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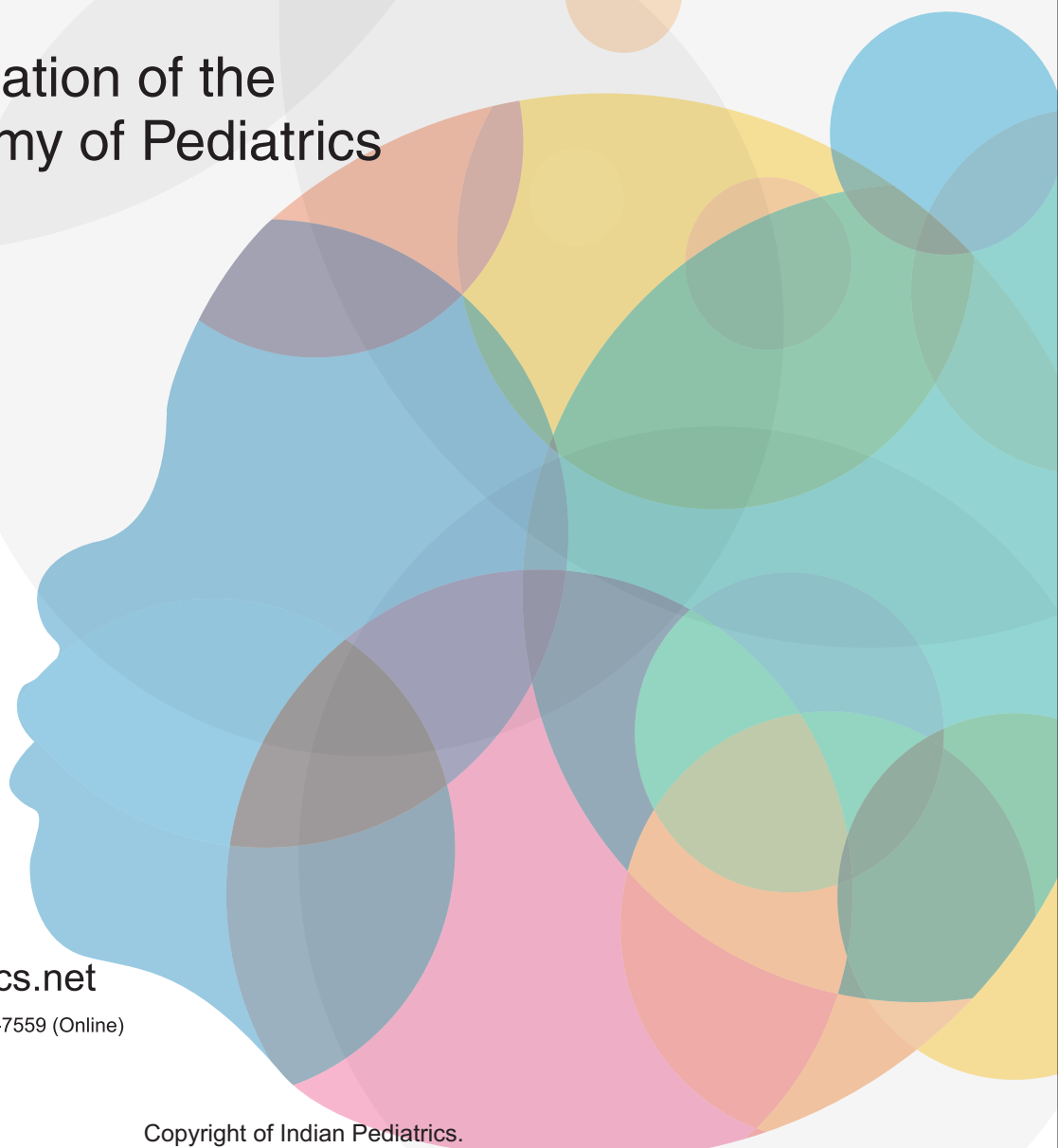

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IAP Guidelines for pediatric skincare state that ideal care of newborn skin comprises of:[1]

- Gentle cleansing[1]
- Protection of barrier function[1]
- Prevention of skin dryness[1]
- Promotion of normal development of the skin[1]

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- Prevention of skin dryness[2]

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IAP: Indian Academy of Pediatrics, HMP: Hydrophobically Modified Polymer

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Under-Five Mortality: IAP Can Make A Difference!

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It is perhaps for a reason that the Indian Academy of Pediatrics (IAP) has chosen to time its Presidential installations in the month of January every year. The turn of the calendar symbolically gives the new incumbent an opportunity to start the term on a good note and infuse fresh vision into the organization. Hence, at the outset, I deem it my privilege to wish you on the New Year. As I embark on my Presidential journey, I thank every member of IAP for reposing faith in me and it shall be my endeavor to live up to the promise that is bestowed on the Chair. As I assume charge of office, I recognize the magnitude of my responsibility and happily accept the challenge of continuing a tradition built over half a century of valuable contributions made by my predecessors, not to mention the general body of members.

Great organizations are built not just by leaders, but more so by the large scale impact it can have on society. Leaders come and go, but the achievements of the organization should always take the society forward in the right direction.One such domain in which IAP can make a huge difference today is under-5 mortality. If there is any sphere of life where the profession of pediatrics has made a tangible difference, it is in ensuring that every child born has a better chance of survival than ever before. During my own childhood days and those of the generations before, it was common to come across families who had lost at least one child. If this is no longer the case, the primary reason is better child care.

A LOOMING PROBLEM

Today it is fashionable for us to reckon child birth as a 'miracle' of life. But in olden times, it was survival of the child that was a real miracle. During the turn of the last century, the child mortality rate in India was as high as 53 percent in India. In children under the age of five, 509 deaths per thousand births were recorded in 1880. Over half of all children born during the period did not survive past the age of five. Though child mortality figures have kept fluctuating since then, there has been a steady decline over the decades. Over the last 50 years, under-5 mortality rate (U5MR) of India was declining at a moderating rate to shrink from 207.55 deaths per thousand live births in 1971 to 35.7 deaths per thousand live births in 2020.

It is estimated that 5.2 million children under five years died worldwide in 2019, mostly from preventable and treatable causes. Since 1990, under-5 mortality has declined worldwide as a result of socioeconomic develop-ment and implementation of child survival interventions. Even though India's U5MR has also seen a similar decline in the past years, the rate of decline in India is slow when compared to its neighboring countries. The current U5MR in India stands at 36 deaths per 1000 live births. This means that in every two minutes, three under-5 children die in India.

THE WAY AHEAD

In many ways, child survival is a barometer for national development. Child mortality rates are intrinsically linked to economic advancement. Monaco, Iceland and Japan are among the top three countries with the lowest infant mortality rates with around two infant deaths per 1000 infants within their first year of life. UK has infant mortality of 4.3 while USA has 6.5 per thousand live births. Nutrition, health status of women and availability of tertiary care facilities are important factors contri-buting to reduction in child mortality.

India has set a target to reduce under-5 mortality to 23 per 1000 live births by 2025 in its National Health Policy. But according to the latest data, if the child mortality trends observed were to continue, the country is likely to miss its child survival targets. India is one of the world's largest and most populous countries, made up of 28 states, 8 union territories and 748 diverse districts. The child mortality figures are not uniform across the country – 17 states and 246 districts would need a higher rate of improvement than they have now, if the country has to meet its child survival targets.

It is very clear from the above narrative that concerted national level effort has to be invested to actualize a quantum leap in reducing child mortality rate in India. Due to the enormous complexities involved in governing a

diverse country like India, many geographical regions remain underserved in the national mission. Government organization and resources alone may find it difficult to address the issues. It is in this context that IAP will have a major role to play in augmenting resources and contributing to the national effort.

HOW IAP CAN HELP?

Being a national level professional body having more than 33,000 professional pediatricians and a presence in almost every district, IAP is a formidable force which can play a constructive role. After undertaking an in-depth study, IAP has formulated a new project 'U5MR 25 BY 25' to support the government in implementing strategies to accelerate reduction of under-5 mortality rate in India. Based on the available data, this project will focus on 18 Indian states that are performing poorly, viz., Arunachal Pradesh, Assam, Bihar, Chhattisgarh, Gujarat, Haryana, Jammu & Kashmir, Jharkhand, Karnataka, Madhya Pradesh, Maharashtra, Odisha, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh and West Bengal.

From these states, 257 districts of concern have been identified for special attention. Among them, 94 districts have high U5MR and low annual rate of reduction, 57 have high U5MR and medium annual rate of reduction, 46 have high U5MR and high annual rate of reduction, and 60 have medium U5MR and low annual rate of reduction. Out of these, IAP intends to focus on 50 districts spread out in eight states, which are most relevant and feasible in this context, after discussion with Government of India functionaries.

The five main strategic components include evidence-based interventions, providing focused technical and implementation support, capacity building and skill development of health workforce, advocacy regarding malnutrition, water, sanitation and air pollution, and demonstration of community models to address the issue of malnutrition. These activities will be focused on the selected 50 districts in the first phase and later replicated to the other districts of concern.

As the incumbent President, I call upon every branch and member alike to join hands to make this project a success. While contributing to the national well-being, success in this endeavor will also give us the satisfaction of having made a difference to child health in our own region, and thereby enhance IAP's stature as a professional body to reckon with.

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INVITED COMMENTARY

From Therapeutic Hypothermia to Targeted Temperature Management in Low-Resource Settings

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In high-income countries, therapeutic hypothermia reduces death or survival with moderate or severe disability at 18 months in infants with moderate and severe encephalopathy [1], and has been the standard of care for over a decade. Use of cooling therapy in low- and middle-income countries (LMICs), where the highest burden of encephalopathy occurs, has been more controversial. HELIX, the largest cooling trial in the world, recruiting 408 infants with moderate or severe encephalopathy from India, Sri Lanka and Bangladesh, recently reported that therapeutic hypothermia does not reduce death or disability at 18 months after moderate or severe encephalopathy [2].

Although non-randomized trials cannot inform the safety or efficacy of an intervention, retrospective data from Indian Neonatal Collaborative including 352 infants (211 cooled) from 17 neonatal units is consistent with the HELIX trial data – on regression analysis therapeutic hypothermia was not associated with reduced neonatal mortality [3]. The authors found that severe encephalo-pathy, persistent pulmonary hypertension and adminis-tration of Epinephrine during resuscitation were associated with decreased odds of survival to hospital discharge. The report does not include data on neurodevelopmental outcomes of children – the current standard of effectiveness of any neonatal neuroprotective intervention.

While the data on several important variables including perinatal sentinel events, seizure onset, bleeding tendencies, inotropic support, nurse:infant ratio, hyperthermia in non-cooled infants, and outcome of infants transferred to other hospitals (all presumed as survivors) were not reported, these data do raise further questions: Firstly, the median umbilical cord pH was 7.18 (IQR 7 to 7.28) and only 48 (14%) of the 352 infants had a cord pH less than 7. Hence most infants would not have met the high-income country cooling criteria. Secondly, only 62 (17%) received mechanical ventilation, with the majority ventilated for less than 24 hours unlike the HELIX trial and high-income country cooling trials. Thus, most cooled infants were less sick than those enrolled in the trials in high-income countries. Unless a standardized neurological examination using certified examiners or amplitude-integrated electroence-phalography is used, infants with mild encephalopathy can be misclassified as moderate, not just in LMICs, but in high income countries as well and many such infants may receive cooling therapy [4]. Despite the lower severity of encephalo-pathy, 62 (17%) infants died or were discharged against medical advice, and further 16 transferred to another hospital [3]. The clinical status of the infants discharged against medical advice or transferred to other hospitals is not presented. Infants of 34 and 35 weeks gestation were included in the report, although the numbers and severity of encephalopathy is not documented; it should be noted that neither the safety nor the efficacy of hypothermia for moderate or severe encephalopathy among late preterm infants has yet been demonstrated.

Where do these data leave clinicians in low-resource settings? The pooled data from all randomized trials in LMICs, including the HELIX trial, now provide definitive evidence that therapeutic hypothermia does not reduce death or disability after moderate or severe encephalo-pathy, and hence continued cooling in these settings cannot be justified [5]. It is possible that the better outcomes seen in the control arm of the HELIX trial might have been due to better targeted temperature manage-ment at 36.5°C unlike the original high-income cooling trials [1] that had hyperthermia in 14% to 39% of the control arm infants. In pediatric [6] and adult [7] trials of hypothermia for cardiac arrest, targeted temperature management (normothermia) had similar outcomes to hypothermia therapy [6,7].

However, not everyone is convinced that hypothermia is not safe or effective in moderate or severe encephalopathy in LMICs. Some argue that the population in LMICs is very diverse and that there is a subgroup of infants who have access to high quality antenatal, intrapartum and neonatal care as in high income countries, who might benefit from therapeutic hypothermia [8].

While all these arguments are valid, several issues need to be considered. Firstly, all the cooling trials reported from India including the THIN trial from a private sector hospital had nurse to infant ratios of 1:3-4 or greaterdespite using low-cost manual cooling devices [9]. Secondly, the population characteristics of infants in these trials are very similar to the HELIX trial, with low incidence of acute perinatal sentinel events (<10%) and high (>80%) incidence of seizures at randomization (baseline) [10]. This may indicate acute on chronic hypoxic-ischemic injury. Finally, there are very limited published data on burden of neonatal encephalopathy amongst inborn babies from private sector hospitals in India, and this situation is very complex due to very high rates of caesarean sections. In the present study, seven hospitals did not have a single infant with encephalo-pathy, although details of these hospitals and caesarean rates are not provided.

Clinicians in low-resource settings need to decide if it is appropriate to continue an expensive and possibly ineffective cooling therapy, or shift to a less resource-intensive and evidence-based targeted temperature management at 36.5°C.

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INVITED COMMENTARY

Stop Not Till The Goal Is Reached

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It is a catch-22 situation when we ponder if intelligence quotient (IQ) comes first to be able to attain a higher education so as to improve socio-economic conditions, or do socioeconomic conditions come first to give access to quality education and probably a good nutrition, which would in turn affect the IQ [1]. Science is arguing on both the sides [2-5]. With the latest National Family Health Survey (NFHS)-5 data unravelling in front of us, we notice that infant mortality rate (IMR) has decreased remarkably from the previous NFHS-4 figures. But, we also know that nutrition and infant and young child feeding (IYCF) indicators suggest otherwise. Moreover, out of 342 districts, stunting has worsened in 176 districts, as per the NFHS-5 data [6]. The buck does not stop at just saving lives and treating childhood illnesses for us pediatricians; shouldn't we also be focusing on thriving these little ones? Do we know these chronically undernourished children are not only seen in poor families but the problem is pervasive in all wealth quintiles? In fact, in the richest, fourth and middle wealth quintiles, 22.2%, 29.2% and 36.4% children are stunted, respectively, as per the NFHS-4 [7]. Even when these chronically undernourished children are given an opportunity to a good education, whether or not they attain the highest potential remains questionable! It is an urgency as our country is ranked at 101 out of 116 in 2021 Global Hunger Index (GHI), there is a serious level of hunger with a score of 27.5. Undernutrition, wasting, stunting and child mortality rate are the four indicators which get incorporated in GHI [8]. Further, the World Health Assembly endorsed the sustainable developmental goals (SDGs) to target a reduction in the number of stunted children globally by 40% by 2025 (United Nations, 2015).

Improving the socioeconomic indicators of families may be beyond the purview of pediatricians but they can help disseminate evidence-based practices which are known to improve a child's IQ. Breastfeeding is one such powerful factor which not only can save lives but also increases a child's IQ. One additional IQ point can increase lifetime earnings by 1.8-2.4%, as per an economic analyses from the USA [9]. A study in Brazil showed that after adjustment for confounders, infants who were breastfed for 12 months or longer had, on an average, about 4 points higher IQ, about 1 year more of schooling, and a monthly income that was roughly 350 Brazilian Reals higher than did children who were breastfed for less than 1 month [10]. Despite so many benefits of breastmilk and with an increase in the institutional delivery rate in India, we are still struggling to improve the timely initiation of breast-feeding. An alarming rise in the caesarean section rate is a major impediment. One of the secondary analyses of the World Health Organization (WHO) global survey showed that only 39.7% of the infants delivered through cesarean section had initiated breastfeeding within one hour of birth [11]. Coordination and planning with fellow obstetricians and with involvement of the family can play a key role in ensuring early skin-to-skin contact between baby and mother as well as initiating breastfeeding in the operating room.

Besides early initiation of breastfeeding, it is important to teach the correct breastfeeding techniques. A project in urban slums of Mumbai showed that it is possible to reverse not only wasting but also stunting in infants by just teaching the mother cross-cradle hold with 45 points of breastfeeding counselling as well as home-based complementary foods counselling [12]. Growth monitoring with target weight gain on the WHO growth chart is another area where pediatricians can play a big role. Regular plotting of growth with early identification of growth falterers or growth stagnant babies and guiding mothers on IYCF skills is needed. Dietary adequacy among children under-3 years of age is only 9% as per the NFHS 4 data. If our children do not receive important macro- and micro-nutrients due to poor dietary diversity, how will they grow physically as well as cognitively? Families need to know nutrients dense recipes which will provide enough protein, zinc, omega-3, folate, B12, iron, vitamin A, good fats etc. through food routes [12]. Last, but not the least, is teaching families in early childhood development including physical, motor, social-emotional, cognitive and linguistic stimulation of a young child, the module for which was recently released by the Indian

Academy of Pediatrics (IAP) at the Nurturing Care and Early Childhood Development Conference [13].

Stagnation in the key nutrition indicators in spite of all the efforts is alarming for an awakened mind. Either, we have stopped caring for children, or the way we are going about it is wrong. It is time to reflect and respond to this challenge. If we pediatricians can do our bit to help children thrive physically, developmentally and cognitively, I am sure it will give them the wings to not only fly but soar high in their lives.

सह नौ यशः। सह नौ ब्रह्मवर्चसम्।।

[May we succeed together. May we attain glory of the self together]

Let us work towards it and may the wisdom of the ancients guide us!

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RESEARCH PAPER

Childhood Head Growth and Educational Attainment in an Indian Cohort

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Received: April 08, 2021; Initial review: May 18,2021; Accepted: August 16, 2021.

Background: There is minimal information about the association of head growth at different stages of childhood with cognitive ability.

Objective: To determine the relationship of newborn head size and head growth during infancy, childhood and adolescence with attained education, a proxy for cognitive ability.

Study design: Prospective birth cohort study.

Setting: Married women living in South Delhi between 1969 and 1973.

Participants: The New Delhi Birth Cohort study followed up 8030 newborns born in 1969-1973 with head circumference, weight and height measurements at birth and 6-12 monthly until adulthood. Of these, 1526 men and women were followed up at the age of 26-32 years.

Outcomes: Association between years of schooling, as an indicator of cognitive ability, and newborn head circumference and conditional measures of head growth during infancy, childhood and adolescence.

Results: In unadjusted analyses, newborn head size was positively associated with years of education [(β (95% CI)=0.30 (0.14 to 0.47) years per SD head circumference], as was head growth from birth to 6 months [β (95% CI)=0.44 (0.28 to 0.60) years per SD conditional head growth], 6 months to 2 years [β (95% CI)=0.31 (0.15 to 0.47) years per SD conditional head growth] and 2 to 11 years [β (95% CI)=0.20 (0.03 to 0.36) years per SD conditional head growth]. There were similar findings for height and body mass index (BMI). In the adjusted model containing all growth measures, gestational age, and socio-economic status (SES) at birth as predictors, only SES was positively associated with educational attainment.

Conclusion: Educational attainment in this population is positively associated with socioeconomic status and its influence on inter-related early life (fetal, infant and childhood) factors like nutritional status and brain growth.

Keywords: *New Delhi birth cohort, Head circumference, Educational attainment, Cognitive development.*

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Head circumference during fetal life and childhood correlates with brain size and brain weight [1]. Moreover, it has been shown that head circumference correlates with total brain volume in pre-pubertal children [2-4]. Head circum-ference is approximately 65% of adult values at birth and 94% at 5 years [5], while the equivalent values for brain volume are 36% and >95%, respectively [6,7]. Popu-lation based studies and some cross-sectional studies have shown that both head circumference and brain volume in children and young adult correlate with cognitive ability [3,4,7-15].

Findings suggest that infant brain growth may be more critical for cognitive ability than fetal or later childhood brain growth [16]. It is not clear whether only head growth, or overall nutrition predicts cognitive function. Large European studies [10,15] have shown that the head circumference at birth and at 5-years of age were positively associated with later cognitive scores, independent of concurrent weight and height.

We used the conditional analysis method to investigate associations of head size at birth and head growth during specific periods in infancy and childhood with educational attainment, as a proxy for cognitive ability, in the New Delhi Birth Cohort [18].

Invited Commentary: Pages 11-12.

METHODS

During 1969-73, 20755 married women living in South Delhi were recruited, of whom 9169 became pregnant, resulting in 8030 singleton live newborns, forming the New Delhi Birth Cohort [18]. The enrolled women were followed up every two months. The exact gestational age, occipito-frontal head circumference, weight and length of the babies born to them were recorded within 72 hours of birth, and at ages 3, 6, 9 and 12 months, and 6-12 monthly thereafter until age 21 years. Head circumference was measured using steel measuring tapes to the nearest 0.1 cm. Height and weight

were measured using standardized procedures. Follow-up was interrupted between 1980 and 1983 due to a lack of funding, and removal of unauthorized housing, which led to a large drop in cohort numbers [18]. Socioeconomic indicators (both parents' education, household size, type of housing, household income, toilet facilities, drinking water source and use of health facilities) were collected during pregnancy or within 3 months post-delivery.

Between 1999-2002, 2584 men and women, then aged 26-32 years, were retraced and 1526 participated in a study of cardio-metabolic risk markers in relation to early life growth [18].Participants' educational attainment was recorded in seven categories from no schooling to a professional qualification. Paternal occupation at the time of the cohort member's birth was recorded at this follow-up. Head circumference, height and weight were re-measured.

Statistical analysis: We converted head circumference measurements (**Web Table I**) to SD scores using Royston method [19], based on a cubic spline fit to the head measurements and assuming the head measurements are symmetrical at the defined ages, and used linear interpolation to estimate head circumference SD scores at the exact ages of 6 months, 2 years and 11 years, provided that genuine measurements were made within 6 months, 1 year and 2 years, respectively. The 6-month measurements were made in 98% within 2 weeks of that age, 80% of 2-year measurements were made within one month, and 76% of 11-year measurements were made within 6 months. We back-transformed the SD scores to provide estimates of head circumference at these ages in cm. We followed similar procedures for height and body mass index (BMI). The ages chosen define clinically important stages of human growth: newborn size as a summary of fetal growth; six months as the end of predominant breast-feeding; two years as the end of infancy, completion of weaning and growth hormone becoming the main endocrine regulator of growth; eleven years as the approximate end of pre-pubertal growth; and young adulthood reflecting the completion of adolescent growth.

We calculated sex-specific conditional growth variables for head circumference, height and BMI. These are the standardized residuals resulting from regression of the SD score for the body measurement at a particular age on the SD scores for the same measurement at preceding ages [9,20]. For example, conditional head growth from 6 months to 2 years is the standardized residual from the regression of head SD score at 2 years on the SD scores for head size at birth and 6 months. These growth measures, which were calculated for birth-6m (early infancy), 6 month to 2 year (late infancy), 2-11 year (childhood) and 11 year-adult (adolescence) are, by construction, uncorrelated, and represent growth during specific age periods, independent of earlier growth. Further details about conditional growth variables are provided as Supplementary Methods**.**

Educational attainment was converted from the original seven categories into years of education, from none (0 years) to a professional qualification (17 years). Socioeconomic status (SES) is a potential confounder of the association between childhood growth and educational attainment. We created a combined measure of SES at birth by standardizing the individual variables and deriving the first principal component.

Using all recorded measurements, we used multiple imputation to generate values for missing entries of head circumference, height and BMI at birth, 6 months, 2 years, 11 years and adulthood; and SES components and gestational age at birth.

The association between growth and educational attainment was assessed initially by unadjusted univariate analysis, followed by multiple models of multivariate regression analysis, taking head circumference, height and BMI separately (Model 1), and then in combination (Model 2). We adjusted for gestational age and the combined SES variable (Model 3) and finally, replaced the combined SES variable with its individual components (Model 4). We report pooled analyses, adjusted for sex. We present the multiple imputation-based results for the full study sample (all who had educational attainment ascertained in young adulthood, *N*=1526), while the results from the complete case analysis (participants with complete growth, SES and gestational age data, *N*=558) are shown in supplementary material.

To check the representativeness of our sample, we used independent sample *t*-tests to compare newborn and infant measurements between those studied as adults and included in this analysis and the remainder of the original cohort, and (among those studied as adults) between those with complete growth, SES, and education data (complete case sample) and the remainder. Analyses were conducted using SPSS version 20 and STATA version 14.

