ONSD) is used as non-invasive technique for estimating raised intra cranial pressure (ICP) in adults but its accuracy in children is always questioned. In this prospective study, authors compared the ONSD in CT images with ultrasonographic measurements in children with head trauma and raised ICP. To predict elevated ICP, the AUC for ONSD at 3 mm was 0.956 (95% CI 0.896-1). At a cut-off level of 5.1 mm, the sensitivity and specificity of ONSD for elevated ICP were 92.9% and 94.0%. All sonographic ONSD measurements and ratios were significantly correlated with readings calculated from cranial CT images. Hence, bedside ocular US seems to be a promising and useful tool to determine ICP in children with head trauma.

Is early activity resumption after pediatric concussion safe? PedCARE multicentre randomixed clinical trial (Br J Sports Med. 2022;56:271-78)

There is always a dilemma in resuming physical activity (PA) following concussion injury in children. In this multicenter, single-blinded randomized clinical trial, authors have randomized 456 participants (10-18 y) with concussion, in 4-week stepwise return-to-PA protocol at 72 hours post-concussion even if symptomatic (experimental group (EG)) or to a return-to-PA once asymptomatic protocol (control group (CG)). No AE were identified. ITT analysis showed no strong evidence of a group difference at 2 weeks (adjusted mean difference=-1.3 (95% CI:-3.6 to 1.1)). Symptoms at 2 weeks did not differ significantly between children/youth randomized to initiate PA 72 hours post injury versus resting until asymptomatic. Hence, resumption of PA is safe and may be associated with milder symptoms at 2 weeks.

Single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children *(Ann Emerg Med. 2016;67:e593-601)*

In this randomized controlled trial, authors investigated whether a single dose of oral dexamethasone (a single dose of 0.3 mg/kg) is non-inferior to prednisolone (1 mg/kg per day for 3 days) in the emergency department (ED) treatment of asthma exacerbations in children (2 to 16 years). Out of total 245 enrolments authors did not find any difference in PRAM scores at day 4 (0.91 versus 0.91; absolute difference 0.005; 95% CI -0.35 to 0.34) in both the groups. Sixteen children (13.1%) in the dexamethasone group received further systemic steroids within 14 days after trial enrolment compared with 5 (4.2%) in the prednisolone group (absolute difference 8.9%; 95% CI 1.9% to 16.0%). The hospital admission rates or the number of unscheduled return visits to a health care practitioner were similar in both the groups. Hence, single dose dexamethasone can also be used for acute exacerbations of asthma in children.

Every one-minute delay in EMS on-scene resuscitation after out-of-hospital pediatric cardiac arrest lowers ROSC by 5 *(Resusc Plus. 2020;5:100062)*

Prehospital care plays important role in the survival of out of the hospital cardiac arrest victims. In this study, authors tried to determine which aspect of pre-hospital care impact outcome after cardiac arrest. They consecutively studied data of 133 pediatric cardiac arrest, 20 children achieved return of spontaneous circulation (ROSC) and 9% children were discharged alive. Epinephrine administration (P <0.001), bystander treatment before EMS arrival (P=0.002), older age (P=0.002), shorter time to EMS arrival (P=0.005), and AED placement were predictors of ROSC. The only significant predictor of survival to hospital discharge that was identified was shorter time to EMS arrival (P=0.001). Each additional minute for the EMS to arrive resulted in 5% decreased odds of ROSC and hospital admission, and 12% decreased odds of surviving to hospital discharge.

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Spina Ventosa of Metacarpal

An eight-year-old boy was brought to the hospital with the complaints of trauma to his left palm one year back, followed by abscess formation that drained by itself without any medical/ surgical intervention. However, since last one month, the swelling had reappeared. No history of fever or pain was present. At another hospital, culture of pus taken from the swelling yielded MSSA and the child was given 7 days of oral antibiotics but the swelling persisted. On his next visit, he had developed two more swellings, one below his left clavicle and the other at his left axilla. On examination, he was underweight. He had significant bilateral cervical lymphadenopathy at levels IIa, IIb, and Va. He had an abscess measuring 4 cm x 3cm below the left clavicle and another at the left axilla measuring 2 cm x 2.5 cm. He had a non-discharging sinus on his left palm with contracture (**Fig.1**). Rest of the systemic examination was within normal limits. *X*-ray of the left hand (**Fig. 2**) showed a lytic lesion in distal diaphysis of third metacarpal with sclerotic margin and associated soft tissue swelling. Mantoux test was reactive. Chest *X*-ray showed right paratracheal and right hilar lymphadenopathy. Fine needle aspiration cytology (FNAC) of his cervical, infraclavicular and axillary lymph node revealed epithelioid cell granuloma with background necrosis and mixed lymphocytic infiltrate. Pus for cartridge based nucleic acid amplification test (CBNAAT) detected *Mycobacterium tuberculosis* with Rifampicin sensitivity. The child was diagnosed with spina ventosa of metacarpal bone and started on anti-tubercular therapy (ATT).