RESULTS

Table I shows the cohort's childhood head circumference, height, weight and educational attainment and **Table II** shows their SES data. Eighty-four percent of the men and 92% of the women were educated to secondary school level or above while 52% of men and 64% of women were graduates. Compared with the remainder of the original cohort, participants studied as adults were longer at birth, and shorter and lighter at age 11 years, but these differences were small [birth length (95% CI) 0.15 (0.02 to 0.28) cm; 11-year height (95% CI) 0.77 (0.29 to 1.24) cm; 11-

Table I Anthropometry and Educational Attainment of the Cohort Members, at Birth, Childhood and At Adult Follow-up (*N*= 2084)

Parameters	*Full sample, n=1526*				*Complete case sample, n=558*			
	Male (n=886)		*Female (n=640)*		*Male (n=322)*		*Female (n=236)*	
	n	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*
At birth								
Gestational age (weeks)	791	38.7 (2.6)	588	39.1 (2.5)	322	38.7 (2.4)	236	39.2 (2.3)
Head circumference(cm)	851	33.7 (1.3)	612	33.2 (1.1)	322	33.7 (1.3)	236	33.2 (1.0)
Height (cm)	820	48.6 (2.1)	590	48.1 (1.9)	322	48.6 (2.1)	236	48.3 (1.9)
Weight (kg)	834	2.9 (0.4)	592	2.8 (0.4)	322	2.8 (0.4)	236	2.7 (0.4)
Body mass index (kg/m^2)	820	12.0 (1.2)	590	11.9 (1.2)	322	12.1 (1.3)	236	11.8 (1.2)
At 6 months								
Head circumference (cm)	869	42.1 (1.2)	629	40.9 (1.2)	322	42.1 (1.2)	236	41.0 (1.0)
Height (cm)	836	65.3 (2.4)	613	63.7 (2.4)	322	65.3 (2.4)	236	63.6 (2.1)
Weight (kg)	836	7.0 (0.9)	613	6.4 (0.9)	322	7.1 (0.8)	236	6.3 (0.8)
Body mass index (kg/m^2)	836	16.4 (1.6)	613	15.7 (1.6)	322	16.5 (1.6)	236	15.7 (1.5)
At 2 years								
Head circumference (cm)	838	46.9 (1.3)	606	45.7 (1.2)	322	46.8 (1.3)	236	45.7 (1.2)
Height (cm)	840	81.1 (3.6)	609	79.6 (3.6)	322	80.9 (3.4)	236	79.4 (3.4)
Weight (kg)	834	10.3 (1.3)	609	9.8 (1.2)	322	10.3 (1.2)	236	9.7 (1.2)
Body mass index (kg/m^2)	833	15.8 (1.2)	604	15.4 (1.2)	322	15.8 (1.2)	236	15.3 (1.2)
At 11 years								
Head circumference (cm)	832	52.1 (1.4)	603	52.2 (1.5)	322	52.1 (1.4)	236	52.1 (1.5)
Height (cm)	831	135.9 (5.7)	607	134.2 (7.4)	322	135.4 (5.6)	236	134.0 (6.9)
Weight (kg)	834	28.4 (4.7)	608	27.6 (5.4)	322	27.9 (4.1)	236	27.3 (5.2)
Body mass index (kg/m^2)	830	15.3 (1.7)	606	15.2 (1.8)	322	15.2 (1.5)	236	15.1 (1.7)
Adult								
Head circumference (cm)	884	56.6 (1.8)	640	53.8 (1.7)	322	56.6 (1.7)	236	53.8 (1.7)
Height (cm)	886	169.7 (6.4)	638	154.9 (5.7)	322	169.7 (6.2)	236	154.5 (4.9)
Weight (kg)	886	71.8 (14.0)	640	59.2 (13.4)	322	71.5 (14.0)	236	58.2 (12.9)
Body mass index (kg/m^2)	886	24.9 (4.3)	638	24.6 (5.1)	322	24.7 (4.2)	236	24.3 (5.1)
Years of education (n %)	886		638		322		236	
No education (0 y)		10 (1.1)		10 (1.6)		1 (0.3)		1 (0.4)
Primary school (3 y)		29 (3.3)		14 (2.2)		14 (4.3)		5 (2.1)
Middle school (8 y)		99 (11.2)		25 (3.9)		32 (9.9)		8 (3.4)
Secondary school (12 y)		150 (16.9)		82 (12.8)		46 (14.3)		36 (15.3)
Secondary school + (13.5 y)		138 (15.5)		99 (15.5)		59 (18.3)		34 (14.4)
Graduate (15 y)		354 (40.0)		312 (48.8)		135 (41.9)		121 (51.3)
Professional (17 y)		106 (12.0)		98 (15.3)		35 (11.0)		31 (13.1)

The 'complete case analysis' (N=558) included participants with no missing data. They had all 15 body measurements recorded from birth to young adulthood, plus all 10 early life socio-economic status variables, plus gestational age at birth. The 'full sample' (N=1,526) refers to all participants whose educational attainment was recorded in young adulthood during phase 5 of the New Delhi Birth Cohort follow-up, but were missing one or more of the above 26 variables.

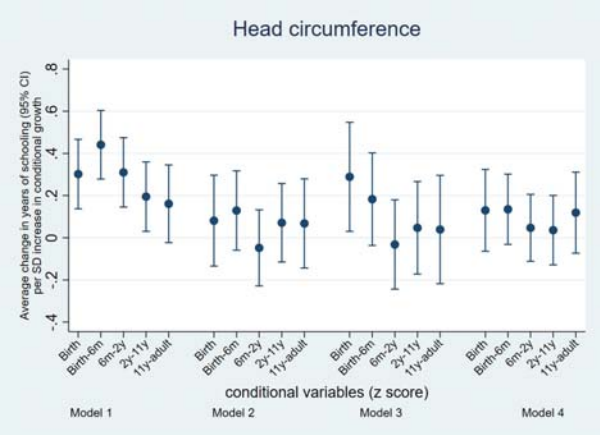
year BMI (95% CI) 0.21 (0.07 to 0.34) kg/m^2] (**Web Table II**). Compared with the remainder of those studied as adults, the complete case sample had a lower BMI at age 11 years (0.22 kg/m^2, 95% CI 0.03 to 0.40) but there were no significant differences for the other measurements.

In the unadjusted model, head size at birth and head growth at 0-6 month, 6 month – 2 year and 2-11 year were positively associated with years of attained education (Model 1 in **Fig. 1** (*a*), **Table III** and **Web Table III**). The strongest association was with head growth from birth to 6 month; one SD increase in head growth between birth and 6 months was associated with a 0.44 year increase in education. There were similar findings for height and BMI. There was a significant interaction of birth head circumference with head growth from birth to 6 months in relation to educational attainment (P=0.02). The positive association of 0-6 months conditional head growth with

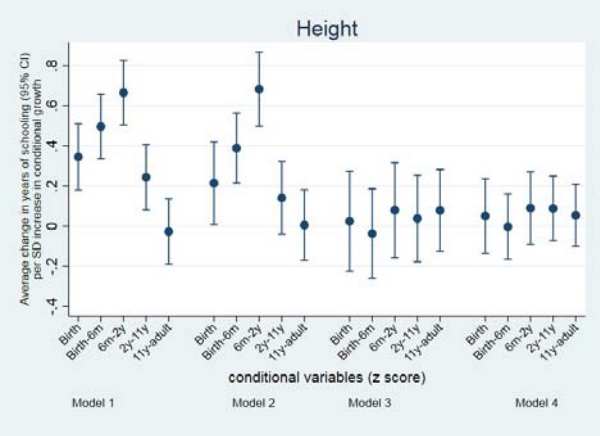
Table II Socioeconomic Characteristics of Cohort Members at Birth (*N*= 2084)

Variables	*Full sample (n=1526)*	*Complete case sample (n=558)*	*Correlation*[a]
Maternal education (y), n=1366			0.78
Illiterate (0 y)	386 (28.3)	178 (31.9)	
Completed primary school (3 y)	264 (19.3)	105 (18.8)	
Completed middle school (7 y)	236 (17.3)	114 (20.4)	
Matriculation (10 y)	293 (21.4)	120 (21.5)	
College (12 y)	187 (13.7)	41 (7.3)	
Type of housing, n=1055			0.47
Thatched hut (rented)	5 (0.5)	0 (0)	
Thatched hut (owned)	4 (0.4)	1 (0.2)	
Masonry build (rented)	135 (12.8)	58 (10.4)	
Masonry build (owned)	539 (51.1)	283 (50.7)	
Flat (rented)	175 (16.6)	105 (18.8)	
Flat (owned)	165 (15.6)	94 (16.8)	
Bungalow (rented)	8 (0.8)	5 (0.9)	
Bungalow (owned)	24 (2.2)	12 (2.2)	
Household income (INR)[a], *n*=1056	690 (459, 1200)	696 (456,1200)	0.79
Father's occupation, n=1504			0.28
Unemployed	3 (0.2)		
Unskilled manual labor	28 (1.9)	11 (2.0)	
Semi-skilled manual labor	161 (10.7)	62 (11.1)	
Skilled manual labor	328 (21.8)	124 (22.2)	
Clerical	741 (49.3)	286 (51.3)	
Professional or running a large business	243 (16.2)	75 (13.4)	
Health service usage[b], *n*=1057	1057 (69.3)		0.59
No/low health services use	336 (31.8)	163 (29.2)	
Intermediate use	366 (34.6)	201 (36.0)	
Highest use	355 (33.6)	194 (34.8)	
Sanitation, *n*=1057			0.63
No household toilet	179 (16.9)	66 (11.8)	
Non-flush toilet	495 (46.9)	275 (49.3)	
Flush toilet	383 (36.2)	217 (38.9)	
Water supply, *n*=1057			0.60
No piped water	124 (11.7)	54 (9.7)	
Shared piped water	540 (51.1)	277 (49.6)	
Sole use piped water	393 (37.2)	227 (40.7)	
Crowding index (people/room),[a] *n*=1055	4 (3,6)	4 (3,5.5)	-0.72
Child dependency,[a] *n*=1057	1.0 (0.7, 2.0)	1.0 (0.6, 1.6)	-0.56
Paternal years of schooling, n=1430			
Illiterate (0 y)	123 (8.6)	2 (0.4)	
Completed primary school (3 y)	132 (9.2)	19 (3.4)	
Completed middle school (8 y)	211 (14.8)	40 (7.2)	0.31
High school certificate (12 y)	404 (28.3)	82 (14.7)	
High school+ (13.5 y)	155 (10.8)	93 (16.7)	
Graduate (15 y)	280 (19.6)	256 (45.9)	
Professional degree (17 y)	125 (8.7)	66 (11.7)	

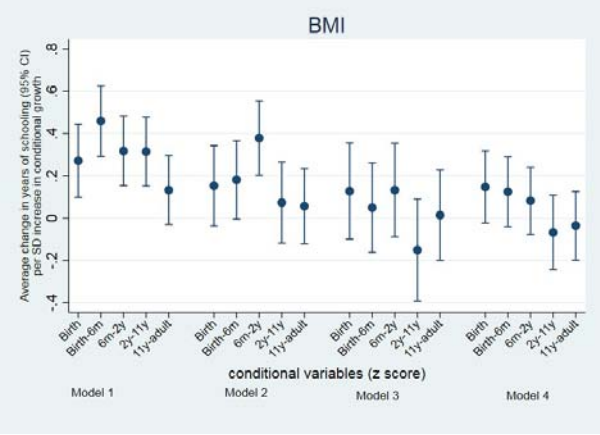
Data presented no. (%) or [a]median (IQR). [b]Combination score of any health-promotion or preventative health service utilization during the antenatal and postnatal period (e.g. antenatal care, child immunization). The 'complete case analysis' (N=558) included participants with no missing data. They had all 15 body measurements recorded from birth to young adulthood, plus all 10 early life socioeconomic status variables, plus gestational age at birth. The 'full sample' (N=1526) refers to all participants whose educational attainment was recorded in young adulthood during phase 5 of the New Delhi Birth Cohort follow-up, but were missing one or more of the above 26 variables. Crowding index (-0.72),child dependency (-0.56) and paternal years of schooling (0.31). Correlation of various variables with socioeconomic status score; maternal education (0.78), type of housing (0.47), household income (0.79), water supply (0.60).



(*a*)



(*b*)



(*c*)

Footnote: *Model 1: Head circumference (a), height (b) or BMI (c) separately; Model 2: Head circumference, height and BMI included together in the model; Model 3: Additionally adjusted for gestational age and the combined SES variable; Model 4: Replacing the combined SES variable with its individual components. Associations are statistically significant where the confidence intervals exclude 0.*

Fig. 1 Change in years of attained education per SD change in head circumference, height and body mass index at birth, and conditional growth in head circumference, height and BMI during infancy, childhood and adolescence.

attained education was significant in all four quartiles of birth head circumference, but stronger in the smallest quartile at birth (β=0.875 years of education per SD 0-6 month head growth, P<0.001) compared with the 2nd, 3rd and 4th quartiles (β=0.467, P=0.002; β=0.464, P=0.02; and β=0.328, P=0.04, respectively).

The positive associations of head size were not significant after adjusting for height and BMI (Model 2). In this joint model, height growth 0-6 month and 6 month – 2 year, and BMI gain 6 month-2 year remained positively associated with attained education. Gestational age was unrelated to educational attainment, while higher SES (the first principle component and individual components) was strongly positively associated with both educational attainment and childhood growth (Model 3, **Web Tables IV** and **V**). After adjusting for gestational age and SES (models 3 and 4) there were no associations with childhood head, height or BMI growth. Model 4 had a better overall fit than Model 3. The body size/growth measurements explained approximately 8% of the variability in attained education and SES a further 16%. Similar results were obtained in the complete case sample (**Web Table III**) except for a positive association of BMI gain from 6 month to 2 year with educational attainment.

DISCUSSION

Newborn head size and head growth up to 11 years were positively associated with years of education, which we used as a proxy for cognitive ability. The strongest associations were with early head growth (birth to 2 years). Height growth up to 2 years, and BMI at birth and BMI gain from 6 month-2 year were also positively associated with educational attainment. The associations of head size and growth with attained education were not significant after adjusting for height and BMI during the same age intervals. None of the associations of body size with educational attainment were significant after further adjustment for SES at birth, which was strongly positively related to attained education.

The positive association between newborn head circumference and attained education is consistent with previous literature. While some studies have shown positive associations between head circumference at birth and later cognitive ability, assessed by psychometric testing or achieved education [9-15], others found no association [13-15]. Similar to our results, other studies showing positive effects have also reported modest effects of head circumference on cognitive scores [9,12]. We found that the association was not significant after adjusting for newborn length and BMI, suggesting that overall prenatal growth, rather than specifically brain growth, was related to later educational attainment. Though many previous

Table III Association of Head Circumference, Height and Body Mass Index at Birth and Growth During Childhood With Years of Education

Predictor (Standardized score)	*Model 1: Unadjusted*		*Model 4: Adjusted* [a]	
	β (95% CI)	*P value*	*β (95% CI)*	*P value*
Head circumference (cm)				
Birth	0.30 (0.14 to 0.46)	<0.001	0.15 (-0.05 to 0.34)	0.1
Birth-6 mo	0.44 (0.28 to 0.60)	<0.001	0.14 (-0.03 to 0.31)	0.1
6 mo-2 y	0.30 (0.14 to 0.46)	<0.001	0.03 (-0.13 to 0.19)	0.6
2 y-11y	0.20 (0.04 to 0.38)	0.01	0.03 (-0.14 to 0.20)	0.7
11 y-adult	0.15 (-0.02 to 0.33)	0.07	0.08 (-0.10 to 0.26)	0.3
Height				
Birth	0.31 (0.14 to 0.48)	<0.001	0.01 (-0.18 to 0.20)	0.9
Birth-6 mo	0.49 (0.33 to 0.66)	<0.001	0.00 (-0.17 to 0.17)	0.9
6 mo-2 y	0.68 (0.52 to 0.85)	<0.001	0.11 (-0.08 to 0.28)	0.2
2 y-11 y	0.24 (0.08 to 0.40)	0.003	0.09 (-0.07 to 0.24)	0.2
11 y-adult	-0.01 (-0.17 to 0.16)	0.9	0.10 (-0.06 to 0.25)	0.2
Body mass index				
Birth	0.27 (0.09 to 0.44)	0.004	0.14 (-0.04 to 0.33)	0.1
Birth-6m	0.44 (0.27 to 0.62)	<0.001	0.13 (-0.04 to 0.30)	0.1
6m-2y	0.31 (0.14 to 0.48)	<0.001	-0.02 (-0.20 to 0.15)	0.8
2y-11y	0.35 (0.19 to 0.51)	<0.001	-0.03 (-0.18 to 0.13)	0.7
11y-adult	0.13 (-0.04 to 0.29)	0.1	-0.00 (-0.17 to 0.17)	0.9

R^2 for model 1 for head circumference, height, and socioeconomic status were 0.5, 0.09 and 0.05, respectively. R^2 for model [1] for socoioeconomic status was 0.24. [a]Model 4 Adjusted for SES components and gestation.

studies have reported that, newborn head circumference along with birthweight and length were positively related to later cognitive performance [10-12], only one, a large Swedish study [10] demonstrated that head circumference remained a significant predictor, even after adjusting for weight and length.

Our findings of the unadjusted analyses, showing strong association with head growth between birth and 6 months are consistent with previous studies [9,11,13,15,16]. The association of early infancy head growth with educational attainment was stronger among participants in the lowest quartile of birth head circumference, possibly reflecting severe intrauterine growth restriction followed by relatively favorable conditions in infancy. We did not find any studies with longitudinal follow-up measures of head growth through adolescence, highlighting the importance of the New Delhi cohort growth data. In our study, head growth after 11 years was not significantly related to attained education. MRI studies have shown that brain volume peaks before the onset of puberty, after which the correlation between head circumference and brain size becomes weaker [2,7].

In our study, infant and childhood head growth was not related to attained education after adjustment for concurrent height and BMI gain, which independently of head growth, predicted higher attained education, thus re-establishing the fact that good overall nutrition, freedom from illness, enabling exploration and play, are important contributors to neuro-development [22].The 1970 UK birth cohort study found that head growth, independent of weight and height, was associated with cognitive scores at 10 years [15]. Many studies have reported that infant weight and length gain are positively related to later cognitive scores [11,16,17]. A meta-analysis of data from five cohorts from low- and middle-income countries (LMICs) showed that height gain from birth to 2 years is positively associated with attained schooling, a stronger association than was found for later height gain, or for weight gain during either period [22].

SES at birth was an independent predictor of attained education in this study, probably explained by its effect on multiple parameters including nutrition, exposure to childhood illness, availability of playthings and learning materials, quality of parental stimulation, and quality of education [24,25]. SES is thus likely to be both a confounder of the association between head size/growth and education, and an 'upstream' factor determining head growth and brain development.

The main strengths of the study were the frequent longitudinal body measurements from birth to adulthood, and detailed early life SES indicators. A limitation was that educational attainment, though frequently used in

WHAT IS ALREADY KNOWN?

- Previous studies have shown positive associations of head circumference of newborns, infants and children with later cognition.

WHAT THIS STUDY ADDS?

- Newborn head circumference and head growth in infancy, when adjusted for various parameters, do not have any association with educational attainment. Socio-economic status is the only factor predicting educational attainment in this population.

epidemiological studies, is a fairly crude measure of cognitive ability. In high income countries, cognitive function and years of education are strongly correlated [21], but may be less so in India, where access to education is influenced by family wealth and other socio-cultural factors. Nevertheless, it constitutes a practical metric for improving human capital in LMICs. Another limitation was cohort attrition, resulting in a final sample which was 19% of the original birth cohort. However, early life head size was similar between the analysis sample and the original cohort.

In conclusion, higher socioeconomic status predicted greater educational attainment in this urban Indian population, possibly through its influence on overall nutrition, somatic growth and other related factors. The findings support measures to reduce socioeconomic inequalities, promote maternal health and support infant nutrition and nurturing, for optimal neurodevelopment.

Ethics clearance: Maulana Azad Medical College, New Delhi; No. F.501(134)03/EC05/MC(ACA)/12358 dated 11.08.2005.
Contributors: SKB has led the New Delhi Birth Cohort Study since the cohort's inception in 1969. The current study was designed by SP, HPSS, SKB, CHDF and CO. Data analysis was carried out by SP, CO, ND, SS and HPSS. The manuscript was drafted by SP, CHDF and CO, and critically modified by ND, ZSP, SS, SKB and HPSS. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Note: Supplementary matter related to this article is available at *www.indianpediatrics.net*

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CLIPPINGS

Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): Lancet Glob Health. 2021 Sep; 9(9): e1273-e1285.

This multicounty open-label, randomized controlled trial was conducted to examine whether therapeutic hypothermia alongside optimal supportive intensive care reduces death or moderate or severe disability after neonatal encephalopathy in south Asia. Seven tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh, took part in this trial.The Infantswere enrolled at or after 36 weeks of gestation who had moderate or severe neonatal encephalopathy and neededcontinued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min of age (for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home. The primary outcome was a combined endpoint of death or moderate or severe disability at 18–22 months, assessed by the Bayley Scales of Infant and Toddler Development (third edition) and a detailed neurological examination.After screening 2296 infants, 408 eligible infants who areassigned to eitherthe hypothermia group (202) or to the control group (206). The study revealed50% infants in the hypothermia group and 47% infants in the control group died or had a moderate or severe disability (risk ratio 1·06; 95% CI 0·87–1·30; p=0·55), and 42% infants in the hypothermia group and 31% infant in control group (31%; p=0·022) died, of whom 72 (36%) and 49 (24%; p=0·0087) died during neonatal hospitalization. The authors concluded that therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months after neonatal encephalopathy in low-income and middle-income countries, on the other hand increased death alone. Therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle-income countries, even when tertiary neonatal intensive care facilities are available.The study highlighted a therapy that is unsafe and ineffective in a well-resourced setting is unlikely to be beneficial in sub-Saharan Africa and advised for a future research which should focus on understanding the origins and timing of brain injury in these settings and in preventing neonatal encephalopathy.

Safety and efficacy of Immediate Kangaroo Mother Care (i-KMC) after birth (N Engl J Med 2021; 384: 2028-38.

This randomized, controlled trial was conducted with an objective to find out the safety and efficacy of kangaroo mother care initiated soon after birth among infants with low birth weight. The study was conducted in five hospitals in Ghana, India, Malawi, Nigeria, and Tanzania involving infants with a birth weight between 1.0 and 1.799 kg who were assigned to receive immediate kangaroo mother care (intervention) or conventional care in an incubator or a radiant warmer until their condition stabilized and kangaroo mother care thereafter (control). The primary outcomes were death in the neonatal period (the first 28 days of life) and in the first 72 hours of life.A total of 3211 infants and their mothers were randomly assigned to the intervention group (1609 infants with their mothers) or the control group (1602 infants with their mothers). Neonatal death occurred in 12% infants in intervention group vs.15.7% in the control group in first 28 days of life (relative risk of death, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P=0.001); neonatal death in the first 72 hours of life occurred in 4.6% in the intervention group (4.6%)vs.5.8% in control group (relative risk of death, 0.77; 95% CI, 0.58 to 1.04; P=0.09).The study found that in infants with a birth weight between 1.0 and 1.799 kg, who received immediate kangaroo mother care had lower mortality at 28 days than those who received only conventional care with kangaroo mother care initiated after stabilization. The study highlightedthe importance of immediate KMC after birth. which is safe and efficacious.

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Web Table I Head Circumference Centile Values in the New Delhi Birth Cohort

Age (y)	*Centiles (cm)*						
	3%	*10%*	*25%*	*50%*	*75%*	*90%*	*97%*
Males							
0	31.37	32.10	32.85	33.68	34.50	35.25	35.98
0.25	36.86	37.63	38.41	39.28	40.14	40.92	41.69
0.5	39.69	40.48	41.27	42.16	43.04	43.84	44.63
1	42.12	42.91	43.71	44.61	45.50	46.30	47.10
2	44.48	45.26	46.05	46.93	47.81	48.60	49.39
3	45.76	46.53	47.31	48.18	49.05	49.83	50.60
4	46.64	47.41	48.19	49.06	49.92	50.70	51.47
5	47.39	48.16	48.95	49.83	50.70	51.49	52.27
6	48.00	48.80	49.61	50.51	51.41	52.22	53.02
7	48.48	49.30	50.14	51.06	51.98	52.82	53.64
8	48.89	49.71	50.55	51.47	52.40	53.24	54.06
9	49.15	49.99	50.83	51.77	52.79	53.55	54.39
10	49.29	50.15	51.02	51.99	52.96	53.83	54.69
11	49.37	50.27	51.18	52.19	53.20	54.11	55.00
12	49.48	50.41	51.36	52.41	53.46	54.40	55.33
13	49.70	50.66	51.62	52.70	53.78	54.75	55.71
14	50.08	51.04	52.02	53.10	54.19	55.17	56.13
15	50.56	51.52	52.49	53.57	54.65	55.62	56.58
16	51.05	52.00	52.97	54.03	55.10	56.06	57.01
17	51.50	52.44	53.40	54.46	55.52	56.47	57.41
18	51.88	52.82	53.77	54.83	55.88	56.83	57.77
19	52.16	53.11	54.07	55.14	56.20	57.12	58.14
20	52.40	53.41	52.36	53.31	54.26	55.11	55.96
21	50.64	51.49	52.34	52.40	54.25	55.11	55.95
26-33	50.55	51.49	52.44	53.49	54.54	55.49	56.43
34-39	50.96	51.97	53.00	54.14	55.28	56.31	57.32

Contd..

Table continued from pre page

Females							
0	31.13	31.81	32.49	33.25	34.00	34.69	35.36
0.25	36.05	36.78	37.51	38.33	39.14	39.88	40.60
0.5	38.70	39.44	40.18	41.02	41.85	42.59	43.33
1	41.09	41.83	42.58	43.42	44.25	45.00	45.74
2	43.29	44.07	44.86	45.75	46.63	47.42	48.20
3	44.71	45.48	46.26	47.13	48.00	48.79	49.56
4	45.81	46.55	47.31	48.15	48.99	49.74	50.49
5	46.56	47.32	48.08	48.94	49.79	50.55	51.31
6	47.29	48.06	48.85	49.72	50.59	51.37	52.14
7	47.96	48.74	49.52	50.40	51.27	52.06	52.83
8	48.24	49.03	49.83	50.72	51.61	52.41	53.20
9	48.46	49.29	50.14	51.07	52.01	52.85	53.68
10	48.85	49.75	50.66	51.67	52.68	53.59	54.49
11	49.32	50.29	51.28	52.37	53.47	54.46	55.43
12	49.80	50.83	51.88	53.04	54.21	55.25	56.29
13	50.19	51.25	52.33	53.52	54.72	55.80	56.86
14	50.43	51.48	52.54	53.71	54.89	55.95	57.00
15	50.56	51.56	52.57	53.69	54.82	55.83	56.83
16	50.61	51.56	52.52	53.58	54.64	55.60	56.54
17	50.65	51.55	52.46	53.47	54.49	55.40	56.30
18	50.66	51.53	52.41	53.39	54.37	55.25	56.12
19	50.68	51.52	52.38	53.34	54.30	55.16	56.01
20	50.62	51.50	52.36	53.31	54.26	55.11	55.96
21	50.64	51.49	52.34	53.30	54.25	55.11	55.95
26-33	50.55	51.60	52.44	53.49	54.54	55.49	56.43
34-39	50.96	51.97	53.00	54.14	55.28	56.31	57.32

Web Table II Representativeness of the study sample: a) Comparison of newborn and childhood growth data between those included in the current study and the remainder of the original cohort; and b) Comparison of newborn and infant data between (among those studied as adults) those who had the full set of size, SES and educational attainment measures and those who did not

Body size at birth, growth variables and SES components	Total number of members in the original cohort	Total members in Adult Phase	Gender-adjusted Regression coefficient (95% CI) (Original Cohort-Adult Phase) v Adult Phase	p-value	Gender-adjusted Regression coefficient (95% CI) {Adult Phase-Complete case analysis) v Complete case (N=558)	p-value
At birth						
Head circumference (cm)	7034	1463	-0.07 (-0.14 to 0.01)	0.06	0.01 (-0.12 to 0.13)	0.9
Height(cm)	6940	1457	-0.15 (-0.28 to -0.02)	0.02	-0.02 (-0.24 to 0.20)	0.8
Body mass index(kg/m^2)	6934	1457	-0.05 (-0.12 to 0.03)	0.2	0.02 (-0.11 to 0.15)	0.7
At age 6 months						
Head(cm)	7295	1498	-0.05 (-0.12 to 0.03)	0.2	-0.05 (-0.18 to 0.07)	0.4
Height(cm)	7125	1464	-0.10 (-0.26 to 0.05)	0.1	0.08 (-0.17 to 0.33)	0.5
Body mass index(kg/m^2)	7050	1439	-0.10 (-0.19 to -0.00)	0.05	-0.11 (-0.27 to 0.05)	0.2
At age 2 years						
Head (cm)	5300	1444	0.05 (-0.03 to 0.13)	0.2	0.03 (-0.10 to 0.17)	0.6
Height (cm)	5202	1410	0.15 (-0.09 to 0.39)	0.2	0.23 (-0.15 to 0.61)	0.2
Body mass index(kg/m^2)	4890	1324	-0.02 (-0.10 to 0.06)	0.6	0.07 (-0.06 to 0.20)	0.3
At age 11 years						
Head (cm)	3235	1435	0.09 (-0.01 to 0.19)	0.08	0.01 (-0.15 to 0.16)	0.9
Height (cm)	3233	1431	0.77 (0.29 to 1.24)	0.002	0.55 (-0.14 to 1.24)	0.1
Body mass index(kg/m^2)	3233	1426	0.210.07 to 0.34)	0.002	0.22 (0.03 to 0.40)	0.02

Web Table III Associations of Head Circumference, Height and Body Mass Index at Birth and Growth During Childhood with Years of Education (Complete Case Analysis)

Predictor (Standardized score)	*Model 1: Unadjusted*		*Model 2: Mutually adjusted for other body measurements*		*Model 3: Further adjusted for SES and gestation*		*Model 4: Further adjusted for SES components and gestation*	
	β (95% CI)	*p-value*	*β (95% CI)*	*p-value*	*β (95% CI)*	*p-value*	*β (95% CI)*	*p-value*
Head								
Birth	0.32 (0.06 to 0.57)	0.01	0.22 (-0.11 to 0.55)	0.1	0.22 (-0.09 to 0.53)	0.1	0.18 (-0.12 to 0.49)	0.2
Birth-6m	0.50 (0.24 to 0.77)	<0.001	0.13 (-0.18 to 0.43)	0.4	0.16 (-0.12 to 0.44)	0.2	0.13 (-0.15 to 0.41)	0.3
6m-2y	0.17 (-0.09 to 0.43)	0.2	-0.20 (-0.49 to	0.1	-0.12 (-0.39 to	0.3	-0.12 (-0.38 to	0.3
2y-11y	0.09 (-0.16 to 0.35)	0.4	-0.08 (-0.35 to	0.5	-0.00 (-0.26 to	0.9	-0.03 (-0.28 to	0.8
11y-adult	0.11 (-0.14 to 0.36)	0.3	-0.02 (-0.29 to	0.8	-0.01 (-0.25 to	0.9	-0.00 (-0.24 to	0.9
R-square	0.05							
Height								
Birth	0.18 (-0.08 to 0.44)	0.1	-0.05 (-0.36 to	0.7	-0.09 (-0.38 to	0.5	-0.08 (-0.37 to	0.5
Birth-6m	0.46 (0.20 to 0.72)	0.001	0.37 (0.09 to 0.66)	0.01	-0.03 (-0.30 to	0.8	-0.07 (-0.34 to	0.6
6m-2y	0.54 (0.30 to 0.79)	<0.001	0.59 (0.30 to 0.88)	<0.001	0.06 (-0.22 to 0.35)	0.6	0.08 (-0.20 to 0.36)	0.5
2y-11y	0.32 (0.07 to 0.58)	0.01	0.25 (-0.03 to 0.53)	0.08	0.08 (-0.18 to 0.34)	0.5	0.07 (-0.19 to 0.33)	0.5
11y-adult	-0.15 (-0.40 to	0.2	-0.10 (-0.37 to	0.4	0.01 (-0.24 to 0.26)	0.9	0.02 (-0.23 to 0.26)	0.9
R-square	0.08							
Body Mass Index								
Birth	0.17 (-0.09 to 0.43)	0.2	0.09 (-0.20 to 0.39)	0.5	0.11 (-0.16 to 0.38)	0.4	0.07 (-0.20 to 0.34)	0.6
Birth-6m	0.51 (0.27 to 0.75)	<0.001	0.32 (0.03 to 0.60)	0.03	0.20 (-0.06 to 0.46)	0.1	0.21 (-0.05 to 0.47)	0.1
6m-2y	0.49 (0.24 to 0.74)	<0.001	0.55 (0.28 to 0.83)	<0.001	0.33 (0.07 to 0.59)	0.01	0.36 (0.10 to 0.61)	0.006
2y-11y	0.27 (0.01 to 0.53)	0.04	0.06 (-0.25 to 0.37)	0.7	-0.09 (-0.37 to	0.5	-0.05 (-0.33 to	0.7
11y-adult	0.11 (-0.14 to 0.36)	0.3	0.09 (-0.17 to 0.34)	0.5	0.07 (-0.17 to 0.31)	0.5	0.05 (-0.19 to 0.28)	0.6
Socio-economic	-	-	-	-	1.41 (1.13 to 1.68)	<0.001	-	-
Gestational age	-	-	-	-	0.09 (-0.16 to 0.33)	0.4	0.04 (-0.20 to 0.28)	0.7
R-square	0.07		0.13		0.25		0.29	

The complete case analysis is limited to participants with complete measurements for all variables (N=558). Missing data: Years of attained education was available for 1,526 men and women. Of the 15 body size variables: head circumference, length or height and BMI at birth, 6 months, 2 years, 11 years and in young adulthood, data were complete for 958 (63%). A further 352 (23%) were missing up to three of the 15 measurements. Socio-economic status data was complete for 962 of the 1,526 (63%); a further 88 (6%) were missing only one socio-economic status variable. See supplementary Table VI for frequency of missing data for each variable.

Web Table IIIa Associations of Head Circumference, Height and Body Mass Index at Birth and Growth During Childhood with Years of Education (Data Used to Generate Fig. 1)

Predictor (*Standardised score*)	*Model 1:Unadjusted*		*Model 2:Mutually adjusted for other body measurements*		*Model 3:Further adjusted for SES, gestation*		*Model 4:Further adjusted for SES components and gestation*	
	β (95% CI)	*p-value*	*β (95% CI)*	*p-value*	*β (95% CI)*	*p-value*	*β (95% CI)*	p-value
Head circumference								
Birth	0.30 (0.14 to 0.46)	<0.001	0.10 (-0.12 to 0.32)	0.3	0.32 (0.06 to 0.58)	0.01	0.15 (-0.05 to 0.34)	0.1
Birth-6m	0.44 (0.28 to 0.60)	<0.001	0.14 (-0.05 to 0.33)	0.1	0.18 (-0.04 to 0.40)	0.1	0.14 (-0.03 to 0.31)	0.1
6m-2y	0.30 (0.14 to 0.46)	<0.001	-0.06 (-0.24 to	0.5	-0.05 (-0.26 to 0.17)	0.6	0.03 (-0.13 to 0.19)	0.6
2y-11y	0.20 (0.04 to 0.38)	0.01	0.07 (-0.12 to 0.25)	0.4	0.05 (-0.17 to 0.27)	0.6	0.03 (-0.14 to 0.20)	0.7
11y-adult	0.15 (-0.02 to 0.33)	0.07	0.05 (-0.14 to 0.23)	0.6	0.04 (-0.20 to 0.27)	0.7	0.08 (-0.10 to 0.26)	0.3
R-square	0.05							
Height								
Birth	0.31 (0.14 to 0.48)	<0.001	0.16 (-0.06 to 0.37)	0.1	-0.05 (-0.31 to 0.21)	0.7	0.01 (-0.18 to 0.20)	0.9
Birth-6m	0.49 (0.33 to 0.66)	<0.001	0.38 (0.20 to 0.56)	<0.001	-0.02 (-0.25 to 0.21)	0.8	0.00 (-0.17 to 0.17)	0.9
6m-2y	0.68 (0.52 to 0.85)	<0.001	0.69 (0.50 to 0.88)	<0.001	0.10 (-0.13 to 0.34)	0.3	0.11 (-0.08 to 0.28)	0.2
2y-11y	0.24 (0.08 to 0.40)	0.003	0.13 (-0.05 to 0.31)	0.1	0.04 (-0.18 to 0.25)	0.7	0.09 (-0.07 to 0.24)	0.2
11y-adult	-0.01 (-0.17 to	0.9	0.05 (-0.13 to 0.22)	0.6	0.10 (-0.10 to 0.31)	0.3	0.10 (-0.06 to 0.25)	0.2
R-square	0.09							
Body Mass Index								
Birth	0.27 (0.09 to 0.44)	0.004	0.15 (-0.05 to 0.35)	0.1	0.13 (-0.10 to 0.37)	0.2	0.14 (-0.04 to 0.33)	0.1
Birth-6m	0.44 (0.27 to 0.62)	<0.001	0.17 (-0.03 to 0.36)	0.08	0.03 (-0.19 to 0.24)	0.8	0.13 (-0.04 to 0.30)	0.1
6m-2y	0.31 (0.14 to 0.48)	<0.001	0.37 (0.19 to 0.55)	<0.001	0.12 (-0.10 to 0.34)	0.2	-0.02 (-0.20 to 0.15)	0.8
2y-11y	0.35 (0.19 to 0.51)	<0.001	0.13 (-0.06 to 0.32)	0.1	-0.11 (-0.35 to 0.13)	0.3	-0.03 (-0.18 to 0.13)	0.7
11y-adult	0.13 (-0.04 to 0.29)	0.1	0.06 (-0.11 to 0.23)	0.5	0.02 (-0.19 to 0.23)	0.8	-0.00 (-0.17 to 0.17)	0.9
Gestational age	-	-	-	-	-0.09 (-0.30 to 0.13)	0.4	-	-
Socio-economic status	-	-	-	-	1.55 (1.33 to 1.77)	<0.001		
R-square	0.05		0.08		0.10		0.24	

Web Table IV Associations of (a) Head Circumference, (b) Height and (c) Body Mass Index at Birth and Growth During Childhood With Individual SES Components and the First Principle Component

SES Variables (SD scores)	*(a) HEAD CIRCUMFERENCE (cms) (GENDER ADJUSTED REGRESSION COEFFICIENT (95% CI))*				
	Birth	*Conditional growth Birth-6m*	*Conditional growth 6m-2y*	*Conditional growth 2y-11y*	*Conditional growth 11y-adult*
1st principle component					
Maternal education	-0.02 (-0.10 to 0.06)	0.13 (0.05 to 0.21)	0.10 (0.03 to 0.18)	0.04 (-0.04 to 0.12)	0.06 (-0.02 to 0.14)
Type of Housing	0.01 (-0.07 to 0.08)	0.05 (-0.02 to 0.12)	-0.04 (-0.11 to 0.04)	-0.05 (-0.12 to 0.02)	-0.02 (-0.09 to 0.05)
Income	-0.05 (-0.13 to 0.02)	0.11 (0.04 to 0.19)	0.11 (0.03 to 0.18)	0.07 (-0.01 to 0.14)	0.07 (-0.01 to 0.14)
Parental occupation	0.08 (-0.00 to 0.16)	0.18 (0.10 to 0.26)	0.08 (-0.01 to 0.16)	0.09 (0.01 to 0.17)	0.01 (-0.08 to 0.09)
Utilities	-0.02 (-0.10 to 0.06)	0.11 (0.03 to 0.20)	0.12 (0.04 to 0.20)	0.03 (-0.05 to 0.11)	0.03 (-0.05 to 0.11)
Sanitation	-0.05 (-0.02 to 0.12)	0.07 (-0.00 to 0.14)	0.02 (-0.05 to 0.10)	-0.02 (-0.10 to 0.05)	0.04 (-0.03 to 0.11)
Water	0.04 (-0.04 to 0.11)	0.03 (-0.05 to 0.11)	0.01 (-0.07 to 0.09)	0.04 (-0.04 to 0.12)	-0.06 (-0.13 to 0.02)
Crowding Index	0.00 (-0.08 to 0.09)	-0.07 (-0.16 to 0.01)	-0.14 (-0.22 to -0.05)	-0.12 (-0.20 to -0.04)	-0.03 (-0.11 to 0.06)
Child dependency ratio	0.06 (-0.03 to 0.15)	-0.12 (-0.21 to -0.03)	-0.09 (-0.18 to 0.01)	-0.05 (-0.14 to 0.04)	-0.08 (-0.17 to 0.01)
Paternal years of schooling	0.02 (-0.07 to 0.10)	0.12 (0.03 to 0.21)	0.10 (0.01 to 0.18)	0.06 (-0.03 to 0.14)	0.05 (-0.03 to 0.14)
SES Variables (SD scores)	*(b) HEIGHT (cms) (GENDER ADJUSTED REGRESSION COEFFICIENT (95% CI))*				
	Birth	*Conditional growth Birth-6m*	*Conditional growth 6m-2y*	*Conditional growth 2y-11y*	*Conditional growth 11y-adult*
1st principle component					
Maternal education	0.05 (-0.04 to 0.13)	0.23 (0.15 to 0.31)	0.29 (0.22 to 0.37)	0.12 (0.04 to 0.20)	-0.12 (-0.20 to -0.05)
Type of Housing	0.03 (-0.05 to 0.11)	0.02 (-0.05 to 0.10)	0.04 (-0.03 to 0.11)	0.01 (-0.07 to 0.08)	-0.02 (-0.09 to 0.06)
Income	0.00 (-0.08 to 0.08)	0.20 (0.12 to 0.27)	0.29 (0.22 to 0.36)	0.12 (0.04 to 0.20)	-0.10 (-0.17 to -0.02)
Parental occupation	0.07 (-0.02 to 0.16)	0.20 (0.12 to 0.29)	0.20 (0.12 to 0.28)	0.15 (0.06 to 0.23)	-0.09 (-0.17 to -0.01)
Utilities	-0.05 (-0.13 to 0.04)	0.14 (0.06 to 0.23)	0.17 (0.09 to 0.25)	0.10 (0.02 to 0.18)	-0.12 (-0.20 to -0.04)
Sanitation	0.03 (-0.05 to 0.10)	0.08 (0.01 to 0.16)	0.10 (0.03 to 0.18)	0.06 (-0.02 to 0.13)	-0.05 (-0.13 to 0.02)
Water	0.09 (0.02 to 0.17)	0.13 (0.05 to 0.21)	0.08 (0.01 to 0.16)	0.08 (-0.00 to 0.16)	-0.04 (-0.12 to 0.04)
Crowding Index	0.00 (-0.09 to 0.09)	-0.13 (-0.22 to -0.05)	-0.32 (-0.39 to -0.24)	-0.21 (-0.29 to -0.12)	0.06 (-0.03 to 0.14)
Child dependency ratio	0.08 (-0.02 to 0.17)	-0.16 (-0.25 to -0.07)	-0.28 (-0.36 to -0.19)	-0.07 (-0.16 to 0.02)	0.05 (-0.04 to 0.14)
Paternal years of schooling	-0.01 (-0.10 to 0.09)	0.29 (0.21 to 0.38)	0.24 (0.15 to 0.32)	0.09 (0.00 to 0.18)	-0.09 (-0.17 to 0.00)
SES Variables (SD scores)	*(c) BMI (kg/m^2) (GENDER ADJUSTED REGRESSION COEFFICIENT (95% CI))*				
	Birth	*Conditional growth Birth-6m*	*Conditional growth 6m-2y*	*Conditional growth 2y-11y*	*Conditional growth 11y-adult*
1st principle component					
Maternal education	0.03 (-0.05 to 0.12)	0.14 (0.07 to 0.22)	0.10 (0.02 to 0.18)	0.23 (0.15 to 0.31)	0.07 (-0.01 to 0.15)
Type of Housing	0.05 (-0.03 to 0.12)	0.03 (-0.04 to 0.10)	0.09 (0.02 to 0.16)	0.02 (-0.06 to 0.09)	-0.03 (-0.10 to 0.04)
Income	-0.08 (-0.16 to 0.00)	0.08 (0.01 to 0.15)	0.04 (-0.03 to 0.12)	0.23 (0.15 to 0.30)	0.05 (-0.03 to 0.12)
Parental occupation	0.09 (0.00 to 0.17)	0.14 (0.06 to 0.22)	0.03 (-0.05 to 0.12)	0.12 (0.03 to 0.21)	0.04 (-0.04 to 0.13)
Utilities	-0.07 (-0.15 to 0.02)	0.09 (0.01 to 0.17)	0.11 (0.03 to 0.19)	0.17 (0.08 to 0.25)	0.05 (-0.03 to 0.13)
Sanitation	0.07 (-0.01 to 0.14)	0.09 (0.02 to 0.16)	0.05 (-0.03 to 0.12)	0.04 (-0.03 to 0.12)	0.02 (-0.06 to 0.09)
Water	0.11 (0.03 to 0.19)	0.07 (-0.01 to 0.14)	0.02 (-0.06 to 0.10)	0.07 (-0.01 to 0.15)	0.02 (-0.06 to 0.09)
Crowding Index	0.06 (-0.03 to 0.15)	-0.07 (-0.15 to 0.01)	-0.09 (-0.17 to 0.00)	-0.18 (-0.27 to -0.09)	-0.06 (-0.14 to 0.02)
Child dependency ratio	0.14 (0.05 to 0.24)	-0.22 (-0.30 to -0.13)	-0.09 (-0.18 to 0.00)	-0.11 (-0.20 to -0.01)	-0.04 (-0.13 to 0.05)
Paternal years of schooling	0.01 (-0.09 to 0.10)	0.12 (0.04 to 0.21)	0.09 (0.00 to 0.18)	0.15 (0.06 to 0.24)	0.12 (0.03 to 0.21)

RESEARCH PAPER

Short-term Outcome and Predictors of Survival Among Neonates With Moderate or Severe Hypoxic Ischemic Encephalopathy: Data From the Indian Neonatal Collaborative

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Background: Among term and late preterm infants, hypoxic ischemic encephalopathy (HIE) is an important cause of mortality, and neurologic morbidity among survivors.

Objective: The primary objective was to study the incidence of survival to discharge among late preterm and term infants with moderate or severe HIE. Secondary objectives were to explore variation in the management of HIE across participating sites and to identify the predictors of survival.

Setting: Indian Neonatal Collaborative (INNC), a network of 28 neonatal units in India.

Study design: Retrospective cohort.

Participants: Late preterm (34-36 weeks) and term (37-42 weeks) infants with moderate to severe HIE from 2018-2019.

Outcome: The primary outcome was survival to discharge (including discharged home and transfer to other hospital). A multivariate logistic regression model was constructed to identify the predictors of survival.

Results: Of 352 infants with moderate or severe HIE, 59% received therapeutic hypothermia. Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE (aOR 0.04; 95% CI 0.02-0.10), persistent pulmonary hypertension (PPHN) (aOR 0.22; 95% CI 0.08-0.61) and requirement of epinephrine during resuscitation (aOR 0.21; 95% CI 0.05-0.84) were independently associated with decreased odds of survival to discharge.

Conclusion: Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE, requirement of epinephrine during resuscitation and PPHN decreased the odds of survival.

Keywords: *Asphyxia, Hypothermia, Management, Outcome*.

Among term and late preterm infants, hypoxic ischemic encephalopathy (HIE) is an important cause of mortality, and neurologic morbidity among survivors [1]. In 2002-2003, the National Neonatal Perinatal Database (NNPD), a network of neonatal units in India comprising of 18 units across the country, reported that the incidence of HIE was 1.4% among institutional deliveries, and perinatal asphyxia was the commonest primary cause of neonatal mortality (28.8%) and stillbirth (45.1%) [2]. A recent systematic analysis of global, national, and regional causes of child mortality identified HIE as the third important cause (20%) of neonatal deaths in India [3,4]. However, data about the various factors influencing the outcome are lacking. Therapeutic hypothermia (TH) is the standard of care for HIE in developed countries, but the adoption rate and techniques may differ in low- and middle-income countries (LMICs) [5]. Since the management of the neonates with HIE has undergone major changes in the last decade and nationally representative data were lacking, we planned this study to look at short term outcomes and factors associated with decreased survival in late preterm and term infants with HIE.

Invited Commentary: Pages 9-10

METHODS

We used data from the Indian Neonatal Collaborative (INNC), a network of 28 tertiary care neonatal intensive care units

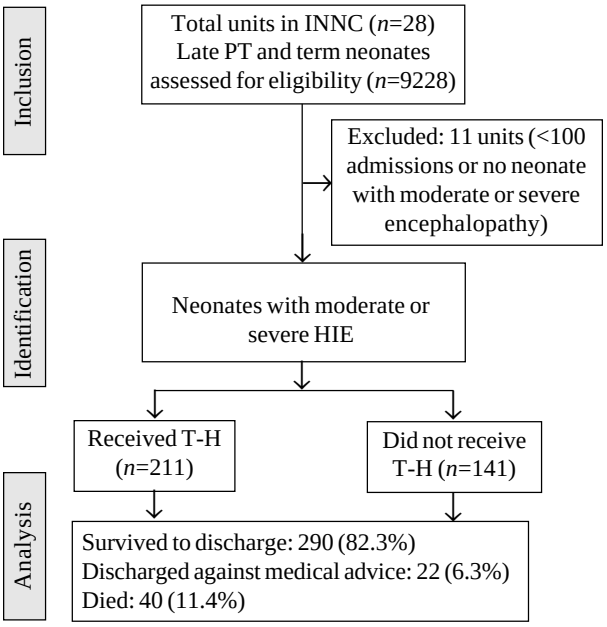
(NICUs) from both public and private sectors across India, contributing real time data anonymously to a common database. This was a retrospective cohort study including late preterm (34-36 weeks) and term (37-42 weeks) infants with moderate or severe HIE admitted between January, 2018 and December, 2019. The demographic details, clinical data including resuscitation details, Apgar score, and Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) score were recorded. Modified Sarnat and Sarnat staging was used to categorize HIE. The primary objective was to study the incidence of survival to discharge, which was defined as either discharged home or transferred to other hospital. The secondary objective was to explore variation in the management of HIE across participating sites and to identify the predictors of survival.

Statistical analysis: Proportion and frequency statistics were used for the baseline characteristics. Chi-square tests were used for the association between categorical variables and outcome. A multivariable logistic regression model for identifying the predictors of survival was created by including independent variables based on biological plausibility, and the results of univariate analysis (P<0.1). P value <0.05 was considered significant. Stata 14.0 was used for analysis.

RESULTS

Participating units differed in terms of admission characteristics, with predominantly intramural admissions at some sites, and exclusively extramural admissions at other. Of the 9228 late preterm and term infants enrolled in the database during the study period, 352 (3.8%) infants (65.3% male) developed moderate or severe encephalo-pathy (**Fig. 1**). The median gestational age was 39 weeks and mean (SD) birth weight was 2844 (467) gram; 305 (86%) had moderate encephalopathy (**Table I**). Sixty-two (17%) infants received mechanical ventilation support and the median duration of ventilation was <1 day in infants with moderate encephalopathy while this was >1 day in infants with severe encephalopathy (P<0.001). Only 12 out of 28 centres were providing TH to these infants (**Web Table I**). Around 60% (n=211) of the infants received TH as a part of management, most commonly (87%) with phase change material (PCM) (**Table I**).