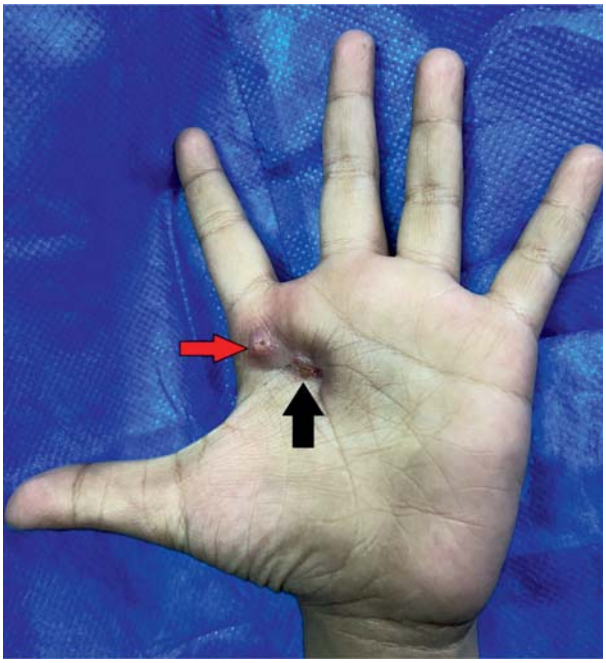

Fig. 1 Non-discharging sinus (black arrow) on palm of the left hand with contracture (grey arrow).

Spina ventosa (tuberculous dactylitis) of the short bones of the hands and feet is characterized by a cystic, ballooned-out appearance of the involved bone. It is a rare extrapulmonary manifestation with incidence of 0.6-6% in children, and is uncommon after the age of 5 years. Pain and swelling are the most common presenting features, followed by sinus discharges. Definitive diagnosis of dactylitis is made on radiographic and histopathologic examinations. The significance of a history of trauma being reported by a third of patients is unknown. Concomitant pulmonary affection is also uncommon. The absence of sequestration and presence of diffuse osteopenia distinguishes it from pyogenic osteomyelitis, which is often acutely painful and associated with high fever. Single lesion may be confused with syphilitic dactylitis (where bone is thickened by periosteal reaction). Spina ventosa responds well to anti-tubercular therapy. Current recommendations for the treatment include a two-month intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a six- to twelve-month continuation phase of izoniazid and rifampicin. We started our patient on anti-tubercular therapy and he is currently in the intensive phase with good ongoing response in the form of non-progression of the lesion.

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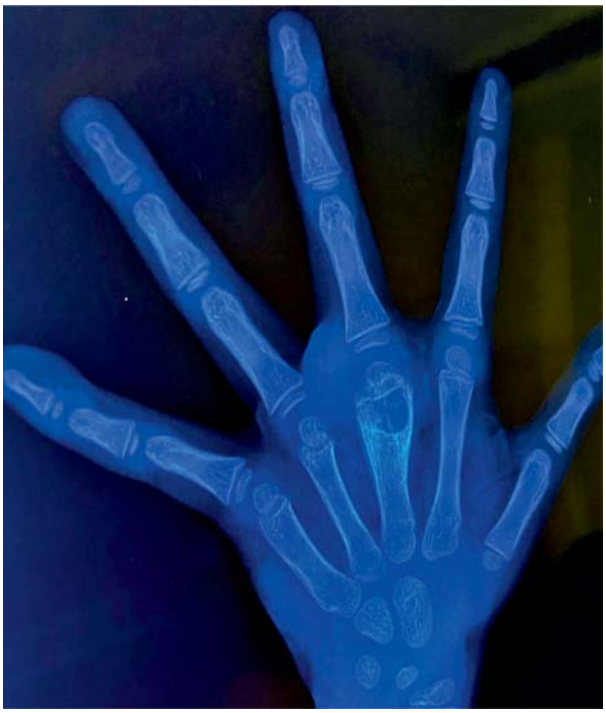

Fig. 2 *X*-ray of the left hand showing lytic lesion in the distal diaphysis of the third metacarpal with sclerotic margin and associated soft tissue swelling.

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