The mortality was 11.4% (n=40) in the study population. A total of 290 (82.3%) infants survived to discharge, while 22



INNC: Indian neonatal collaborative; PT: preterm; HIE: hypoxic ischemic encephalopathy; TH: therapeutic hypothermia.

Fig. 1 Study flow diagram.

Table I Characteristics of Neonates With Hypoxic Ischemic Encephalopathy (N=352)

Neonatal characteristics	*Value*
Gestation wk[a]	39 (37-40)
Birth weight, g[a]	2900 (2526-3137)
Intramural births	270 (76.7)
Male sex	230 (65.3)
Multiple birth	1 (0.3)
Meconium-stained liquor	122 (34.7)
SNAPPE II	33 (18-45)
Cord blood gas[b]	
pH[a]	7.18 (7.00-7.28)
pH <7	48 (22)
Base excess[a]	-14.0 (-11 to -17)
Hypoxic ischemic encephalopathy	
Moderate	305 (86.6)
Severe	47 (13.4)
Therapeutic hypothermia	211 (59.9)
Mode of cooling[c]	
Servo-controlled	20 (9.4)
Phase change material	184 (87.2)
Ice packs	5 (2.3)
Persistent pulmonary hypertension	29 (8.2)
Seizures requiring ≥2 anticonvulsants	77 (21.9)
Duration of hospital stay, d	8 (6-12.7)
Disposition	
Discharged home	274 (77.8)
Transferred to other hospital	16 (4.5)
Discharge against medical advice	22 (6.3)
Death	40 (11.4)

Data presented as no. (%) or [a]median (IQR). SNAPPE II, score for neonatal acute physiology with perinatal extension-II; BE, base excess; [b]cord blood gas available for 220 infants; [c]Used other modes in 2 neonates.

Table II Predictors of Survival to Discharge Among Late Preterm and Term Infants With Moderate to Severe HIE

Predictor	*Adjusted OR (95% CI)*	*P value*
Female sex	1.17 (0.58-2.37)	0.64
Extramural birth	1.34 (0.55-3.24)	0.51
Meconium-stained liquor	0.82 (0.40-1.69)	0.60
Severe HIE	0.04 (0.02-0.10)	<0.001
Therapeutic hypothermia	1.22 (0.58-2.57)	0.59
PPHN	0.22 (0.08-0.61)	0.004
Seizures requiring ≥2 anticonvulsants	1.54 (0.64-3.70)	0.33
Epinephrine during resuscitation	0.21 (0.05-0.84)	0.02

HIE, Hypoxic ischemic encephalopathy; PPHN, Persistent pulmonary hypertension.

(6.3%) infants left against medical advice. Data regarding the neurological status at disposition were lacking due to variable assessment protocol at discharge; however, information about the feeding status was available. Most infants (76%) were on direct breastfeeds at discharge.

A multivariate logistic regression model was created by including variables based on the results of univariate analysis and biological plausibility. After adjusting for confounders, severe HIE (aOR 0.04; 95% CI 0.02-0.10), persistent pulmonary hypertension (PPHN) (aOR 0.22; 95% CI 0.08- 0.61), and requirement of epinephrine during resuscitation (aOR 0.21; 95% CI 0.05-0.84) were independently associated with decreased odds of survival to discharge (**Table II**). Therapeutic hypothermia (aOR 1.22; 95% CI 0.58-2.57) was not a significant predictor.

DISCUSSION

The incidence of asphyxia could not be calculated from the INNC data, as all live births are not captured in the database. However, the neonatal and postnatal charac-teristics and outcomes are available. Survival to discharge among infants with moderate or severe HIE was >80% in most centers. The case fatality rate was 11.4% among moderate or severe HIE.

Therapeutic hypothermia for perinatal asphyxia in LMICs has not been shown to be associated with a statistically significant reduction in neonatal mortality or neurodevelopmental morbidity [6]. The results of a multicentre study (HELIX trial) from LMICs was recently published [7]. In this study, therapeutic hypothermia was not a significant predictor of survival. The apparent lack of impact of TH on outcomes could be due to differences in clinical management protocols or related to factors like perinatal infection, fetal growth restriction, differences in inborn/outborns (differences in obstetric management) and nurse:patient ratio, which were not assessed in the current study. Cost of the cooling device is a significant factor for providing TH. A multicentre study has earlier shown the feasibility and safety of a phase change material-based cooling device in Indian neonatal units [8]. A recent study from India has confirmed that therapeutic hypothermia induced by phase changing material reduced brain injury detected on magnetic resonance imaging (MRI) in infants with moderate HIE [10].

After adjusting for confounders, severe HIE, PPHN, and requirement of epinephrine during resuscitation were independently associated with decreased odds of survival to discharge. The reason for the pulmonary hypertension in these infants was not assessed in the current study. Large studies looking at the predictors of survival in HIE in the TH era are lacking. However, a few small studies have reported severe HIE [11], low birthweight, preterm, intramural birth, severe asphyxia, and no formal/primary education of parents [12] as independent predictors. A study from Japan reported outborn births, low Apgar score at 5 minute, use of epinephrine, low cord blood pH and abnormal brain magnetic resonance imaging as significant factors associated with poor outcome [12]. Similarly, a recent study suggested that MRI and neurophysiologic tests (EEG or aEEG) were potential predictors of adverse outcome [13]. However, data on these investigations were not available for this cohort.

The strength of the study is the use of data collected in real time from the largest network of tertiary care NICUs in India, including public and private centers. Limitations include the lack of data regarding cause-specific neonatal mortality and inability to calculate the incidence of HIE. Another limitation was the lack of uniform protocol amongst the participating units for the management of the infants with moderate or severe HIE, which could have affected the overall efficacy of TH.

To conclude, moderate or severe encephalopathy due to perinatal asphyxia was an important reason for admission to the NICU among late preterm and term infants. Around 60% of these infants received TH, but the device used differed between centres. Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE, epinephrine during resuscitation and PPHN decreased the odds of survival to discharge, while TH was not a significant factor.

Ethics clearance: The participation in the INNC database was approved by Institutional ethics committee at individual centers. No personal identifiers were retained.

Contributors: CK, NP: conceptualized and designed the study. CK, GP, NP: designed the data collection tools; NP, TPO, ASA, BT, DC, SR, MS, NSK, AAM, SK, BS, SM, PK: coordinated and supervised the data collection at respective centers and interpreted the data. CK, NP: performed the statistical analysis; CK, GP, NP:

drafted the initial manuscript; NP, TPO, ASA, SM, PK: critically reviewed the manuscript for important intellectual content. NP and PK revised the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Note: Supplementary matter related to this article is available at *www.indianpediatrics.net*

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Web Table I Admissions and Survival to Discharge Among Individual Centers for Neonates with Hypoxic Ischemic Encephalopathy (*N*=352)

Site	*Moderate or severe encephalopathy*	*Received therapeutic hypothermia (n=211)*	*Survived to discharge (n=290)*
Site 1	6	4 (67)	3 (50)
Site 2	3	1 (33)	1 (33)
Site 3	7	6 (85)	7 (100)
Site 4	11	3 (27)	4 (36)
Site 5	16	6 (37)	15 (93)
Site 6	13	0	11 (84)
Site 7	12	6 (50)	11 (91)
Site 8	12	6 (50)	11 (91)
Site 9	34	5 (14)	26 (76)
Site 10	2	1 (50)	2 (100)
Site 11	6	0	3 (50)
Site 12	7	0	6 (85)
Site 13	196	168 (85)	164 (83)
Site 14	3	0	3 (100)
Site 15	3	2 (67)	3 (100)
Site 16	17	0	17 (100)
Site 17	4	3 (75)	3 (75)

Note: Eleven units had fewer admissions so not analysed. Data presented as no. (%).

RESEARCH PAPER

Clinico-Etiologic Profile of Macroscopic Hematuria in Children: A Single Center Experience

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Objective: To study the demographic, clinical and etiological profile of macroscopic hematuria in children presenting to a tertiary care hospital. **Methods:** This prospective observational study, conducted between January, 2018 and December, 2019, enrolled children aged 3 months to 12 years, presenting with gross hematuria. **Results:** Of the 62 children (44 males) enrolled, (mean (SD) age of 7.3 (2.6) years), glomerular hematuria was seen in 59.7%. Post-infectious glomerulonephritis was the commonest etiology of glomerular hematuria; hypercalciuria and renal calculi predominated among non-glomerular hematuria. After a median (IQR) follow up of 8 (6,14.2) months, microscopic hematuria persisted in 10 (7, glomerular hematuria) children. The median time to resolution of gross as well as microscopic hematuria tended to be longer in glomerular etiologies. **Conclusion:** Majority of children with gross hematuria had glomerular etiologies, thus requiring monitoring and follow-up.

Key words: *Glomerular hematuria, Outcome, Post-infectious glomerulonephritis.*

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Evaluation of a child with gross or macroscopic hematuria should essentially rule out serious underlying renal disease having grave prognosis. While prevalence of microscopic hematuria has been well-described [1,2], the incidence and profile of macroscopic hematuria in children is hardly reported [3]. Authors describing acute glomerulonephritis (AGN) in children [4-6] have not reported facts from the perspective of gross hematuria. Since the lack of utility of routine screening for microscopic hematuria in healthy children has been well-established in large follow-up studies [2], it is worthwhile to focus on children having visible hematuria and understand their profile. Hence, this study aimed to determine the demographic, clinical and etiological profile of gross hematuria in children presenting to a tertiary care hospital.

METHODS

This prospective, observational study, conducted between January, 2018 and December, 2019, enrolled children aged 3 months to 12 years presenting with gross hematuria. Children with hematuria following surgery of the kidney/urinary tract, post-renal biopsy, post- catheterization, or associated with perineal/genital inflammation were excluded. Ethics approval was taken from institutional ethics committee. Children with gross hematuria (confirmed by the presence of > 5 red blood cells (RBC)/high power field (hpf) on microscopic examination), were enrolled after informed consent.

Clinical features considered indicative of glomerular etiology included cola-colored/smoky urine, oliguria, edema, rash, arthritis, with or without history of pyoderma/ sore throat or recurrent synpharyngitic episodes. Children with fresh blood/clots in urine, urine sediment, pus, associated pain abdomen/loin or painful micturition, voiding symptoms, fever, or family history of renal stones, were considered likely to be having non-glomerular hematuria.

Microscopic urine examination showing >5 RBC/hpf with >20% dysmorphic RBC, along with moderate proteinuria (dipstick ≥2+) with or without casts was considered to be glomerular hematuria [7]. Final categorization in to glomerular and non-glomerular hematuria was made based on findings in history, clinical examination and urinalysis. Further work-up to elicit the etiology and management was as per departmental protocol, based on standard guidelines [7].

Statistical analyses: We used SPSS 21.0 software for analyses. Continuous variables were compared by independent *t* test/Mann-Whitney *U* test, and categorical variables were compared by chi-square test. Time to event was compared by Cox-regression survival analysis. $P<0.05$ was considered significant.

RESULTS

A total of 62 children (48 males) with a mean (SD) age of 7.3 (2.6) years were evaluated for gross hematuria. Concomitant or past upper respiratory tract infection and pyoderma were seen in two patients each, while voiding symptoms were found in three children. Edema, hypertension and oliguria were seen in 25 (40.3%), 22 (35.5%) and 19 (30.6%) children, respectively. Twenty-three (39.7%) children had deranged renal functions, two of whom had chronic kidney disease (CKD), the rest having acute kidney injury (AKI).

Based on urinalysis, clinical, biochemical and imaging parameters, 37 (59.7%) children were diagnosed to have glomerular hematuria, 21 (33.8%) had non-glomerular hematuria and four had hematuria of uncertain origin (**Table I**).

Infection-related glomerulonephritis (IRGN), was the commonest cause of glomerular hematuria, seen in 17 (45.9%) children, with 10 of these children (58.8%) having raised anti-streptolysin O (ASO) antibody titres. Ten children with glomerular hematuria presented as rapidly progressive glomerulonephritis (RPGN). The mean (SD) C3 in children with glomerular hematuria was 88 (56.5) mg/dL. Sixteen children underwent renal biopsy (9 RPGN, 3 Henoch-Schonlein purpura (HSP) nephritis, 7 glomerular hematuria with normal serological tests). Biopsies from the children with RPGN showed diffuse proliferative glomer-ulonephritis in 3, C3 glomerulonephritis in 4, anti-glomerular-basement membrane disease and mesangio-proliferative GN in one child each. Two of them had no crescents, one showed 100% crescents, while the rest showed 13-77% crescents. Three children biopsied for HSP nephritis showed mesangioproliferative glomerulo-nephritis with IgA and C3 deposits, all having Oxford score of M0E0S0T0 with C1 in 2 children. Both the children having IgA nephropathy had scores M0E0S0T0C0.

Table I Diagnosis in Children With Gross Hematuria (*N*=58)

Diagnosis	*No. (%)*
Glomerular origin (n=37)	
Post-infectious glomerulonephritis	17 (45.9)
Henoch Schonlein purpura	4 (10.8)
Hemolytic uremic syndrome	2 (5.4)
Miscellaneous[a]	2 (5.4)
C3 glomerulonephritis	4 (10.8)
Mesangioproliferative glomerulonephritis	3 (8.1)
IgA nephropathy	2 (5.4)
Unknown	3 (8.1)
Non-glomerular origin (n=21)	
Hypercalciuria	7 (33.3)
Renal calculus	5 (23.8)
Urinary tract infection	3 (14.3)
Chronic kidney disease	2 (9.5)
Unknown	4 (19.0)

[a]*One child each had idiopathic nephrotic syndrome and anti-GBM disease.*

Hypertension and AKI were each seen in 21 (56.7%) children with glomerular hematuria. Eight out of the 21 children (38%) with AKI (6 RPGN and 2 Hemolytic Uremic Syndrome) required dialysis, 5 of whom recovered, one died, one got transferred to another hospital, and one progressed to CKD requiring regular hemodialysis. Thus renal functions recovered in 18 (85.7%) of those with AKI.

In children with non-glomerular hematuria, hyper-calciuria (7; 33%) and renal calculi (5; 23.8%) constituted the most common causes. The mean (SD) 24-hour calcium excretion of six of the children with hypercalciuria was 6.26 (1.54) mg/kg/day and one child had spot urine calcium/ creatinine ratio of 0.2 with calcium oxalate crystals in urinalysis. On ultrasonography, five children had renal calculi, one had bilateral hydro-ureteronephrosis and one had bilateral small kidneys, the latter two children having deranged renal functions, as a part of CKD. Three children died; one child had RPGN (C3GN) and the other two had end stage renal disease at presentation.

Comparison of parameters showed age and gender of children to be comparable between glomerular and non-glomerular groups, while hypertension and deranged renal functions were significantly more in glomerular hematuria. Though the median (IQR) time to resolution of gross hematuria [9 (3,15) months and 3 (2,10) months in glomerular versus non-glomerular hematuria, respectively)] as well as of microscopic hematuria [4 (1,12) months and 1 (0.2,2) in glomerular versus non-glomerular hematuria, respectively] tended to be longer in glomerular etiologies, survival analysis failed to show statistical significance.

Barring four children who had a follow-up of <1 month, the rest had a median (IQR) follow-up of 8 (6,14.2) months. At the last follow up, microscopic hematuria was persisting in 10 children, 7 of whom had glomerular etiologies, 83.8% being free of any hematuria; 9 children were having hypertension, all with glomerular hematuria.

DISCUSSION

We prospectively enrolled and studied 62 children with macroscopic hematuria over two years and found glomerular causes to be more common and persistence of hematuria in one-sixth of the patients.

More than half of the children with gross hematuria were due to glomerular origin, unlike the profile observed by others, where the non-glomerular causes predominated [8,9]. The latter studies belong to a geographical and ethnic background different from ours. It is possible that in a

WHAT THIS STUDY ADDS?

- Glomerular etiologies predominated in children with macroscopic hematuria seeking medical care, with post-infectious glomerulonephritis being more common than IgA nephropathy.

developing country, there may be a delay in presentation or a referral bias to a speciality centre. Further, the present study showed that IRGN was the leading diagnosis in children with gross hematuria of glomerular origin, a finding which contradicts existing reports where IgA nephropathy has been the commonest glomerular etiology of macroscopic hematuria [8-11]. Even considering that some cases of IgA nephropathy may have been missed among the cases with unproven etiology in our study; still, the figure of IRGN clearly surpasses the number of IgA nephropathy. It should be acknowledged that though the incidence of IRGN has abated in industrialized countries, it is still one of the most common renal disorders in children in developing countries [12,13] and therefore, accounts for the major proportion of macroscopic hematuria.

Nearly one-third of the children in this study presented as RPGN, higher than that reported in previous pediatric studies [6-9]. While long-term follow-up studies, describing crescentic GN have shown a plethora of etiologies of RPGN [4,14], our study of over two years, found diffuse proliferative and C3 dominant GN as the commonest findings in RPGN. Though nearly 35% of children with AKI in our study required dialysis support, the recovery rate (over 85%) was higher, compared to existing literature [15].

While 16% children were not free of RBC in their urine, at the last follow-up, nearly a quarter of the children with gross hematuria had persistent hypertension. Studies dealing only with glomerulonephritis report 0-35% children having persistent urinary abnormalities and hypertension at follow-up [4,11,13].

Children presenting with gross hematuria need thorough evaluation and risk stratification, because glomerular causes could account for a major proportion, especially in developing countries.

Ethics clearance: Institutional Ethics Committee, MAMC; No. F.1/IEC/MAMC/58/03/2017/No. 33, dated August 23, 2017.
Contributors: KM conceived and planned the study with critical inputs from MK.AP and KDZ helped in collection of data under supervision of KM. LS was involved in supervising laboratory related investigations. KM analyzed the data and wrote the primary draft. All authors approved the final manuscript.
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RESEARCH PAPER

Clinical Profile and Renal Ultrasound Characteristics of Children With Nutcracker Syndrome in Turkey

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Objective: We aimed to evaluate the clinical profile and radiological findings of children with nutcracker syndrome (NCS) and to assess the association between the parameters. **Methods:** A retrospective analysis of the clinical, laboratory and radiological parameters of children diagnosed with NCS between January, 2011 and October, 2017 was done. **Results**: Of a total of 29 patients [19 girls, 65.5%] with NCS, having a mean (SD) age of 10.8 years, 72.4% had BMI <-2SD. Approximately half of the patients (51.7%) were asymptomatic. Left flank pain was commonest (9/29; 31%) symptom, followed by macroscopic hematuria (4/29; 13.8%). Isolated proteinuria was seen in 9 children. There was no significant difference between the symptomatic and asymptomatic patients in terms of Doppler ultrasonography findings. All patients were followed up conservatively, 5 received enalapril therapy for moderate proteinuria. **Conclusion:** NCS should be considered in children, especially with low BMI, presenting with orthostatic proteinuria and hematuria, with or without left flank pain after ruling out the common causes.

Keywords: *Flank pain, Hematuria, Left renal vein, Proteinuria*, *Doppler ultrasound.*

Nutcracker phenomenon refers to compression of the left renal vein (LRV) most commonly between aorta and superior mesenteric artery [1], resulting in dilatation of LRV and increased venous pressure. Nutcracker syndrome (NCS) or left renal vein entrapment syndrome may be anterior NCS resulting from compression of the renal vein between the aorta and mesenteric artery, and posterior NCS resulting from compression of the LRV between the aorta and corpus vertebrae [1,2]. Patients with NCS often remain asymptomatic and are usually diagnosed incidentally during radiological examination. However, in some cases, it may manifest as macroscopic hematuria, moderate to severe proteinuria, severe flank pain and varicocele [3]. Autonomic disturbances and gonadal vein syndrome (dysmenorrhea, dyspareunia and varicocele) have rarely been reported [4].

The diagnosis of NCS, may be confirmed by renal vein Doppler ultrasonography (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA) or renal venography (RV). Though renal vein DUS is an easy and non-invasive method with a sensitivity of 70-90% and a specificity of 89-100% [5,6], there is no clear consensus on the measurement values, thereby making the assessment partially subjective.

This study was done to describe the clinical, laboratory and radiological findings of children diagnosed with NCS and to assess the relationship between the clinical features and the radiological measurements.

METHODS

This retrospective study included children from 0-18 years of age, presenting to our child nephrology outpatient clinic between January, 2011 and October, 2017, who were diagnosed with NCS. Clinical symptoms and investigation details were retrieved from records. Cases had been diagnosed with NCS based on their symptoms, clinical findings and left renal vein DUS findings. The study was approved by the ethical board of our hospital.

Findings of urinalysis were interpreted as per standard recommendations [7]. Radionuclide scintigraphy was done to rule out scars in patients with proteinuria and recurrent urinary tract infection.

In children suspected to have NCS, the diagnosis had been confirmed using pre-defined criteria of DUS [3,8] viz., hilar/aortomesenteric diameter ratio of left renal vein ≥4; angle between the superior mesenteric artery and the aorta <45º; collateral formation between renal hilum and retroperitoneum; and, peak velocity ratios between aorto-mesenteric and renal hilum portions ≥5. DUS was done using ultrasonography device (Toshiba Aplio 500, Toshiba Medical Systems) with high frequency linear and convex probe. In a small number of cases in which adequate data

could not be generated by DUS, CTA or MRA methods were used.

Statistical analysis: IBM SPSS Statistics 24 program (IBM Corp.) was used for statistical analysis. The relationships between continuous variables were examined by correla-tion analysis. Comparison of independent groups was done using Mann Whitney U test. The significance level was taken as 95% CI and a *P* value <0.05.

RESULTS

A total of 29 patients [19 girls, 65.5%] with NCS, having a mean (SD) age of 10.8 (3.2) years were included. The mean (SD) time of follow-up was 39 months. The mean BMI was 15.8 kg/m^2 (**Table I**), with 72.4% having a BMI <-2SD; nearly half (51.7%) were asymptomatic. While the most common symptom was left flank pain in 9 (31%) children, isolated proteinuria was the most frequent abnormality in urine in 9 (31%) children (**Table I**). There were no patients with extrarenal symptoms. The mean (SD) 24-hour urine protein excretion was 9.1 mg/m^2/h. None had nephrotic-range proteinuria (>40 mg/m^2/hr). Majority 27/29 (93.1%) had anterior NCS

The ratio of left renal hilum diameter to aortomesenteric diameter varied between 1.4-7.7 with a mean value of 5.0. In addition, the mean value of the velocity ratio of aortomesenteric and hilar portions of LRV was 4.0. The mean (SD) aortomesenteric angle (AMA) value was 29.8 (8.5)^o. The hilum/aortomesenteric region diameter ratio [5.2 (2.0-7.5) vs 4.5 (1.4-7.7); *P*=0.12], aortomesenteric region /hilum velocity ratio [4.5 (1.0-10.0) vs 3.4 (2.0-6.0); *P*= 0.71], and the aortomesenteric angle [30.5 (18.0-49.0) vs 30.0 (9.0-42.0) degree; *P*=0.56] were not significantly different between symptomatic and asymptomatic children, respectively with nutcracker syndrome.

Table I Clinical and Laboratory Characteristics of Children With Nutcracker Syndrome

Characteristics	*Value*
Girls, *n* (%)	19 (65.5)
Age (y); mean (SD)	10.8 (3.2)
BMI *z*-score, median (IQR)	-1.0 (-3.2,-1.4)
Symptomatic,[a] *n (%)*	14 (48.3)
Left flank pain	9 (31)
Macroscopic hematuria	4 (13.8)
Urinary findings,[b] *n* (%)	
Isolated proteinuria	9 (31)
Isolated microscopic hematuria	3 (10.3)
Isolated macroscopic hematuria	4 (13.8)
Microscopic hematuria and proteinuria	5 (17.3)
Tenderness and microscopic hematuria	5 (17.3)
Tenderness and proteinuria	2 (6.9)

BMI: Body mass index. [a]*One child had pelvic pain.* [b]*One child had pelvic pain, microscopic hematuria and proteinuria.*

All patients were followed conservatively and none of the patients required surgical treatment. Five patients received enalapril for proteinuria. Enalapril was also used in two patients having type 1 diabetes besides NCS.

DISCUSSION

Nutcracker syndrome has been described as one of the less known causes of hematuria and proteinuria in individuals of all ages from late childhood to middle-aged adults. Though rare, it is possible that many patients investigated for hematuria or proteinuria, could have had underlying NCS, which was missed due to lack of awareness.

As reported in literature, our study also found that NCS is found commonly in and around the pubertal age group [3,5], with a higher frequency among females [9]. It is thought that venous congestion in the pelvic region due to the vasodilator effect of progesterone, increases pain, and women are more symptomatic and thus more easily diagnosed [8]. However, the symptom frequency was similar in both genders in our study. With rapid increase in length and hence low BMI during puberty, the angle between the superior mesenteric artery (SMA) and the aorta is narrowed, and this may cause a compression of LRV and NCS [8]. Our study showed a high proportion (72.4%) of children having low BMI.

In our study, almost similar proportions of children were present in the symptomatic and asymptomatic groups. Consistent with previous reports [10], the abdominal or left flank pain was not severe and did not need treatment. Our study re-confirms that proteinuria in these children is usually mild. There was no evidence of renal impairment in any of our patients over the follow-up period. NCS usually does not lead to chronic kidney disease because it affects one kidney and entrapment symptoms improve with age.

As per recommendations, DUS was performed as the first imaging modality in our study. It is known to have a 69-90% sensitivity and 89-100% specificity for the diagnosis of NCS [5,11-13]. To the best of our knowledge, there are as yet no accepted radiological criteria for diagnosing NCS in children. Measurements during childhood vary due to age, LRV sampling area is smaller and the AMA value is wider compared to adults [5,6,14]. Due to the high sensitivity and specificity of AMA measurements [14], there is no requirement to meet all diagnostic criteria in pediatric patients for the diagnosis of NCS. In our study, though all patients did not meet all the diagnostic criteria completely, but the majority of them were diagnosed with NCS using DUS. In contrast to some previous studies, we found that the hilum/

WHAT THIS STUDY ADDS?

- No difference was found in Doppler ultrasound measurement parameters between symptomatic and asymptomatic children with nutcracker syndrome.

aortomesenteric diameter and aortomesenteric/hilum velocity ratio was not higher in the symptomatic group. [9,12].

With increasing age and weight of the children, up to 75% decrease in clinical symptoms is reported, and the need for surgery is extremely low [15]. None of the patients with NCS in our study required surgical treatment.

The main limitations of our study are that it is single-center and retrospective. Since the study was retrospective, the association between exercise and the patients' symptoms other than proteinuria could not be assessed.

To conclude, NCS should be considered in children, especially with low BMI, presenting with orthostatic proteinuria and hematuria, with or without left flank pain. After common causes of hematuria and proteinuria are reasonably ruled out by clinical history, examination and urinalysis, it is prudent to radiologically evaluate for NCS before subjecting the patient to invasive procedures including renal biopsy. NCS is a relatively benign cause of proteinuria and hematuria, which can be managed conservatively with close follow up, depending on the severity of symptoms.

Ethics clearance: Institutional Ethics Committee of Health Science University, Kecioren Training and Research Hospital; No.1540 dated 10/2017.
Contributors: EGB: concept and designed the study and analyzed data; ACY: concept and designed the study and drafted the manuscript; OG: collected the data and helped in data analysis; ACT, BB: conducted behavioral assessments. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Clinical Profile and Outcome of Emergencies in Pediatric Chronic Kidney Disease

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Objective: To describe the clinical profile and outcome of emergencies in children with chronic kidney disease (CKD). **Methods**: This retrospective analysis studied children with CKD presenting with acute emergencies. The clinical profile, renal and patient outcomes were compared between incidentally diagnosed - iCKD, previously diagnosed not on dialysis - pCKD and those on maintenance dialysis - dCKD groups. **Results**: 82 children (67 boys, median age – 8 years) with 99 visits were included. Uremic encephalopathy was the most common emergency in iCKD (64.7%) and pCKD (38.4 %), and access-related infections (32.1%) in dCKD group. Children with iCKD had higher Pediatric Risk of Mortality score (P<0.001), emergent initiation of dialysis (P=0.03) and discontinuation of treatment (P<0.001) when compared to the pCKD group. **Conclusion**: Uremic encephalopathy and access-related infections were the most common emergencies in children with CKD. Incidentally diagnosed CKD had a worse clinical profile and outcome.

Keywords: *Dialysis, Emergency department, Uremic encephalopathy*.

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Chronic kidney disease (CKD) related life-threatening emergencies like hyperkalemia, severe hypertension, heart failure, have been shown to be preventable by timely care and regular follow up [1]. Unfortunately, for many patients with CKD in developing counties, the first contact with the nephrologist is in the emergency department (ED) when they present with life-threatening complications [2]. These late presentations often require intensive care, and urgent, unplanned initiation of dialysis, leading to poor outcomes with high risk of treatment failure and mortality [2]. In children, delayed diagnosis is not uncommon, especially in resource-poor settings [3]. In children on dialysis, poor compliance to therapy, inadequate therapy, and socio-economic factors may result in unplanned visits to ED and life-threatening complications.

There is limited exploration of ED visits in pediatric CKD from developing countries in literature. This study was conducted to know the clinical profile and outcomes of acute emergencies in children with CKD.

METHODS

The study is an analysis of hospital records of children with CKD presenting with acute emergencies to the ED of a tertiary care hospital between January, 2016 and December, 2018. Clearance of the protocol with waiver of informed consent was obtained from institutional ethics committee. We extracted and included data of children (1 month to 18 years) with CKD stages III-V/VD, presenting with CKD-related emergencies. Emergencies unrelated to CKD and emergencies in children with renal transplan-tation were excluded. Repeated ED visits requiring hospitalization in the same child were considered as separate events. Based on the severity of illness, patients were admitted in pediatric intensive care unit (PICU) or in High-dependency unit (HDU).

Children diagnosed as CKD for the first time during the ED visit, and children with known diagnosis of CKD stage III-V but not on dialysis were categorized as incident-CKD (iCKD) and prevalent-CKD (pCKD), respectively. Those on maintenance continuous ambulatory peritoneal dia-lysis (CAPD) or hemodialysis (HD) were categorized as dialysis-CKD (dCKD).

Estimated glomerular filtration rate (eGFR) was calculated using modified Schwartz formula [4]. Staging of CKD was based on the highest eGFR documented in the preceding three months for pCKD, according to KDIGO guidelines [5]. Definitions of acute CKD-related emergencies were as per standard guidelines [6]. All emergencies were managed according to standard protocols. Pediatric risk of mortality score (PRISM IV) was calculated

at the time of admission to PICU [7]. PRISM IV score <10 and >10 were categorized as mild risk and moderate-to-high risk for mortality, respectively [8]. Renal outcome was defined as dialysis-dependency at discharge among those not on dialysis, while mortality and duration of hospital stay were considered as patient outcomes.

Statistical analysis: All analyses were performed using R statistical software version 3.6.1. Continuous variables were compared using Mann-Whitney *U* test and Kruskal-Wallis test and categorical variables using chi-square test. Odds ratio (95%CI) for outcome measures was calculated using logistic regression.

RESULTS

There were 118 visits to the ED, of which 19 in children with renal transplantation were excluded. Eighty-two children (67% boys) with 99 visits were included. Among these, 17 (20.7%), 26 (31.7%) and 39 (47.5%) children belonged to iCKD, pCKD and dCKD groups, respectively. Fourteen children in dCKD group required more than one hospital admission. Demographic profile of the cohort is described in **Table I**. In dCKD group, 36 (92.3%) were on CAPD and 3 (7.6%) on maintenance-HD through arteriovenous fistula. The median (IQR) eGFR in iCKD and pCKD groups was 11mL/min/1.73m^2 (10,12.1) and 23 mL/min/1.73m^2 (19,35) (P<0.001). About one-third of children (35.3%) required admission to PICU, with a higher proportion in iCKD group (P=0.07).

Children with iCKD had higher number of complications compared to pCKD and dCKD groups (P<0.001) (**Table II**). The most common emergency was uremic encephalopathy in iCKD (64.7%) and pCKD (42.3%), and infections (32.1%) in dCKD group, with peritonitis being the most common infection (25%). Among the 14 children in dCKD group having more than one admission, preventable causes (hypertensive emergencies, hyperkalemia, cardiac failure) accounted for 54.5% admissions. Patients in iCKD group had a higher median PRISM IV scores (P<0.001) and a higher proportion of children with PRISM score >10 (P=0.001) compared to other groups. Serum calcium, bicarbonate and hemoglobin concentrations were significantly lower in the iCKD group compared to other groups.

Hyperkalemia (median potassium 6.4 (6.3, 6.8) meq/L) was seen in 8 children. Six of these had ECG changes of hyperkalemia, none had ventricular tachycardia and five required dialysis. Children with hypertensive encephalopathy (n=19) were managed with sodium nitroprusside (n=9) and intravenous labetalol (n=10). The need for emergent initiation of dialysis was significantly higher in the iCKD (76.47%) compared to pCKD (42.3%) group (P=0.03). Hemodialysis was the most common modality for emergency dialysis (83.3%).

Table I Profile of Children With Chronic Kidney Diseases Presenting With Acute Emergencies

Characteristics	*iCKD (n= 17)*	*pCKD (n= 26)*	*dCKD (n=39)*
Age (y)[a]	5.0 (0.9, 9.0)	9.0 (6.0, 13.8)	9.0 (5.0, 15.0)
Weight (*z*-score)[b]	-2.4 (-3.6, -1.7)	-3.2 (-4.2, -2.6)	-3.5 (-4.5, -2.4)
Height/length (*z*-score)	-3.5 (-4.7, -3.3)	-3.6 (-3.9, -3.3)	-3.6 (-4.3, -3.1)
CKD stage[a]			
III- IV[c]	3 (17.6)	21 (80.7)	-
V[c]	14 (82.3)	5 (19.23)	-
Vd	-	-	39 (100)
eGFR (mL/min/1.73m^2)[c]	11 (10,12.1)	23 (19,35)	-
Etiology of CKD[a]			
Non-glomerular	12 (70.5)	20 (76.9)	32 (82.0)
Glomerular	5 (29.4)	6 (23.0)	7 (17.9)

Values in median (*IQR*) or [a]no. (%). *CKD-chronic kidney disease; iCKD-incident CKD; pCKD-prevalent CKD; dCKD-dialysis CKD; eGFR-estimated glomerular filtration rate.* [b]*P=0.05,* [c]*P<0.001. – indicates not applicable.*

In pCKD group, on comparing the children requiring maintenance dialysis with those continued on conservative management at time of discharge, median (IQR) eGFR prior to admission was comparable (23 (19, 37) vs 22 (19, 31) mL/1.73m^2/min; P=0.815), but lower hemoglobin (7.4 (6.7,8.3) vs (8.8 (8.3, 10.3); P=0.04) and higher number of complications (2 (2,4) vs 1 (1,2); P=0.003) during admission were noted.

Treatment discontinuation was significantly higher in iCKD group (P<0.001) and more prevalent among patients of lower socioeconomic status (11.6%, P=0.25). After adjusting for severity of illness at admission, children in iCKD group were significantly more likely to have emergent initiation of dialysis (OR (95%CI) 4.43 (1.13-17.34); P=0.03) and treatment discontinuation (OR (95%CI) 21.81 (3.90-121.84); P <0.001) compared to pCKD group.

DISCUSSION

This retrospective analysis of emergencies in children with CKD found that about 21% of the cohort was newly diagnosed with CKD while presenting with an acute life-threatening emergency. Uremic encephalopathy was the most common etiology in iCKD and pCKD group. Repeat hospitalizations were more common in dCKD group.

Prevalence of newly diagnosed CKD (21%) in our study is comparable to previous data from India (25%) [3,9]. We

Table II Clinical Profile and Outcome of Children With Chronic Kidney Diseases Presenting to the Emergency Department

Characteristics	*iCKD(n=17 visits)*	*pCKD(n=26 visits)*	*dCKD(n=56 visits)*
Emergencies per admission[a,b]	2 (2,4)	2 (1,3)	1 (1,2)
Biochemical profile[a]			
Hemoglobin (g/dL)[c]	6.1 (5.4, 6.5)	8.4 (7.3, 9.1)	7.6 (6.8, 9.6)
Plasma bicarbonate (mEq/L)[b]	11.3 (8.1,15.3)	14.7 (13,21.4)	20.5 (17.1,21.6)
Serum potassium (mEq/L)	5.4 (4.4, 6.3)	4.7 (3.9,5.7)	4.7 (4.1,5.4)
Serum calcium (mg/dL)[b]	7.8 (7.1, 8.1)	8.8 (7.4, 9.2)	9.2 (8.4, 9.6)
Etiological profile			
Hypertensive emergencies	6 (35.3)	4 (15.4)	15 (26.8)
Severe hyperkalemia[d]	2 (11.8)	2 (7.7)	2 (3.5)
Symptomatic hypocalcemia	4 (23.6)	4 (15.4)	4 (7.1)
Severe anemia	4 (23.6)	6 (23.1)	11(19.6)
Acute cardiac dysfunction	6 (35.3)	2 (7.7)	9 (16.1)
Uremic encephalopathy[c]	11(64.7)	11(42.3)	5 (8.9)
Severity of illness			
Admission to PICU	10 (58.8)	9 (34.6)	16 (28.5)
PRISM IV score [a,b]	11.5 (10.2,13.7)	8 (7.0,9.0)	10.5 (9.2,12.5)
Mechanical ventilation	3 (30)	3 (33.3)	10 (62.5)5 (31.2)
Inotropes	5 (50)	3 (33.3)	
Emergent initiation of RRT[c]	13 (76.4)	11 (42.3)	-
Indications for RRT[e]			-
Uremia	8 (61.5)	5 (50)	
Volume overload	6 (46.1)	6 (60)	
Hyperkalemia[d]	2 (15.4)	1 (10)	
Hemodialysis	11 (84.6)	9 (81.8)	
Acute peritoneal dialysis	2 (15.4)	2 (18.2)	-
Time interval for initiation of dialysis (d)[a]	1 (1,1)	1 (1,1.5)	-
Outcome			
Discharged[b]	11 (64.7)	24 (92.3)	55 (98.2)
Dialysis dependency at discharge	12 (70.7)	11 (42.3)	-
Duration of hospital stay (d)[a]	13.0 (9.0, 23.0)	5.0 (4.0, 10.2)	8.5 (5.0, 16.0)
Discontinuation of treatment[b]	6 (35.3)	2 (7.6)	0 (1 died)

Data presented as no. (%) or [a]median (IQR). - indicated not applicable. CKD-chronic kidney disease; iCKD-incident CKD; pCKD-prevalent CKD; dCKD-dialysis CKD; PICU-pediatric intensive care unit; PRISM IV-pediatric Risk of Mortality IV; RRT-renal replacement therapy; HD-hemodialysis; PD-peritoneal dialysis. [c]P<0.05. [^]Compared only between two groups; [d]With ECG changes; [e]RRT in one child of iCKD group for refractory acidosis.

found that iCKD presented with more severe illness and need for emergent dialysis. Studies in adults have shown that late referral is associated with more severe complications at time of presentation [10-12]. A similar study in adults from Africa found that uremia and sepsis accounted for about 80% admissions [11]. In contrast, a study from the developed world showed that cardiopulmonary complications were the most common emer-gencies in adults with advanced CKD [13]. These differences probably reflect delayed diagnosis and inadequate dialysis in resource-poor settings.

Emergent initiation of dialysis and its indications were similar to the reported proportion seen in adults [11]. In our study, majority of children were initiated on RRT early in contrast to delay in initiation of dialysis noted in other studies [11]. Majority of our CKD patients (42.3%) remained dialysis-dependent at discharge and required unplanned initiation of maintenance dialysis, comparable with previous studies in adults reporting 30% [14]. Cardiovascular disease, low hemoglobin levels and low serum albumin were associated with sudden unexpected fall in eGFR and precipitous initiation of dialysis [14]. Among those who discontinued treatment, all patients were dialysis-dependent and a majority belonged to low socioeconomic status and iCKD group. Low socio-economic status and lack of insurance support were identified as important risk factors for discontinuation of treatment in resource-poor settings [10,11]. A systematic review showed that disease awareness, access to healthcare, and geographical remoteness were important reasons for delayed diagnosis [15].

WHAT THIS STUDY ADDS?

- Children incidentally diagnosed to have chronic kidney disease in the emergency department had more severe complications and were at high risk for emergent initiation of dialysis.

Though our study has the inherent limitations of a retrospective study, it highlights the prevalence of preventable emergencies, and need for multiple admissions in children with CKD, which could potentially be avoided by better ambulatory care. A significant proportion of children in late stages of CKD required unplanned initiation of maintenance dialysis which can be prevented by increased clinical scrutiny and informed decision making for early planned initiation of dialysis in this high-risk group.

Ethics clearance: Institutional Ethics Committee, St John's Medical College, Bengaluru; No. 350/2018, dated Nov. 29, 2018.
Contributions: MA: data collection, analysis of the data and writing of the manuscript; NK: study design, supervision of data collection and analysis and writing of the manuscript; LAV: study design, analysis of data and writing of the manuscript; AV: writing of the manuscript and critical review of the manuscript. All authors approved the final draft of the manuscript.
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RESEARCH PAPER

Orbital Cellulitis in a Pediatric Population - Experience From a Tertiary Center

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Objective: To describe our experience in treating children afflicted with orbital cellulitis. **Methods**: A retrospective analysis of hospital records of children afflicted with orbital cellulitis was conducted between 2005-2018. Clinical, laboratory and radiology characteristics as well as management, microbiological data, and outcomes were collected. **Results**: Of the 94 patients, painful restriction of ocular motility was observed in 37.2% and proptosis in 34%, whereas, only 18% of the children presented with both classical signs. Children aged older than 9 years presented with markedly elevated inflammatory markers i.e., leukocytosis and C-reactive protein (CRP). Only a minority (12, 12.4%) required functional endoscopic sinus surgery. **Conclusion**: Our data support the general approach that orbital cellulitis should be initially managed conservatively with close monitoring; since, only a minority of patients require surgical intervention.

Keywords: *Management, Subperiosteal abscess, Streptococcus, Surgery*.

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Orbital cellulitis, an inflammation of the post-septal tissue of the eye, is more prevalent in the pediatric population, and is considered a serious medical condition with potential life-threatening complications, ocular as well as intracranial. In most cases, the infection results mostly from sinus disease. Worldwide, pediatric centers differ in their diagnostic and clinical practice, consequently, practice guidelines for the management in children are lacking [1]. Although, several studies have endeavored to outline criteria for surgical management, the majority have only been small case series [2,3]. Therefore, we share our tertiary center's experience in treating a relatively large cohort of children with orbital cellulitis in order to discover the specific population who could benefit from one approach over the other.

METHODS

This review of hospital records was conducted at the Schneider Children's Medical Center of Israel, the largest pediatric hospital in Israel. Medical records of all previously healthy hospitalized children between January 1, 2015 and 31 December, 2018 were included. Orbital cellulitis was defined as any clinical sign of orbital involvement, proptosis, painful extraocular motion, ophthalmoplegia, visual impairment or chemosis, and/or post-septal inflammation observed on computed tomo-graphy (CT) [4]. Children were excluded due to any anatomic defects of the orbit or known chronic medical history. For each enrolled case, demographic, clinical, laboratory, microbiology and imaging data were obtained. Broad coverage with beta-lactam antibiotics (mainly, second and third generation cephalosporin) and clinda-mycin was initiated. Imaging studies were performed in cases of severe manifestation or suspected complications.

The study was approved by the institutional Helsinki committee and our institutional review board.

Statistical analysis: All analyses were performed using the IBM-SPSS program (IBM Corp.) Version 22.0. Chi-square test and one way ANOVA were used for the analysis. A *P* value of <0.05 was considered statistically significant in the regression analysis.

RESULTS

During the study period, we treated 94 cases (62 males) of orbital cellulitis, all unilateral . Mean age at presentation was 5.6 years (range: 9 months-16 years). At presentation, fever >38 ºC (72.3%) and nasal congestion (20.2%) were most commonly recorded (**Table I**). Interestingly, fever was significantly more common in younger than 9 year children compared to older children (*P*<0.05). Clinically, whereas, all children presented with periorbital edema, a painful restriction of ocular motility was observed in 37.2% and proptosis in 34%. Only 17 (18%) children presented with both classical signs (proptosis and pain in ocular motility). The

average white blood cell count (WBC) was 14.7×10^9/L (range: 4.4-35×10^9/L) and C-reactive protein 9.2 mg/dL (range 0.06-35 mg/dL). The levels of acute phase reactants were significantly higher in the younger children (**Table I**). In 57 (60.6%) of the cases, sinusitis was observed either by an ENT examination or imaging. Of the 94 cases, 67 (68%) had undergone a CT (35 at admission and 34 during hospitalization); two children underwent a second CT during hospitalization. Of these, 30 (44.7%) were diagnosed with a subperiosteal abscess.

Seven children, out of the 12 who had undergone functional endoscopic sinus surgery (FESS), demons-trated positive cultures with Group A streptococcus. An analysis of these patients showed no correlation between any of the clinical, laboratory or imaging findings, inclu-ding the presence of a subperiosteal abscess and surgical intervention. To date, all of the children have fully recovered.

DISCUSSION

Our study examined the clinical presentation and outcomes of a relatively large cohort of pediatric orbital cellulitis cases presented to a large affiliated center. In accordance with previous studies [5-7], our data supports the finding that sinusitis is a major preceding cause of orbital cellulitis in children. Of interest, in our study, pansinusitis was the leading diagnosis comparable to other studies [7], and the classic presenting symptoms of orbital cellulitis were seen in only 18% children.

Table I Demographic and Clinical Characteristics of Pediatric Patients With Orbital Cellulitis (*N*=94)

Characteristic	*All patients*	*Age <9 y n= 70*	*Age ≥9 y n=24*
Male	62 (65.9)	46 (65.7)	16 (66.7)
Fever >38°C	68 (72.3)	59 (84.3)	9 (37.5)
Previous antibiotic treatment	19 (20.2)	16 (22.8)	3(12.5)
Length of hospital stay (d)[c]	8.63 (3.1)	8.61 (3.0)	8.7(3.6)
Symptoms			
Nasal congestion	19 (20.2)	11 (15.7)	8(33.3)
Headache	16 (17)	10 (14.3)	6 (25)
Examination findings			
Redness/swelling of eyelid	94 (100)	70 (100)	24 (100)
Limitation/pain in eye movement	35 (37.2)	24(34.2)	11 (45.8)
Proptosis	32 (34)	25 (35.7)	7 (29.1)
Laboratory markers[b]			
Leukocytosis >15×10^9/L[a]	38 (40)	32 (45.7)	6 (25)
CRP >10 mg/dL[a]	33 (35.1)	28 (40)	5 (20.8)
Imaging findings	(*n*=67)	(*n*=47)	(*n*=20)
Cellulitis and/or sinusitis	37 (55.2)	25 (53)	12 (60)
Subperiosteal abscess	30 (44.7)	21(44.7)	9 (45)

Values in no. (%) or [c]mean (SD). [a]P<0.05 for comparison between the two age groups. [b]before/at presentation.

Severe ocular presentation remain a classic indicator for surgery [6], nevertheless, previous studies have reported other risk factors for a more severe disease. Rudloe, et al. [8] found that proptosis, pain with external ocular movement, and ophthalmoplegia were associated with a more serious disease and presence of an abscess [8]. Yet, 50.5% of our patients afflicted with an abscess, did not experience these symptoms. We believe that in addition to these signs, a clinical evaluation with a high index of suspicion is warranted, especially in cases of periorbital edema which often limits the physical exam. In these suspected cases, a CT examination should be considered [9,10]. Our rate of CT scans is similar to a large US-based multicenter observational study reporting a median CT scan rate of 74.7% [11]. At present, no universal imaging protocol exists [12]. We believe that a CT scan should be reserved for those pediatric patients where the results would assist in determining a change in medical treatment from antibiotic treatment only to surgical intervention. Other reasons for contemplating imaging studies is the inability to perform a complete eye evaluation, proptosis, ophthalmoplegia, pain with external ocular movement, deteriorating visual acuity or central symptoms (i.e. seizures, focal neurologic deficits, or altered mental status) [10-12].

At our center, the children diagnosed with orbital cellulitis were treated with a combination of intravenous 2nd/3rd generation cephalosporins and clindamycin, considering the local prevailing organisms [13,14].

In the past, orbital cellulitis was considered a surgical disease, especially in the presence of a subperiosteal or intra-orbital abscess, necessitating immediate surgical drainage in addition to antibiotic therapy [15]. Surgical intervention was required for only the minority of our described cases. Interestingly, no clinical findings or laboratory markers had predicted which patients would require an intervention, including age, as had been previously described [16]. When reviewing each specific case, 10 out of the 12 children showed clinical and laboratory deterioration (eye examination and laboratory results). Overall, our data support the general approach that orbital cellulitis in children should be initially conservatively managed. Closely monitoring this treatment protocol is essential since a minority of patients who fail to respond to empiric therapy can rapidly deteriorate, and develop complications as previously described [17,18].

Our study has several limitations. Firstly, its retrospective nature. Secondly, due to the relatively rarity of orbital cellulitis, the number of children enrolled in the study

WHAT THIS STUDY ADDS?

- Orbital cellulitis in children can be successfully managed with a conservative approach, and only a minority of patients requires surgical intervention, if they show no improvement in clinical and laboratory parameters.

was limited. Nonetheless, this is still one of the largest pediatric cohorts reported. Furthermore, the fact that the study occurred in one large affiliated center gave us the opportunity to observe trends which might change over time. Although, strong recommendations regarding proper surgical interventions were not presented due to the small number of cases requiring surgical intervention, our study stresses the importance of proper management and close monitoring of pediatric cases.

We believe, that most children diagnosed with orbital cellulitis can be managed conservatively, with only a few requiring surgical intervention. Pediatricians as well as ear, nose and throat physicians and ophthalmologists should be aware of every aspect of this uncommon but, nevertheless, serious medical condition. Larger prospective studies are essential in order to update our knowledge and find the optimal management for each child.

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RESEARCH PAPER

Barriers to the Delivery and Uptake of Water Sanitation and Hygiene (WASH) Promotion and Infant Diarrhea Prevention Services: A Case Study in Rural Tribal Banswara, Rajasthan

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Objective: We aimed to identify key barriers to Water Sanitation and Hygiene (WASH) promotion and infant diarrhea prevention services delivered by Accredited Social Health Activists (ASHAs) in rural India. **Methods**: A case-study was conducted across nine tribal villages in Banswara district (Rajasthan), where in-depth observational and qualitative data was collected from frontline health workers and infant caregivers. **Results**: ASHAs' prioritization of their incentive-based link-worker tasks over their health activist roles, limited community mobilization, and lack of monitoring of such activities hindered the delivery of WASH promotion and infant diarrhea prevention services. Caregivers' lack of trust in ASHA's health knowledge and preference for private providers and traditional healers also hindered the uptake of ASHA's health promotion services. **Conclusions**: Strengthening ASHAs' health activism roles and building trust on frontline health workers' knowledge among tribal communities will be the key to address the determinants of child malnutrition and stunting and accelerate progress towards the national development agenda.

Keywords: *Accredited Social Health Activist (ASHA), Frontline health worker, Malnutrition.*

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Diarrheal diseases remain a pressing concern for child health in rural India, as they are still the third leading cause of child mortality and linked to child malnutrition and stunting [1,2]. Improved water, sanitation and hygiene (WASH) conditions can prevent a large proportion of diarrheal diseases [1]. To raise awareness about safe WASH practices and infant diarrhea infection risks at the grass-root level, Accredited Social Health Activists (ASHAs) bear an important role. ASHAs serve as: *i*) link-workers, facilitating access to the healthcare system and providing community-level care to the rural populations, and *ii*) as health activists, raising awareness on the social determinants of health. Alongside other frontline health workers, ASHAs are expected to provide child health, hygiene and nutrition education and mobilize communities towards safe WASH, using platforms like the Village Health and Nutrition Days (VHND) [3]. The ASHA's performance is incumbent upon multiple factors, including personal factors such as her education and domicile; professional factors such as recruitment, training and incentives; and, organizational factors such as monitoring and supervision [4]. Factors that hinder the delivery of WASH promotion and diarrhea infection risk awareness services in particular, have not yet been adequately investigated.

Understanding potential gaps in WASH promotion and infant diarrhea prevention services at the grass-root level may prove crucial to unlocking current bottlenecks for the acceleration of progress to meet national and international child stunting targets (e.g., POSHAN mission) [5]. We draw upon in-depth qualitative and observational evidence collected during a community-based case-study in the rural tribal district of Banswara, Rajasthan, to unravel unique community perspectives and identify key barriers for the delivery and uptake of WASH promotion and infant diarrhea prevention services.

METHODS

The case-study was conducted across nine tribal villages of two administrative blocks of Banswara district, where over 93% of the population is rural and 75% from scheduled tribes

[6]. In rural Banswara, over 50% of children under-5 are stunted and female literacy remains below 50% [7]. Since ASHA's introduction in 2005, 86% have received at least 10 days of training [8]. Across the study villages, 88% of households have access to an improved drinking-water source and 21% use improved sanitation facilities, as per the household survey of the PANChSHEEEL Project in the same villages [9].

One field researcher (JVG) and two local field investigators who had prior training and experience in qualitative research, conducted daily field visits to the study villages from September to December, 2019. Semi-structured qualitative methods were used with purposive sampling strategies until theoretical saturation on the frontline health workers' and caregivers' perspectives on WASH and child health was reached. Key informant interviews (KIIs) were carried out with all ASHAs and Auxiliary Nurse Midwifes (ANMs) across the case-study villages. To capture the caregivers' perspectives, house-hold visits, which involved semi-structured interviews with caregivers, were carried out across four of the nine case-study villages, which were sub-selected based on those villages with stronger rapport-building with the study team. Households with an under-2 child were selected based on maximum variation purposive sampling criteria. Focus group discussions (FGDs) were carried out in each of the four villages, with 6-9 mothers at a time [10], and maximizing variation among participants by purposively sampling mothers from geographically dispersed households. Semi-structured VHND observations were conducted across four different villages where the study team was invited to attend (**Table I**). All KIIs, FGDs, and VHND observations were conducted at the anganwadi centers and lasted 30-90 minutes.

The study was approved by UCL Research Ethics Committee in the UK and the IIHMR Review Board in India, and written informed consent was obtained.

Table I Semi-structured Data Collection Events

Data collection methods	*Number of events*
KII with ASHAs	10
KII with ANMs	2
FGD with mothers of infants	4
Household visits and semi-structured interviews with caregivers	42
VHND observations	4

KII-key informant interviews, ASHA-accredited social health activist, FGD-focus group discussion, VHND-village health and nutrition day.

Data processing and analysis: Interviews and group discussions were conducted in Wagdi and Hindi by field investigators familiar with the local dialect and culture, and audio-recorded and transcribed verbatim. Anonymized transcripts and field memos from observations were imported into NVivo software for analysis of textual data. We adopted a grounded theory approach, where social phenomena and core themes were derived inductively from the data [10]. Relevant statements were coded into preliminary codes, and after an iterative process and discussion among the social researchers in the study team, the final core themes were defined.

RESULTS

Word clouds drawn from qualitative data revealed that discussions with frontline health workers more often revolved around the causes of infant's diarrheal infections ("water", "hands", "habits"), and discussions with infant caregivers more often involved the consequences of disease ("hospital", "doctors"). Thematic analysis of the data uncovered several core themes hindering the delivery and uptake of current village-level WASH promotion and infant diarrhea prevention services (**Table II**).

Table II Emerging Themes Constraining WASH Promotion and Infant Diarrhea Prevention Services

Barriers to services' delivery	*Barriers to services' uptake*
• ASHAs prioritize link-worker roles over their health activist roles • Limited community mobilization ability by ASHAs, who, despite efforts to raise awareness on health and hygiene, struggle to mobilize the community towards safe WASH habits. • No focus on health and WASH promotion was observed during VHND sessions, which were poorly attended. • Lack of monitoring and accountability of ASHA's WASH and health promotion responsibilities, which facilitated non-compliance	• Caregivers prefer private providers or traditional healers, as they are thought to provide more effective treatment. • Government healthcare facilities are less convenient to attend to, and they are thought to provide scanty treatment. • Lack of trust in ASHAs health knowledge and hygiene advice, due to ASHA's lack of higher education or formal health training. • Locational factors: The geographical distance to ASHAs influenced ASHA's service uptake

ASHA – accredited social health activist, VHND – village health and nutrition day, WASH – water sanitation and hygiene.

ASHAs prioritize link-worker roles over their health activist roles: ASHAs own accounts of their responsi-bilities emphasized the multiplicity of activities they were engaged in, compelling them to prioritize some tasks over others. ASHAs placed an unequal emphasis on their incentive-driven link-worker tasks including antenatal and postnatal visits, escorting mothers for institutional births, and helping in child vaccinations, in detriment of their health activists' role (**Web Box I**).

Limited community mobilization ability: ASHAs were aware of their role as health activists and community mobilizers, raising awareness about health and hygiene among the village community, but appeared to have a limited ability to engage and mobilize communities. ASHAs often claimed that despite their efforts, villagers did not understand or rejected the health and hygiene advice they provided (**Web Box I**). A contrasting perspective was offered by mothers and caregivers of infants, who often claimed not being aware of some poor hygiene and infection risks, and not being told about them by ASHAs.

No focus on health and WASH promotion in VHND sessions: VHNDs, the designated platforms to provide child health, hygiene and nutrition education, were observed to focus exclusively on the delivery of child vaccinations and child growth monitoring and were often poorly attended. ASHAs' role during VHNDs was primarily to provide logistical support to ANMs, but no health promotion activities were observed. ASHAs were unclear on how to utilize the development funds available under the panchayat for local health planning and WASH promotion at VHNDs.

Lack of monitoring and accountability for WASH and health promotion: Daily observations revealed that many anganwadi centers often remained closed and attendance was low. Unlike records of births, child immunizations, and antenatal and postnatal visits, WASH promotion and child health and nutrition education services were not formally monitored. Frontline health workers were asked to keep records of the VHND activities, but records were sometimes populated a posteriori with fabricated accounts. The acceptance of artificial 'paper records' further facilitated non-compliance.

Caregivers prefer private providers or traditional healers: Despite financial constraints, parents reported a clear preference for private providers or traditional healers rather than government healthcare services. Parents often did not trust that ASHAs had the necessary medication or that government hospitals provided effective treatment for child diarrhea. Hence, ASHAs seldom contributed in providing oral rehydration solutions (ORS) or monitoring of diarrheal events, as parents hardly sought her help in those instances. Treatment was mostly sought from so called "Bengali" doctors, informal medical providers without a legal medical license. Parents often thought that treatments such as ORS powder, pills, and diets, more often prescribed by public health services, were less effective than treatments given via drips or syrups, which were more often provided by "Bengali doctors", as the latter were perceived to be more 'medical' methods of higher quality. Traditional spiritual healers, *bhopas*, were often visited to provide healing rituals for different child afflictions; however, diarrhea was generally recognized as a symptom that required medical treatment (**Web Box II**).

Most parents of infants recognized the ASHA's role in providing support during childbirth and for child immunizations, but not for other health services, including advice on acute diarrheal infections. Parents pointed out the lack of higher education (ASHAs are eligible after 8 years of formal education), and relatively limited training as reasons for not trust seeking care from ASHAs for childhood illnesses.

Locational factors: Parents who lived relatively far from the ASHAs residence or the anganwadi center reported not having regular contact with frontline health workers. Families living close to ASHAs frequently reached out to her when their children were ill and were provided with ORS or paracetamol and advised on referral. Some ASHAs were not residents of the villages they served but had still been selected by the local authorities. Villagers reported not seeking or receiving child health support from such ASHAs.

DISCUSSION

ASHAs placed an unequal emphasis on their link-worker and incentivized roles in detriment of their health promotion and activism roles. Kawade, et al. [11], pointed out how ASHAs referred to themselves as 'ASHA workers' rather than 'health activists,' which was interpreted as a reflection of their focus on their roles as link-workers rather than health activism [11]. Another study [4] similarly found that ASHAs were considered to have particularly poor training on counselling and health promotion skills [4]. The National Health Mission evaluation of the ASHA program [8] agreed that ASHA's roles as community mobilizer were "extremely weak" in the Banswara district. Block-level officials in Banswara insisted that ASHA's role was "primarily as a link-worker", with "no time to devote to community mobilization", which partly explains the lack of emphasis on ASHA's health activist role in Banswara. Our findings differed from those of another study in Rajasthan [4], which identified conflicts and unfriendly relationships between ASHAs and ANMs that hindered the delivery of joint services. Instead, ASHAs in our study villages were observed to provide support to ANM during VHNDs.

WHAT THIS STUDY ADDS?

- ASHAs unequal emphasis on their health activist roles in favor of their link-worker roles particularly hindered the delivery of WASH promotion and infant diarrhea prevention services.
- Parents' lack of trust on ASHAs health advice and reliance on private and traditional healthcare providers further hindered the uptake of health promotion schemes among tribal communities.

The infant caregivers in the tribal study communities reported a general mistrust on ASHA's knowledge and on the public healthcare services. A study in Maharashtra [12] similarly concluded that although tribal communities were satisfied with ASHAs' support during childbirth, immunization and family planning, they believed that ASHAs are not knowledgeable on health due to the lack of higher education [12]. Additionally, traditional beliefs about health and disease and a preference for private providers and traditional healers also hindered the uptake of government child health services for infant diarrhea prevention and management.

Given that poor WASH and diarrheal disease are increasingly recognized as primary factors contributing to poor child growth [2], the lack of emphasis and monitoring of ASHA's health activist role could partly explain the recent stagnation on child malnutrition and stunting rates in India [13]. Based on the results and lessons learnt from this study and published evidence, ASHAs' roles in community mobilization and health promotion needs strengthening. Reinforcements on ASHA's role clarity, training, monitoring, and incentive systems for WASH and health promotion will be needed [4], but reinforcements among program managers and governance spheres on the need for health promotion will also be required for the fulfilment of ASHAs as true health activists [14]. It has been suggested that providing certificates of ASHA's health modular trainings could prove useful to increase the community's trust in her health knowledge [12]. Examples could be taken from Chhattisgarh's *Mitanin* program, where frontline health workers were particularly successful at performing as socio-political actors and mobilizing communities [15].

These findings suggest there is a disconnect between India's policy shifts with increased attention, political commitment and funds towards improving WASH and child growth determinants under several flagship programs such as POSHAN Mission, and how they have translated into shifting village-level realities in rural tribal Banswara, which may be part of a larger crisis of care where policy implementation remains an important gap [13].

Strengthening ASHAs health activism and mobilization skills and improving trust and rapport between tribal communities and frontline health workers will be key to address the determinants of child malnutrition and stunting and accelerate progress towards the national development agenda.

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CLIPPINGS

A randomized trial of preterm formula fortification of breast milk in preterm infants (JAMA Pediatr. 2021;175:790-796)

Preterm infants often require fortification of expressed breast milk with human milk fortifiers (HMF) for achieving optimal growth which is often costly and barely affordable by many in Indian scenarios. Also the long term benefits of HMF in terms of growth and neurodevelopment are uncertain. Hence in this double blind control trial Chinnappan etal randomized 123 preterm neonates of less than equal to 34 wks. gestation and receiving at least 100 ml/kg of oral feed or 75% of total feeds as EBM to receive EBM fortified either with HMF or preterm formula (PTF). Outcomes compared were weight gain at discharge or 40 weeks (primary outcome with a noninferiority margin of 2 gm/kg/day)), common morbidities like incidence of NEC, feed intolerance and presence of extra uterine growth retardation at discharge (secondary outcomes). Baseline characteristics of enrolled infants were similar. The primary outcome was noninferior in the PTF as compared to HMF group (mean weight gain15.7 ±3.9 vs 16.3 ± 4.0 g/kg/d; mean difference, -0.5 g/kg/d; 95% CI, -1.9 to 0.7). There was fewer incidence of feed intolerance (1.4 vs 6.8 per 1000 patient-days; incidence rate ratio 0.19; 95% CI, 0.04 to 0.95), as well as the need to stop fortification for more than 24 hrs. in HMF group as compared to PTF group. The rest of the secondary outcomes were similar. In this trial emphasized that use of preterm formula might be a better option for fortification, especially in resource-restricted settings.

Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries (N Engl J Med 2020; 383: 2514-25)

This multicountry, randomized trial was conducted with an objective to find out the safety and efficacy of antenatal glucocorticoids in women in low-resource countries who are at risk for preterm birth. A total of 2852 women from 29 secondary- and tertiary level hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan underwent randomization.The participants were assigned to intramuscular dexamethasone or identical placebo. The primary outcomes were neonatal death alone, stillbirth or neonatal death, and possible maternal bacterial infection; neonatal death alone and stillbirth or neonatal death were evaluated with superiority analyses. The possible maternal bacterial infection was evaluated with a noninferiority analysis with the use of a prespecified margin of 1.25 on the relative scale.

The study revealed that the use of dexamethasone resulted in significantly lower risks of neonatal death alone (relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.97; P=0.03) and stillbirth or neonatal death (relative risk, 0.88; 95% CI, 0.78 to 0.99; P=0.04) than the use of placebo. There was no increase in the incidence of possible maternal bacterial infection alsowas no significant difference in adverse events inbetween groups. The study highlighted that antenatal dexamethasone is safe and efficacious for early preterm birth in low resource countries. Authors advised to conduct further study to determine the most appropriate dosing regimen and safety and efficacy in late preterm pregnancy.

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Web Box I Representative Verbatim Quotes of Service Delivery Barriers
Link-worker role prioritization over health activist role "*We were trained to do the registration of every pregnant lady from 3 months and provide accurate vaccination to them (…), to get the regular weight checks done of women and teach them how to breastfeed. (…) I have an array of works starting from reporting, visiting 10 houses [of pregnant women and new-borns], checking the growth of new-born children, seeing if the child is having diarrhea, keeping tabs on their weight*". [ASHA 04]
Limited community mobilization ability People do not understand hygiene risks: "*The educated crowd understands but the uneducated ones just nod their heads. (…) I don't know if they really understand [about proper hygiene habits] as when we say they often nod head and say yes to everything*". [ASHA 04] People do not listen to the hygiene and health advice: "*We were trained to educate about how to keep the child neat and tidy, proper feeding habits and proper bathroom habits. (…) We tell about vomiting, diarrhea and educate about the benefits of the ORS solution (…) Some villagers follow [advice], and some others don't follow*". [ASHA 06] People do not believe the hygiene and health advice: "*We tell [that drinking river water is not good] but people retort by saying that we have been drinking this water from years and nothing has or will happen.*". [ASHA 10] People reject hygiene and health advice: "*I sometimes give advice, support and suggestion but some people from the community tell me bad words*". [ANM 01] People do not know or receive information on hygiene and health risks: *"We don't know why [child gets diarrhea]. On consulting the doctor, he provides treatment to our kids. He gives us medicine and we pay them. He assures us that our child will heal. He doesn't brief us on the cause of illness. If the treatment doesn't work, we take our child back to the doctor. (…). We just came to know that water can also be contaminated like this. Whenever kids ask for water, we put our hands inside the pot and fetch it to them we didn't know that we were polluting our drinking water".* [Mother 01]
No focus on health and WASH promotion in VHND sessions Lack of clarity on utilizing health promotion and village health planning budgets: "*We don't know what the budget is, 5000 rupees a year are delivered under the VHNSC"* [ASHA 07] "*5000 rupees come* [for the VHNSC], *out of which 200 are given to us to work around the anganwadi. (…) Not now, but earlier we used to receive some money. We spent 2000 rupees, we bought some chairs, and we need to buy some more articles*". [ASHA 08] "*We have money in our bank accounts, but we have not yet used it. 5000 rupees were deposited in our account which is unused as of now. If money is given to the committee or to us we may use but if money is given to the village panchayat then it won't be used*". [ASHA 01]
Lack of monitoring and accountability for health and WASH promotion Village Health Nutrition & Sanitation Committee's activities only exist in paper records: "*The VHNSC Committee is only on the paper records, as sometimes people do not come. The village Sarpanch leaves everything on us…*". [ASHA 04] "[Interviewer] *Have you heard of the VHNSC, is there a committee for this here?" "No, no such thing is here*". [ASHA 05]

Web Box II Representative Verbatim Quotes Under the Core Theme: Service Uptake Barriers
Preference for private providers or traditional healers Private healthcare is thought to be quicker and better: *"The doctor in the Government hospital takes time to cure the illness. It takes 3 days for the treatment to work. (…) the private doctor cures the illness in 2 days and his medicines helps our child to feel better. In private hospital you just have to pay, and they treat you, no hassle".* [Mother 02] There is a medicalised idea of high-quality treatment: *"[People] at times they go to the Bengali doctor only because he gives saline drip (…). The Bengali doctor prescribes a heavy dose of medicine which has resulted in fatal deaths".* [ASHA 02] Traditional spiritual healers are still commonly sought for treatment, although not for diarrhea: *"Yes, we visit the bhopa [spiritual healer]. First, we visit the bhopa and after that, if it doesn't work, we take our child to the hospital for consultation. All the ladies in this room have visited the bhopa. We see the bhopa if a child unnecessarily cries while going to someone's place. We then assume that the child has been attacked by some negative energy. [But if the child suffers from diarrhea, cold or cough] then we consult the doctor.* [Mother 03] *"Herbs don't work against diarrhea. No one believes in such things anymore. Those who trust these things [spiritual healings] end up losing their child after roaming around for several days. When medicines don't work, we take our child to the bhopa. We only take child to bhopa while he is suffering from fever or vomiting, but not during diarrhea".*[Mother 04]
Lack of trust in ASHA's knowledge *"[Diarrhea cases] do not come to us, they [parents] rather go to the ANM sister directly or hospital. Rarely someone comes, when they do we give ORS to them".* [ASHA 08] *"We keep notes of the number of cases of diarrhea and we have to fill a form, but if it counts to 0 then we are scolded by Sir".* [ASHA 04]
Locational factors *"ASHA only provided support during delivery time and for injections. She does not provide support for diarrhea or child health. People go straight to hospital for that. She also lives far away, so even if she has some ORS treatment available, people don't bother and also she doesn't provide support for that".* [Mother 05]

RESEARCH PAPER

Clinical Profile of Children With Cystic Fibrosis Surviving Through Adolescence and Beyond

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Objective: To document morbidities in adolescents with cystic fibrosis (CF) from India. **Methods**: Details of children with cystic fibrosis surviving beyond 15 years of age were extracted from hospital records, and analyzed. **Results**: 43 children [Median (IQR) age 18.7 (17, 20.6) years, were enrolled. Median (IQR) body mass index was 15.82 (13.5, 19.05) kg/m^2. *Pseudomonas* species were isolated from respiratory specimens of 34 (79%) adolescents. Allergic bronchopulmonary aspergillosis (ABPA) and Cystic fibrosis-related diabetes (CFRD) were seen in 12 (28%) and 11 (26%) patients, respectively. Conjugated hyperbilirubinemia and distal intestinal obstruction syndrome (DIOS) were diagnosed in 15 (35%) and 6 (14%) children, respectively. *Pseudomonas* species colonization (P=0.04) and multiple pulmonary exacerbations in last one year (P<0.001) were significant predictors of FEV_1% predicted. **Conclusion**: Malnutrition, chronic airway colonization, ABPA, CFRD, conjugated hyperbilirubinemia and DIOS are morbidities observed in adolescents with CF in India. The data support the need for early screening of CF-associated morbidities.

Key words: *Allergic bronchopulmonary aspergillosis, Colonization, Cystic fibrosis-related diabetes, Pseudomonas*.

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With the increased awareness and availability of diagnostic tests, the number of children with cystic fibrosis (CF) has been increasing in India [1]. Morbidities increase with age due to the development of complications. Information on morbidities of children with CF surviving beyond 15 years is limited, particularly in resource-limited settings. We share our experience of children with CF who survived beyond 15 years.

METHODS

A review of medical records of children above 15 years of age, with CF, attending the pediatric chest clinic at our tertiary care center from January, 1996 to December, 2019 was carried out. Details of demography, clinical profile, course of illness, and laboratory parameters were extracted. Standard methods were used to diagnose various morbidities like chronic bacterial colonization, pulmonary exacerbation, cystic fibrosis-related diabetes (CFRD), allergic bronchopulmonary aspergillosis (ABPA), distal intestinal obstruction syndrome (DIOS), cystic fibrosis-related chronic liver disease, and bone mineralization disorder in CF [2-5].

Statistical analysis: Appropriate statistical tests were applied, using STATA 12.0 software (StataCorp).

RESULTS

Out of a total of 600 children with cystic fibrosis under follow-up in the Pediatric Chest Clinic since 1996, 43 patients who had survived beyond 15 years of age, with available records, were included in the analysis. Demographic and clinical features are depicted in **Table I.**

The CF-related morbidities detected are depicted in **Table II**. We evaluated correlation of BMI of CF patients with numbers of pulmonary exacerbations in last one year (r=0.26, P=0.08) and FEV_1 % predicted (r=0.37, P=0.01). A higher proportion of children with CF, receiving inhaled antibiotics, had ABPA compared to those without inhaled antibiotics (33% vs 25%, P=0.8). Compared to the children without diabetes, the children with CFRD had higher proportions of positive family history (55% vs 16%, P=0.005), consanguinity (27% vs 6%, P=0.04) and earlier onset of symptoms of CF [median (IQR): 03 (1,6) vs 7.5 (2, 36) months, P=0.06]. One child had multiple episodes of DIOS and all the cases of DIOS were managed conservatively. Nasal polyps were detected in 4 (10%) subjects. One patient, aged 22 years, had given birth to a healthy child.

The median (IQR) FEV_1% predicted of our cohort was 50.5% (30%, 70%). Multivariate linear regression analysis showed that *Pseudomonas* species colonization (P=0.04)

Table I Characteristics of Adolescents With Cystic fibrosis (*N*=43)

Variable	
Age (y)[a]	18.7 (17, 20.6)
Follow-up after 15 y of age (y)[a]	3.6 (2, 5.2)
Male gender	26 (60)
Age of onset of symptoms (mo) [a]	6 (2, 24)
Age at diagnosis of CF (mo) [a]	84 (24, 132)
Delta F508 mutation of *CFTR* gene	9 (21)
Inhaled medication	
Bronchodilator + ICS	38 (89)
Bronchodilator + ICS + mucolytic	4 (9)
Not on inhalation medication	1(2)
Oral azithromycin (immunomodulatory dose)	38 (88)
Inhaled antibiotics	
Total	15 (35)
Tobramycin	7 (16)
Tobramycin and colistin	4 (9)
Vancomycin	2 (5)
Gentamycin	2 (5)
Pancreatic enzyme replacement	40 (93)
Clubbing	39 (90)
Grade 1	21 (49)
Grade 2	3 (7)
Grade 3	15 (35)
Pulmonary exacerbations in last one year	
Nil	14 (33)
1	7 (16)
2	15 (35)
3	6 (14)
>3	1 (2)
PFT[a]	
FEV_1, % predicted	50.5 (32, 70)
FVC, % predicted	64 (46, 78)
FEF, % predicted	28.5 (14, 55)
Chest clearance technique	
Not used	5 (12)
Postural drainage	12 (28)
Self-exercise	17 (40)
Postural drainage+ self-exercise	8 (19)
Acapella	1 (2)

Values in no. (%) or [a]median (IQR). ICS-inhaled corticosteroid.

and multiple pulmonary exacerbations in last one year (P<0.001) significantly predicted FEV_1(% predicted) (r^2=0.52) (**Web Table I**).

DISCUSSION

This study describes the various comorbidities in children with CF surviving beyond 15 years of age. Allergic bronchopulmonary aspergillosis (ABPA), Cystic fibrosis related diabetes (CFRD), conjugated hyperbilirubinemia, and DIOS were the common conditions seen.

Table II Morbidities and Outcome of Adolescents With Cystic Fibrosis (*N*=43)

CF related morbidity	*No. (%)*
BMI during last visit[a], kg/m^2	15.82 (13.5, 19.05)
Chronic bacterial airway colonization	
Pseudomonas spp.	34 (79)
Staphylococcus spp.	15 (35)
Klebsiella spp.	2 (5)
E. coli spp.	1 (2)
Staphylococcus spp.+ *klebsiella* / *E. coli* spp.	14 (33)
Age at first *Pseudomonas spp*. colonization, mo*	48.5 (14, 144)
ABPA (allergic bronchopulmonary aspergillosis)	12 (28)
Age at diagnosis of ABPA, y[a]	13 (11,17)
Pulmonary arterial hypertension	4 (10)
CFRD (Cystic fibrosis-related diabetes)	11 (26)
Conjugated hyperbilirubinemia (>2 mg/dL)	15 (35)
Cholelithiasis	2 (5)
Distal intestinal obstruction syndrome	6 (14)
Rectal prolapse	1 (2)
Osteopenia (assessed by DEXA scan, > grade 1)	2 (5)
Depression	1 (2)
Delayed puberty	1 (2)
Outcome	
Continuing follow-up	31 (72)
Death	2 (5)
Lost to follow-up	10 (23)

All values in no. (%) or [a]median (IQR). ICS: Inhaled corticosteroid; DEXA: dual X-ray absorptiometry; BMI: body mass index.

Recently, Dhochak, et al. [6] demonstrated that recurrent respiratory tract infections were a significant risk factor for poor nutritional status of children with CF. Similarly, we also noticed poor nutritional status of CF patients in this study and almost half of our cohort had two or more episodes of pulmonary exacerbation in last one year of follow-up. The higher proportion of pseudomonas species isolation in these pulmonary infections in our study is explained by the higher age (>15 years) of the patients, who are expected to have developed stable core of pathogenic organism selected over the time with repeated antibiotic exposures during exacerbations [7,8].

The association of ABPA in CF with low BMI, and long term use of azithromycin has been shown in a previous study [9]. Thus, use of azithromycin in majority (88%) of patients, low BMI, in addition to adolescent age group may have been possible contributory factors for higher prevalence rate of ABPA (28%) compared to that (7-9%) reported in Epidemiologic Registry of Cystic Fibrosis [10]. The prevalence of CFRD in our study was slightly higher than

WHAT THIS STUDY ADDS?

- Allergic bronchopulmonary aspergillosis (ABPA), cystic fibrosis-related diabetes (CFRD), conjugated hyperbilirubinemia, and distal intestinal obstruction syndrome (DIOS) were the common morbidities in children with CF who had survived beyond 15 years of age in India.

(21.4 %) in the study done by Jain, et al. [11] from India. Although, statistically not significant, children with CFRD in our study had an earlier age of onset of CF, lower BMI and consisted of a higher proportion of females, which is in line with the results of previous studies [12].

In this study, none of the cases had cirrhosis or portal hypertension but occurrence of conjugated hyper-bilirubinemia and cholelithiasis was almost similar to earlier studies [13]. A different genotype of the Indian children [14], may be one of possible factors for slow progression of liver disease. We observed lower lung functions of our cohort compared to that reported in children of the same age group in CF registries of developed countries [15]. Chronic infection with pseudomonas and multiple exacerbations in the past year were demonstrated as significant risk factors for poor lung functions, in our study.

The limitations of this study are its retrospective design and short duration of follow up. Parameters such as quality of life indices and comorbidities like behavioral changes, psychiatric disorders, osteopenia, infertility and pubertal growth have not been assessed. The small sample size may have overestimated the prevalence of ABPA and CFRD.

In conclusion, this study shows CF-related morbidities are more common in Indian adolescents with CF, with pseudomonas species colonization of airway and recurrent pulmonary exacerbation being important predictors of lung function deterioration. We believe that survival and quality of life can be improved with early recognition and aggressive management of these cystic fibrosis related morbidities.

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

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RESEARCH PAPER

Profile of Back-Referrals to Special Newborn Care Units

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Objective: To study the outcomes of neonates back-referred from a tertiary care centre to special newborn care units (SNCUs) for step-down care. **Methods:** This prospective cohort study was conducted at a tertiary care neonatal unit and SNCUs in neighbouring states. We studied preterm and term neonates back-referred to district SNCUs from September, 2018 to April, 2019. The infants were followed up till 3 months corrected age, for mortality, re-hospitalization, emergency visits and unscheduled outpatient visits. Preterm inborn neonates <32 weeks gestation discharged directly to home formed the controls. **Results:** 201 back-referred neonates (study cohort) and 55 preterm neonates discharged to home (controls) were followed up till 3 months corrected age. Amongst the back-referred neonates, 5% died, 7% required re-hospitalization, 11% made emergency visits, and 24% made unscheduled outpatient visits. These outcomes were similar to the controls. **Conclusion**: Back-referral of convalescing neonates is a safe method of utilizing the limited healthcare resources in tertiary care centers in developing country settings.

Key words: *Neonate, Re-admissions, Regionalization, Special care neonatal unit*.

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Neonatal mortality forms a large proportion of infant mortality for which several programs have been launched over the last decade. Prominent amongst them being promotion of institutional delivery, creation of Special Newborn Care Units (SNCUs) at district level and free national ambulance system (108) [1]. Programs like Janani Shishu Suraksha Karyakram and India Newborn Action Plan have brought much needed attention to the maternal and neonatal care [2,3]. As a result, there has been increasing referrals to tertiary care facilities [4]. Tertiary care centres are overloaded and end up providing level II and lower level of care in addition to level III care [5]. This is partly also due to lack of a functional regionalization. Regionalization of perinatal care classifies hospitals at risk-appropriate level and creates a 'system' for referral and back-referral to risk appropriate care. Perinatal regionalization has been recognized as an extremely effective way to reduce neonatal mortality [6].

At our center we have created linkages with district SNCUs and have been back-referring convalescent neonates for ongoing care for past five years. As there has been no formal assessment of the safety and efficacy of the procedure in the Indian context, we planned this study to determine the short-term outcomes of neonates back-referred from our centre to the SNCUs.

METHODS

This prospective cohort study was conducted in our tertiary care centre from 1 September, 2018 to 20 April, 2019. Approval was obtained from the institutional ethics committee and a written informed consent was obtained from all participants The study cohort comprised of all inborn (preterm) as well as out born neonates (term and preterm) back-referred to district SNCUs from our institution. Preterm inborn neonates less than 32 weeks of gestation at birth, who were discharged directly to home during the same period, were enrolled as comparison group. These neonates could not be back-referred as the parents did not agree to be shifted to a step-down hospital, or due to lack of appropriate care facility at the step-down hospital nearest to their home, or in view of the nature of their illness. Preterm neonates less than 32 weeks were chosen as the comparison group because their morbidities are similar to that of the inborn neonates who were back-referred. All back-referred and discharged to home neonates were followed-up from the point of their discharge till 3 months of corrected age for mortality, re-hospitalizations, emergency visits and unscheduled outpatient department (OPD) visits.

The back-referral is typically done when all acute medical problems have resolved and family is willing. All SCNUs are comfortable handling neonates more than 1200 g

but some are also able to manage babies weighing between 1000-1200g.

For this study, a telephonic contact was maintained with parents during the stay in SNCU and after discharge. The discharge criteria followed by SCNUs are that the neonate should have recovered from the primary illness, is maintaining vital parameters including temperature without any assistance, is accepting breast or spoon feeds well, has been gaining weight for at least three consecutive days, currently weighs more than 1500 g and mother is confident of handling the baby. We follow more or less similar criteria at our centre. The actual weight at discharge is often less than 1500 g if all other criteria are met.

Definitive contacts were made in person at 28 days of chronological age, and at 1-month and 3-month corrected age for assessment of the study outcomes. In cases where the family did not return for the scheduled follow-up visit, telephonic contact was made to reschedule the visit. If the family was unable to come (*n*=15) or the child had died (*n*=12), outcome information was collected telephonically.

Statistical analysis: Mortality, re-admissions, visits to emergency and unscheduled OPD visits were calculated as percentages of eligible cohort. The outcomes of inborn neonates who were back-referred and the neonates discharged directly to home were compared by Chi square test with Yates correction.

RESULTS

A total of 215 inborn and outborn admitted neonates were back-referred from our centre to district SNCUs during the study period, and 201 could be contacted, forming the study cohort. In the same period, 60 neonates who were discharged directly to home were enrolled as control group and 55 could be followed up till the end of the study period. The profile of these infants is described in **Table I**.

Table II shows the broad group of illnesses these neonates had during their primary admission to our centre.

Table II Morbidities Among Neonates During Hospital Stay

Morbidity	*Back-referred neonates* (*n*=201)	*Neonates discharged home* (*n*=55)
Sepsis	131 (65)	39 (71)
Respiratory[a]	100 (51)	55 (100)
Neonatal jaundice	84 (42)	37 (67)
Gastrointestinal[b]	42 (21)	8 (15)
Hypoglycemia	31 (15)	9 (16)
Central nervous system[c]	21 (10)	4 (7)
Cardiovascular[d]	10 (5)	4 (7)
Acute kidney injury	11 (5)	1 (2)

Data in no. (%) *[a]Respiratory morbidities- hyaline membrane disease, broncopulmonary dysplasia, transient tachypnea of newborn, meconium aspiration syndrome, pneumonia and apnoea; [b]Gastrointestinal morbidities-necrotizing enterocolitis and feed intolerance; [c]Central nervous system morbidities - hypoxic ischemic encephalopathy and seizures; [d]Cardiovascular morbidities – patent ductus arteriosus and congenital heart disease.*

Reasons for back-referral were inadequate gestation and weight for discharge to home (66%), neonate still on gavage feeds (46%), weaning from caffeine (18%), mother not confident of taking care of the baby at home (17%), antibiotic completion (16%) and oxygen dependency (1%). The back-referred neonates stayed for a median of 10 days in SNCU. The median post menstrual age (PMA) at discharge from SNCU was 35 weeks for the inborn neonates and 39 weeks for the out born neonates. Eight (4%) neonates were re-referred from SNCU to our institute because of occurrence of new episode of sepsis or anemia. Amongst the back-referred neonates, 11 were taken by their parents against medical advice after short period of stay in SNCUs. The reasons given were poor cleanliness in the SNCU, lack of obstetrical care for the post-partum mother, poor water and sanitation facilities, and social issues like death or disease in other family members. These cases were also followed-up.

Table I Baseline Characteristics of Neonates Enrolled in the Study

Variable	*Back-referred neonates*		*Neonates discharged home*
	Inborn (n=139)	*Outborn (n=62)*	*Inborn (n=55)*
Female sex[a]	69 (50)	19 (33)	27 (50)
Gestation (wk)	31 (30,33)	36 (32,37)	30 (29,31)
Birthweight (g)	1305 (1155,1485)	2000 (1400,2615)	1222 (1020,1550)
Weight <3rd centile[a]	40 (29)	18 (29)	0
Hospital stay (d)	12 (8,21)	9 (6,16)	41 (23,64)
PMA at discharge (wk)	34 (32,35)	37 (34,39)	35 (33,37)
Weight at discharge (g)	1386 (1269,1510)	2100 (1500,2800)	1820 (1567,2243)

Data presented as median (IQR) or [a]no.(%). PMA-post menstrual age.

Table III Outcomes of Neonates Back-Referred and Neonates Discharged to Home

Outcome	*Back-referred neonates (n=201)*				*Inborn neonates discharged to home (up to 3 mo CA) (n=55)*
	28 d chronological age (n=136)[a]	*28 d chronological age to 1 mo CA (n=196)*[b]	*1-3 mo CA (n=192)*[c]	*Inborn back-referred neonates (up to 3 mo CA) (n=139)*	
Death	5 (4)	4 (2)	2 (1)	7 (5)	1 (2)
Re-hospitalization[d]	4 (2)	8 (4)	2 (1)	12 (9)	3 (5)
Death or re-hospitalization	8 (6)	12 (6)	3 (2)	19 (14)	4 (7)
Emergency visits[e]	12 (9)	5 (2)	5 (2)	14 (10)	3 (5)
Unscheduled OPD visits	6 (4)	14 (7)	28 (15)	29 (20)	11 (20)

Data in no. (%). CA-corrected age. [a]65 neonates were still admitted in the tertiary care hospital or SNCU at day 28 follow–up; [b]5 neonates died before 28 days and [c]4 neonates died between 28 days chronological age to 1 month CA; [d]includes all re-hospitalizations following scheduled outpatient (OPD) visits, unscheduled OPD visits or emergency visits; [e]includes emergency visits that resulted in death or re-hospitalization. All P>0.05.

Table III shows the outcomes at 3 months corrected age, of the inborn back-referred and directly discharged to home neonates. There was no statistically significant difference in the outcomes.

'Aspiration', pneumonia, apnea, sudden infant death and perinatal CMV were the causes of death in five, two, two, one and one of these infants, respectively. Sepsis was the leading cause of re-hospitalization. The cause of death was assessed from the information provided by parents, admission slips and death certificates that were issued to the families of the deceased neonates.

DISCUSSION

In this prospective cohort study of 201 back-referrals from a tertiary care hospital in India to SNCUs of neighbouring states, 5% of neonates died, 7% required re-hospitalization, 11% made emergency visits and 24% made unscheduled OPD visits during a follow-up period till 3 months corrected age. In the present study, re-admission rates and visits to emergency department were comparable to previous studies of follow-up of high-risk neonates [7-11]. The median duration of stay in any healthcare facility for the back-referred neonates in our study was 24 days, which is comparable to previous studies of NICU graduates [12-14].

The median duration of stay for the back-referred neonates in the SNCU was 10 days for the inborn neonates. These many days of hospital stay at tertiary centre could be saved for other needy neonates. The median discharge weight of the inborn neonates who were discharged from the tertiary centre was 1820 g while the median weight at discharge for inborn neonates from SNCU was 1612 g. The most likely reason for this was a higher proportion of SGA neonates in the inborn cohort who were back-referred (29%) vs comparison group (0).

In view of non-availability of retinopathy of prematurity (ROP) screening services at many SNCUs, parents have to bring the babies back to tertiary care centres on more than one occasion, while still admitted to SNCU. This creates hazardous conditions for the high risk preterm and sometimes a financial burden on the family. Another major bottleneck was transport for back-referral.

The design of the study was built upon what was happening in normal practice. Hence, it was a challenge to find suitable comparison groups, especially for the out born neonates who were back-referred. We did not perform a cost-benefit analysis or estimate the number of extra neonates who might have benefitted from tertiary care. Our study involved a government tertiary care centre in northern India and SNCUs of the surrounding states, and practices may vary in other parts of the country.

We have shown in this study that back-referral of convalescent neonates can be done safely and effectively. With the establishment of a large number of SNCUs and newborn stabilization units (NBSUs), and availability of national ambulance system, it is an opportune time to work on the optimization of the functional aspects of referral, back-referral, inter-facility communication and safe transport.

Ethics clearance: Institutional ethics committee of PGIMER; No. NK/4722/MD/763; dated November 21, 2018.
Contributors: SC: prepared the draft protocol for the study, collected and analysed the data, and wrote the manuscript; SKA: critically reviewed the study protocol and the manuscript; SSS critically reviewed the protocol and manuscript; SV: critically reviewed the protocol, manuscript and supervised statistical analysis; PK: conceived the study, designed the study, critically reviewed the study for important intellectual content and approved the final manuscript.
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WHAT THIS STUDY ADDS?

- Back referral of neonates to special case neonatal units (SNCUs) has comparable mortality, re-hospitalization and unscheduled hospital visits to those discharged directly to home from tertiary facility.

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Coronavirus Disease 2019 (COVID-19) Vaccination for Children: Position Statement of Indian Academy of Pediatrics Advisory Committee on Vaccination and Immunization Practices

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Justification: Data generated after the first wave has revealed that some children with coronavirus 19 (COVID-19) can become seriously ill. Multi-inflammatory syndrome in children (MIS-C) and long COVID cause significant morbidity in children. Prolonged school closures and quarantine have played havoc with the psychosocial health of children. Many countries in the world have issued emergency use authorisation (EUA) of selected COVID-19 vaccines for use in children. In India, a Subject Expert Committee (SEC) has recommended the use of Covaxin (Bharat Biotech) for children from the ages of 2-18 years. The recommendation has been given to the Drugs Controller General of India (DCGI) for final approval. **Objective:** To provide an evidence-based document to guide the pediatricians on the recommendation to administer COVID vaccines to children, as and when they are available for use. **Process:** Formulation of key questions was done by the committee, followed by review of literature on epidemiology and burden of COVID-19 in children, review of the studies on COVID vaccines in children, and the IAP stand on COVID-19 vaccination in children. The available data was discussed in the ACVIP focused WhatsApp group followed by an online meeting on 24 October, 2021, wherein the document was discussed in detail and finalized. **Recommendations:** The IAP supports the Government of India's decision to extend the COVID-19 vaccination program to children between 2-18 years of age. Children with high-risk conditions may be immunized on a priority basis. The IAP and its members should be a partner with the Government of India, in the implementation of this program and the surveillance that is necessary following the roll-out.

Keywords: *Guidelines, SARS-CoV-2, School*.

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Children of all ages are susceptible to coronavirus disease 2019 (COVID-19). Almost 70% of SARS-CoV-2 infections in children are asymptomatic. When symptomatic, the symptoms are usually mild and critical illness and hospitalizations are extremely rare. Children account for ~1.5% of all COVID hospitalizations. Studies done in the initial stages of the pandemic suggested that children do not participate significantly in the chain of transmission [1]. According to the National Centre for Disease Control data as of 26/2/21, 3.9% of cases occurred in the 0-10 year age group and 7.99% in the 11-20 year age group [2]. The morbidity and mortality of COVID-19 in children are much lower than that seen in adults and the elderly [1]. Thus, the assessment of benefit vs risk of COVID vaccination in children is complex.

OBJECTIVES OF COVID VACCINATION IN CHILDREN

Reduction in Disease Incidence, Morbidity and Mortality

The surge in COVID-19 cases following the rapid spread of more transmissible variants has resulted in a steep increase

in the number of cases and hospitalization rates in children in many countries [3,4]. This may be amplified if more transmissible variants predominate in the coming months. This further underscores the need for COVID-19 vaccination in children.

In USA, during the peak of the Delta wave, the weekly hospitalization rate among children aged 0-4 years increased nearly 10 times. Nearly one third of adolescents aged 12-17 years hospitalized with COVID-19 during March 2020-April 2021 required intensive care, and 5% of those hospitalized required endotracheal intubation and mechanical ventilation [3]. The current surge of COVID-19 in UK, is being primarily driven by high levels of infection in school-age children, with more than a third of all recent cases being reported in those under 15 years of age [4]. In USA, during the period from June 20 to July 31, 2021, the hospitalization rate among unvaccinated adolescents (aged 12-17 years) was 10.1 times higher than that among fully vaccinated adolescents, underlining the utility of vaccines in reducing the morbidity and mortality associated with COVID 19 in adolescents [3].

Age distribution data from India revealed that children in the age group 0-10 years accounted for 3.28% of all cases, and individuals 11-20 years accounted for 8.03% of all cases in the first wave. Corresponding figures in the second wave were 3.05% and 8.57%, respectively [5]. Although the proportion remained almost similar in both waves, the second wave involved almost twice the number as in the first wave, with a consequent increase in the absolute numbers of children needing hospitalization and ICU care.

In a study conducted in Tamil Nadu and Andhra Pradesh, in the pediatric age group, the case fatality rate was highest in the 0-4 years age group [median (IQR) 0.16% (0, 0.36)], which was comparable to that observed in the 18-29 years age group but lower than that observed in the older age groups [6].

A systematic review and meta-analysis of severe COVID-19 infection and pediatric comorbidities concluded that children with comorbidities have a higher risk of severe COVID-19 and associated mortality than children without underlying disease [7]. Severe COVID-19 was present in 5.1% of children with comorbidities as compared to 0.2% in children without comorbidities. Children with comorbidities had higher risk of severe COVID-19 [RRR 1.79 (95% CI 1.27-2.51)] and COVID-19-associated mortality [RRR 2.81 (95% CI 1.31-6.02)] as compared to healthy children. Children with obesity had a relative risk ratio of 2.87 (95% CI 1.16-7.07) [8].

In a multi-centric study done in five major institutions across India, 44% of 402 children had some underlying comorbidity, malignancy (leukemia and other malignancy) followed by cardiac disease was the most common underlying comorbidity. In this study, children with underlying disease had an odds ratio of 8.85 (6.07-12.91) for moderate-severe disease [9].In a study done from a dedicated COVID-19 hospital in India, 30 out of 100 admitted children had underlying comorbidities, 60% had severe disease, and the presence of underlying comorbidities and the number of comorbidities were significant predictors of severity of the disease [9].

A review of cases till December, 2020, revealed that 91.5% of COVID-19 deaths were reported from low- and middle-income countries (LMICs), and 83.5% of reported pediatric Covid-19 cases from all included countries were from LMICs. The pediatric deaths/1,000,000 children, case fatality rate (CFR) and ICU admission/1,000,000 children were significantly higher in LMICs than in high-income countries [10]. This data underscores the greater need for vaccination of children in LMICs, for the prevention of COVID-19.

Prevention of Complications

Multi-Inflammatory syndrome in children (MIS-C) first reported in April, 2020, is generally reported during the weeks following a peak in COVID-19 disease. MIS-C may need hospitalization and ICU care in addition to expensive medications [11]. The burden of MIS-C in our country has previously been documented [12-14]. By preventing SARS-CoV-2 disease, COVID-19 vaccines may prevent MIS-C.

Some patients who have recovered from COVID-19 may experience persisting symptoms after the resolution of acute disease [15], the so-called long COVID. Estimates in the literature range from 0-27% [16, 17]; however, similar literature regarding long COVID-19 in children is not available from India. Similar to MIS-C, COVID-19 vaccines may prevent long COVID; although, currently there is no data available to support this statement. A report of three children with subacute neuropsychiatric impairment following COVID-19 and the detection of intrathecal anti–SARS-CoV-2 antibodies also raises the spectre of direct involvement of the central nervous system by the SARS-CoV-2 virus [18].

Reduction of Transmission

School-age children and adolescents can efficiently transmit SARS-CoV-2 to household members, which may lead to hospitalization of adults who are secondarily infected [19]. Recent data suggest that adolescents contribute significantly to household transmission, and rates of transmission by this age group (11-18 years) may be higher than that in adults [20] The highest probability of transmission, given exposure, in an Indian study was shown to be within case-contact pairs of similar age, and

this association was strongest among children aged 0 to 14 years and among adults aged ≥65 years [6].With reopening of schools, outbreaks have been reported from all over the world. High attack rates of 44% have been reported at a youth camp in Georgia, USA suggesting that SARS-CoV-2 can transmit readily in young populations [21].

Vaccination of children may reduce transmission. Some of the COVID vaccines in use have been shown to reduce infection and thus transmission. However, during the Delta surge, vaccinated and unvaccinated individuals had similar viral loads in the nasopharynx [22].

Prevention of psychosocial issues due to prolonged school closure: The COVID-19 pandemic has resulted in drastic changes in the lives of children and adolescents. Restrictive measures, such as nationwide lockdown, school closures, online lectures, and quarantines, have resulted in significant adverse psychological effects on children, and adolescents [23-25]. COVID-19 associated obesity has become a real issue [26]. Children are losing out on their development and learning opportunities, including nutritional deficiencies and delayed immuni-zations. Vaccination and other measures to reduce community transmission may help to avert some of these indirect effects of the pandemic. Although vaccinations and school reopening are not linked, parents will be more confident about sending their vaccinated children to school.

Herd immunity: Herd immunity against COVID-19, either through vaccinations or natural infection, is the logical way to terminate the pandemic. Initially, a population immunity of 65-70% was estimated as the threshold for herd immunity [27]. However, ongoing vaccine hesitancy and the circulation of more transmissible variants have raised the bar for achieving herd immunity. The goal of attaining herd immunity can never be achieved if children, who constitute 20-35% of the population, are excluded from the vaccination process. If unprotected, children could act as reservoirs of infection and may contribute to the rise of variants in the future.

Potential risks of vaccinating children: Myocarditis has been recognized as a rare complication of mRNA vaccines against COVID-19, especially in young adult and older adolescent males [28]. Of the 8.9 million U.S. adolescents aged 12-17 years, who had received Pfizer-BioNTech vaccine, up to July 16, 2021, there were 9246 adverse events reported, of which 9.3% were serious adverse events, including myocarditis (4.3%). It should be noted that most of these cases were mild and resolved spontaneously. The risk, if any, in the younger age groups is unknown.

Vaccine-induced thrombotic thrombocytopenic purpura (VITT) is a rare but potentially life-threatening adverse effect following adeno-vectored COVID vaccines administered to those >18 years [29]. As this vaccine has not been administered below 18 years of age, the risk, if any, in the younger age groups is unknown.

There is also a theoretical risk of COVID-19 vaccines triggering systemic, dysregulated inflammatory response (MIS-C). Post-vaccination surveillance data, with the mRNA vaccines, has not detected any case of MIS-C following vaccination.

VACCINES AVAILABLE FOR PEDIATRIC POPULATION

Internationally, only the Pfizer and the Moderna vaccines have received emergency use authorization (EUA) for use in children between 12 and 17 years of age. The Pfizer vaccine has received EUA for use in children 5-11 years. In India, ZyCov-D (Zydus Healthcare) has received EUA in the age group 12-17 years, while Covaxin (Bharat Biotech Ltd) has received EUA for 2-18 years.

BNT162b2 (Pfizer) Vaccine

In the 12-15-year-old cohort, the geometric mean titer (GMT) of the serum-neutralizing antibodies one month after BNT162b2 dose 2 was higher as compared to the 16 to 25-year- old cohort. This established the non-inferiority and a greater response in adolescents than in young adults [30]. The vaccine efficacy (VE) was 100% (78.1 to 100) in the efficacy trial, with 16 cases in the placebo group and none in the vaccine group [30].

EUA was granted by the USFDA, on May 10, 2020, for use in children 12-15 years of age. This vaccine is now in use in children 12-15 years in European countries, Israel, UK, Dubai, UAE, Singapore, Japan, Philippines, Canada, and Chile. Of the 8.9 million doses of the vaccine administered to adolescents 12-17 years (as of July 16, 2021), serious adverse effects were noticed in 9.3% children. Among the serious adverse effects, myocarditis accounted for 40.3% [24]. The overall rate of myocarditis was 4.3% [31]. Trials for children 6 months to 11 years of age, are ongoing. Children ages 5 to 11 years will receive two-doses of 10 µg each while children less than age 5 years will receive a 3 µg dose.

The SARS-CoV-2–neutralizing antibody GMT in the 5-11 years was 1197.6 (95% CI, 1106.1, 1296.6), as compared to the 16-25 years cohort [1146.5 (95% CI: 1045.5, 1257.2)], proving non-inferiority in the 5-11 years cohort. The reactogenicity and adverse effects profile was similar to that observed in the 16-25 years age group [32]. On 29 October, 2021, EUA was granted by the USFDA for use in children 5-11 years.

mRNA-1273 vaccine (Moderna vaccine)

Adolescents aged 12-17 year received two doses of 100 µg /dose of Moderna vaccines, at 0-28 days. The GMTs of

neutralizing antibodies was 1401.7 (1276.3 to 1539.4) compared to levels of 1301.3 (1177.0 to 1438.8) in young adults, establishing non-inferiority [33]. The VE against COVID-19, 14 days after second dose, in the per protocol cohort was 100% (28.9 to NE: not estimated). On 4 September 2021, this vaccine was granted EUA by the USFDA, for adolescent 12-17 years.The phase 2/3 study (KidCove), is being done in three age cohorts, 6-12 years, 2-6 years and 6 months to 2 years, in two parts. Part 1 is a dose-escalation study. In Part 2, participants will receive two intramuscular injections of mRNA-1273, on 0-28 days, at the dose selected from Part 1. This study involves 13275 participants enrolled from 79 centres across USA [34].

Gam-COVID-Vac (Sputnik)

This vaccine is being studied in 12-17 years in two stages, in stage 1 (Phase I-II) 100 volunteers will be included in two dosing groups and in stage 2 (Phase III) 3000 volunteers will be divided in two age groups, 12-14 years and 15-17 years. Recruitment is ongoing in this trial [35].

Covaxin in Children

A Phase II/III, open-label study was conducted in healthy volunteers in three age groups, 2-6 years, 6-12 years and 12-18 years, with 175 subjects in each group. Each participant was administered two doses of Covaxin (6 µg/0.5 mL) on 0-28 days [36]. Based on data provided by the company to the Special Expert Committee, the vaccine was granted EUA by the Government of India, on October 12, 2021 for use in children 2-17 years. So far, no data is available in the public domain and Drugs Controller General of India (DCGI) approval is still pending.

ZyCov-D

This vaccine has been granted EUA for use in children 12-17 years. The phase 3 efficacy trial done in 28000 subjects included 1400 subjects between 12-17 years of age. No severe side effects related to the vaccine were seen in the 12-18 years age group. The overall vaccine efficacy has been reported as 66.6% [37]. The company has received approval for phase 3 studies in children 2-17 years [38].

Covovax

Covovax, a subunit vaccine developed by Novavax received DCGI approval for phase 3 studies in children [39]. A total of 920 eligible children of ≥2 years of age will be enrolled in this study. The schedule is two doses on days 0-22.

Corbevax

Corbevax, an adjuvanted subunit vaccine by Biological E Limited, had received permission from the DCGI to conduct Phase 2 and 3 clinical trials on children aged 5-18 years [40].

J & J Vaccine

Johnson and Johnson has applied to the Indian drug regulator to conduct a study of its COVID-19 vaccine in adolescents aged 12-17 years [41].

IAP-ACVIP RECOMMENDATIONS

1. The IAP supports the Government of India's decision to extend the COVID-19 vaccination program to children between 2-18 years of age. Children with high-risk conditions should be immunized on a priority basis, as follows:

   i) high-risk population in age group 2-18 years

   ii) children aged 2-18 years living with high-risk individuals

   iii) all population below 18 years of age (in an age de-escalation manner)

Although the Fourth All-India sero-survey showed a positivity of 57.2% in the 6-9 years age group and 61.6% in the 10-17 years age group [43], it should be noted that antibodies and efficacy decline with time. Studies done with the mRNA vaccines have shown that unvaccinated individuals are more than twice as likely to be reinfected with COVID-19 than those who were fully vaccinated after initially contracting the virus. Moreover, the antibody responses were superior in adults hospitalized with COVID-19-like illness, who had prior vaccination with a mRNA vaccine compared to those with prior natural infection [44,45].

The IAP strongly recommends that its members should be made a part of the process of vaccinating children, either by vaccinating in their clinics or as a part of the government initiative.

2. Pediatricians are well acquainted with cold chain, vaccine administration skills, AEFI (adverse events following immunity) recognition and management, and biomedical waste disposal. They also have the infrastructure to maintain the rigorous protocols for vaccination, as put forth by the regulatory authorities. Their rapport with children and their parents will provide the most reassuring situation for vaccinating the children in the clinics and can lessen vaccine hesitancy and vaccine refusal.

Local and district branches of IAP can be involved in the process to disseminate information, education and communication (IEC) activities via print media, social media, radio and television in local languages. This may be important for better acceptance by the parents of COVID-19 vaccines for children.

Pediatricians and parents have to be convinced about

the safety and efficacy of COVID-19 vaccines in children. Study data has to be provided to the pediatricians and parents before embarking on any COVID-19 vaccination programs for children.

3. The IAP supports a school-based vaccination program, as this is the quickest way to achieve maximum immunization coverage. However, this should not be made mandatory, and the parents should be offered a choice of administering the vaccine to their children, in the schools or in the clinics of their pediatricians.
4. School-based centers should have a medical personnel trained to handle emergencies, nursing and administrative staff, emergency medications and equipment, tie-up with the closest hospital for emergency care, and immediate availability of transport to the referral hospitals.
5. The IAP recommends administering currently available COVID-19 vaccines and other scheduled childhood vaccines, either simultaneously or at any interval between them.
6. The IAP recommends the setting up of an active and passive surveillance mechanism for adverse effects of COVID-19 vaccines. This should include surveillance for any link between COVID-19 vaccines and MIS-C, and other adverse effects observed during long-term follow-up. IAP should be a part of this surveillance mechanism. Children have striking differences in their immunological responses to vaccines as compared to adults. Younger children have a more active immune response that may translate into heightened immunological responses and probably reactogenicity. The link, if any, between dysregulated immune responses e.g., MIS-C and vaccination, should be thoroughly studied in the post-marketing surveillance.
7. In children with acute illnesses, the vaccination may be postponed till clinical recovery.
8. Immunodeficiencies due to drugs or diseases are not contraindications for the COVID-19 vaccines to be rolled out for children. The COVID-19 vaccines approved for children are inactivated vaccines.
9. Studies should be initiated to determine the duration of protection and efficacy against variants. This data will be necessary for booster dose recommendations.
10. The government should prioritize research for safer and more effective COVID-19 vaccines for children.

CONCLUSION

India has the largest childhood immunization program in the world, with a well-established and time-tested vaccination network, including cold chain networks. These can be utilized for the COVID-19 vaccination program. India has sufficient manufacturing capability for the vaccine (more than 2.4 billion doses annually), including surgical disposables such as vials, stoppers, syringes, gauze, and alcohol swabs and adequate storage and transportation of the vaccines. Real-time remote temperature monitoring of 29,000 cold-chain points exists through COVID Vaccine Intelligence Network (Co-WIN) vaccine delivery and E-VIN [42].

The vaccination capacity in India has been established with record immunizations of 7-10 million adults in a day. In a span of nine months, India has immunized over a billion individuals with at least one dose of the COVID-19 vaccine. It becomes more important during a pandemic that scarce resources are used efficiently, balancing the principles of equity and justice. The decision to vaccinate healthy children would depend on the availability of one or more suitable vaccines in the quantities enough to immunize the vulnerable population in our country.

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NEWS IN BRIEF

Effect of mixing the vaccines against Covid-19

Vaccines trigger the immune response by imitating an infection, leading to the generation of the memory T-cells and B-cells. This antibody response gets enhanced with the second dose and boosters leading to the generation of antibody levels which will be protective against future infections.But does this response appear / persist, if the type of vaccine has been changed for the second dose?

In a recently published paper by Com-COV-2 Study Group - a multicentre survey network of nine institutions in the UK, researchers studied the effect of mixing of different COVID-19 vaccines on the antibody response. In this study, 1072 participants were studied where the participants were inoculated with a dose of the Pfizer- BioNTech mRNA (BNT162b2), Moderna mRNA (mRNA-1273), Astra Zeneca (chimpanzee non-replicating adenovirus (ChAdOx1 nCoV-19), or Novavax Matrix M-adjuvanted recombinant S protein (NVX-CoV2373) vaccine after an initial dose of Astra Zeneca or Pfizer. Higher levels of binding and neutralizing antibodies were seen with the second dose of Moderna vaccine after a first dose of Astra Zeneca or Pfizer compared to two doses of either Pfizer or Astra Zeneca.

Findings of the present study, provide the data to support the mix and match of COVID-19 vaccines in primary immunization schedules. This will provides the much needed flexibility required to vaccinate the large unvaccinated population in low income countries.

With the emergence of new variant Omicron, it is the need of hour to vaccinate as many people as possible (*BMJ 07 December, 2021*)

Finally something against childhood dental caries

Exact burden of dental caries in India is not known due to poor awareness among the general public about its long term impact on health affecting the growth, early childhood development, learning and limited published literature. A recent meta-analysis estimated that the approxi-mately 52% of children aged 3-18 years have caries in India.

In the absence of a validated risk determining tool, prevention and screening are the best modalities. Recently, United States Preventive Services Task Force (USPSTF) has recommended that the primary care physicians must prescribe oral fluoride supplements to all asymptomatic children aged 6 months to 5 years, living in areas having lesser than 0.6 ppm fluoride levels (fluoride deficient areas). Use of fluoride varnish containing 5% sodium fluoride is also recommended to all childrenaged 6 months to 5 years after the eruption of primary teeth. These recommendations are beyond the routine dental evaluation and referral to the dental health professionals.

More Indian data is needed before recommendations in Indian context are produced to reduce the potentially preventable burden of dental caries in Indian children.
(*JAMA 07 December, 2021*)

Microfluidics: Future of treatment of neonatal jaundice

Neonatal jaundice is the most common morbidity in the first week of life after birth. Almost 60% of term and 80% of preterm babies develop jaundice. Approximately 5-8% of these babies require one or another modality to lower the serum bilirubin levels, in order to prevent neurological damage. Beyond particular levels or in the presence of features suggestive of bilirubin encephalopathy, double volume exchange transfusion (DVET) rapidly lowers the bilirubin levels but in VLBW/ELBW babies it can cause hemodynamic instability.

Researchers at Oregon State University College of Engineering has led to a promising potential therapy for the treatment of neonatal jaundice using microfluidics. Microfluidics is the branch of science which study the behavior of fluids, as they travel through or are confined in microminiaturized devices equipped with channels and chambers. The team has found a simpler and safer alternative to DVET, by treating the patient's blood by circulating it through an external device known as a microfluidic photoreactor. The basic principle is same as that of phototherapy but using the microfluidics helps in lowering the bilirubin at faster rates. Preclinical studies in Gunn rats, using high-intensity light at 470 nm for 4 hours demonstrates a significant reduction in the bilirubin levels without causing an appreciable DNA damage. The rates of bilirubin reduction were similar to those observed with exchange transfusion and on a similar time scale. Mathematical prediction model for the human newborn, suggested that this newer modality will outperform the exchange transfusion at the clinical scale.

Use of microfluidics is a potential promising approach for the treatment of neonatal jaundice, especially in the VLBW/ ELBW, babies without the use of donor blood.
(*Biomicrofluidics 24 November, 2021*)

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Breastfeeding in Coronavirus Disease 2019 (COVID-19): Position Statement of Indian Academy of Pediatrics and Infant and Young Child Feeding Chapter

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Justification: Recent research has provided evidence for lack of transmission of SARS-CoV-2 through human milk and breastfeeding. Updating the practice guidelines will help in providing appropriate advice and support regarding breastfeeding during the coronavirus 2019 (COVID-19) pandemic. **Objectives**: To provide evidence-based guidelines to help the healthcare professionals to advise optimal breastfeeding practices during the COVID-19 pandemic. **Process**: Formulation of key questions was done under the chairmanship of President of the IAP. It was followed by review of literature and the recommendations of other international and national professional bodies. Through Infant and Young child (IYCF) focused WhatsApp group opinion of all members was taken. The final document was prepared after the consensus and approval by all members of the committee. **Recommendations**: The IYCF Chapter of IAP strongly recommends unabated promotion, protection and support to breastfeeding during the COVID-19 pandemic with due precautions.

Keywords: *Guidelines, Human milk, Lactation, SARS-CoV-2, Support.*

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The risk of transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from coronavirus disease 2019 (COVID-19) positive mother to the infant through breastfeeding; and safety of the infants in case of discontinuation of breastfeeding are the major concerns of the healthcare providers and community during the pandemic.

In May, 2020, World Health Organization (WHO), United Nations Children's Fund (UNICEF), Government of India (GOI), Indian Council of Medical Research (ICMR), Centers for Disease Control and Prevention USA (CDC), National Neonatology Forum of India (NNF), Federation of Obstetric and Gynaecological Societies of India (FOGSI), Breastfeeding Promotion Network of India (BPNI) and Infant and Young Child Feeding Chapter of Indian Academy of Pediatrics (IYCF-IAP), recommended early initiation of exclusive breastfeeding for first 6 months and breastfeeding with proper complementary feeding until 2 years and beyond, while using necessary precautions for infection prevention and control, in infants born to mothers with suspected or confirmed COVID-19 [2-9]. These recommendations were based on the health benefits associated with breastfeeding for both mother and child; and relatively mild or asymptomatic illness experienced by infants reported so far. But the rising concerns and insufficient available evidence of mother to infant transmission of SARS-CoV-2 through breastfeeding, contributed to the differing guidelines and recommendations from public health agencies, and international and national authorities [10,11].

Infant feeding practices like avoiding of breastfeeding, promoting artificial feeding and separation of mother and infant has implications on the growth and development and long term adverse health outcomes in the infants. Interruption of breastfeeding causes decrease in milk supply and mother needs help and counselling to restore it later. Hence stopping of breastfeeding should not be advised. India has a high newborn mortality rate and a third of all preterm births in the world [12], and ensuring adequate availability of human milk becomes an important

intervention by the healthcare system for reducing neonatal and infant mortality and morbidity during the pandemic.

Since the last recommendations by the international and national agencies, recent research has provided newer evidence regarding transmission of SARS-CoV-2 from mother to child and through other infant feeding practices. Recent studies have reported increasing titers of antibodies to SARS-CoV-2 in the human milk following vaccination of the lactating mothers, thereby demonstrating the protection against COVID-19 to the mothers and their infants by vaccination [13,14]. Recently GOI has published a circular recommending administration of COVID-19 vaccines in breastfeeding women [15].

With the new available evidence and recent recommendation of vaccination of breastfeeding women by GOI, there is a need to review and update the guidelines to promote, protect and support breastfeeding during the pandemic. This will also help ameliorate the concerns among the frontline healthcare providers, pediatricians, obstetricians and nurses on whether they should encourage the infected mother to breast feed her baby.

OBJECTIVES

To provide evidence-based guidelines to help the healthcare professionals to advise optimal breastfeeding practices during the COVID-19 pandemic.

PROCESS

Formulation of key question was done under the chairmanship of the president of Indian Academy of Pediatrics. A committee of experts was formed by the chairman. It was followed by review of literature regarding risk of transmission and safety of promoting breastfeeding among mothers who are suspected or confirmed positive. The recommendations of other international and national professional bodies were also reviewed in detail. The available data was discussed in an Infant and Young Child Feeding-focused WhatsApp group. Opinion of all members was taken and the final document was prepared after consensus, which was approved by all members of the committee.

RECOMMENDATIONS

The recommendations are tabulated in **Box I.**

Breastfeeding and COVID-19

Breastfeeding not only provides nutrition to the babies but is also benefecial to the mother and the baby in a variety of ways [16-18]. During the SARS-CoV-1 outbreak in 2003, lactoferrin in human milk was known to interact with heparin

Box I Indian Academy of Pediatrics, Infant and Young Child Feeding Chapter Recommendations

- Benefits of breastfeeding and KMC in providing nutrition and prevention of infections cannot be overlooked, which is of crucial importance in developing countries like India.
- Breastfeeding has specific benefits to the infants during COVID-19 pandemic and so encourage, promote, protect and support breastfeeding in all the babies during the pandemic.
- Mothers with suspect or confirmed COVID-19 should initiate early (within one hour after birth) and exclusive breastfeeding and KMC to their babies with due precautions to prevent and control COVID-19 during breastfeeding i.e. ,wearing of appropriate mask, proper washing /sanitizing of the hands before and after feeding session and routinely disinfecting and cleaning the high contact surfaces.
- Mother and baby should stay together as much as possible, unless she is too sick to take care, to have skin to skin contact, to feed their baby responsively and to have access to ongoing support when this is needed, while implementing infection control measures as above.
- If mother is ill, expressed human milk is to be fed to the baby by a care taker who is COVID-19 negative. All care takers should be taught to support mothers specifically in the breast milk expression and feeding the infant with EBM.
- All mothers and healthcare workers attending her should be taught skills of manual expression of breast milk by trained staff.
- For unfortunate cases of mother child separation due to severe illness of mother, mother must be helped to establish breastfeeding through specific re-lactation support.
- If mother's milk is not available, wet nursing (with proper safety procedural precautions) may be adopted or pasteurized donor human milk from a standard human milk bank or comprehensive lactation management center can be fed by the caregiver.
- We recommend the administration of COVID-19 vaccines to all women breastfeeding their infant.
- It is recommended that the lactating mothers and their families should be provided with psychosocial and technical support in confidence building and other aspects of breastfeeding especially in establishing/re-establishing and maintaining the milk supply. Also, counselling and extra support should be provided to the mothers and their family members, by dedicated trained counsellors if possible, regarding breastfeeding and education regarding COVID-19 prevention behaviors.
- Widespread dissemination of this guideline is recommended using various means and presentations, to healthcare workers and public in general. This is especially pertinent when healthcare facilities are disrupted in the pandemic, and IMS promotion lurks stealthily through many avenues.

sulphate glycosaminoglycan (HSPG) cell receptors, interfering with the first anchoring sites of the virus on the cell, and thus preventing the initial contact between the SARS-CoV and host cells. Lactoferrin also blocks the interaction between spike viral protein and HSPC in an angiotensin-converting enzyme 2 (ACE2) receptor, which otherwise results in the full infection [19]. Presence of the oligosaccharides in human milk acts as a barrier to pathogens and as a prebiotic, promote synthesis of a healthy microbiota thereby preventing attachment of viruses to the mucosa and thus preventing infection [20]. Additional protective properties of human milk are provided by the transfer of maternal immune cells like macrophages, neutrophils and lymphocyte and secretory IgG and IgA to the breastfed infant. It also enhances the maturation of both innate and adaptive immune systems and thus protects the infants from infections [17]. Antibodies to SARS-CoV-2 with strong neutralizing capabilities have been isolated in human milk of COVID-19 positive mothers, suggesting active form of protection provided by human milk against COVID-19 [21,22]. Recently, IgA antibodies and other bioactive factors were detected in the human milk from COVID-19 positive mothers suggesting its key role in preventing life threatening infections during COVID-19 pandemic [23].

Risk of Transmission

There is limited but increasing evidence that human milk is not a source of SARS-CoV-2 infection to infants who are breast fed by COVID-19 positive mothers. Transmission of the virus though human milk is the major concern during the COVID-19 pandemic. Earlier studies have reported presence of the virus in human milk. However, these were small studies and case reports with low quality evidence, and failed to show the evidence that the virus was complete and or active in disease causation [21,24-30]. Recent larger prospective cohort studies have not detected SARS-CoV-2 in human milk samples collected from women with symptomatic infection [22,31,32]. Therefore, it cannot be concluded that mere presence of virus in the human milk can be directly related to the transmission of infection from mother to child and these studies confirm that SARS-CoV-2 can rarely get transmitted through human milk. This is further highlighted in recent systematic reviews and meta-analyses [16,17,29].

Recently, GOI and IAP-ACVIP have recommended to vaccinate all breastfeeding women against COVID-19 [15,33]. Studies have demonstrated that maternal vaccination results in high titers of antibodies to SARS-CoV-2 and so is protective for the baby [13]. Based on this recent evidence of specific benefits of breastfeeding during the pandemic, with no chance of transmission of COVID-19 virus through breastfeeding, we need to continue to promote, protect and support breastfeeding.

Separation of Mother and the Baby

WHO guidelines (May 27, 2020) state not to separate mothers with suspected or confirmed COVID-19 unless the mother is too sick to care for her baby, and to provide skin to skin contact including kangaroo mother care. However, because of the insufficient available evidence, some national health agencies advised separation of infants from mothers with suspected or confirmed SARS-CoV-2 and avoidance of breastfeeding [10,11]. A recent study of a public health approach for deciding policy on infant feeding and mother-infant contact in the context of COVID-19 concluded that, deaths among infants affected by a policy of separation and not breastfeeding would be at least 67-times greater than mortality potentially attributable to COVID-19 [34]. The survival benefits of breastfeeding substantially outweigh the very low reported CFR (case fatality rates) among infants with COVID-19. Separation of the mother and infant is therefore unnecessary and is potentially harmful [34]. Mothers should be enabled to stay together as much as possible with their babes, to have skin-to-skin contact, to feed their baby responsively, and to have access to ongoing support when this is needed. Based on the clinical condition of mother and newborn, the decision may be taken on a case-to-case basis (**Table I**).

Recommendations by Other Professional Bodies

In May 2020, WHO updated its recommendation and advised early (within one hour of birth) and exclusive breastfeeding for first 6 months and then appropriate complementary feeding with breastfeeding until 2 years and beyond, while using necessary precautions for infection prevention and control in infants born to mothers with suspected or confirmed COVID-19. Mothers who were too ill to breast feed are advised to feed their expressed breast milk [2]. Other international agencies i.e., UNICEF, CDC, American Association of Pediatrics (AAP), Australian Breastfeeding Association and National bodies GOI, ICMR, NNF, IAP, FOSGI, IYCF Chapter of IAP recommended similar guidelines with respect to breastfeeding during the pandemic [4-8,11,14,35]. The UK Committee for UNICEF (UNICEF UK) Baby Friendly Initiative and Australian Breastfeeding Association have also updated their guidelines based on recent available evidence [14,36].

Contributors: All authors were part of the IAP IYCF team that formulated the guidelines. KB, RMB, ST, RS: conceived the guidelines, prepared the agenda, and executed administratively. KB and RMB: led the discussions and all the members actively participated. RMB, AB, AAK, HBM: reviewed the literature on national and international guidelines. RMB, KB: wrote the first

Table I Feeding Options for the Neonate Born to a Mother With Suspected/Confirmed COVID-19

Mother's clinical status	*Clinical status of the baby*	*Rooming in*	*Feeding option*
Mild COVID-19			
Asymptomatic or symptomatic	Stable	Yes	BF
	Unstable	NICU	EBM>PDHM
Moderate COVID-19			
Stable	Stable	Yes	BF
	Unstable	NICU	EBM>PDHM
Unstable	Stable	Caretaker	EBM>PDHM>Wet nursing
	Unstable	NICU	EBM>PDHM
Severe COVID-19[a]			
Unstable	Stable	Care taker	EBM>PDHM>Wet nursing
	Unstable	NICU	EBM>PDHM
Death of the mother	Unstable	NICU	EBM (wet nurse's) > PDHM

COVID-19: coronavirus disease 2019, BF: direct breastfeeding, EBM: expressed breast milk, PDHM: pasteurized donor human milk. The sign '>' is used to show that the preceding option is the more preferred of the two.

draft. The first draft was peer reviewed by ST, RS, MP, UB, AB, JS, OK, DG, GVB, RK, PG: provided intellectual inputs and overall guidance at every step; PG, GVB, RK: provided the administrative support from the Indian Academy of Pediatrics (IAP) and coordinated between the team and executive board members of IAP. The final document was drafted and edited by KB and RMB. All authors approved the final recommendations of the guidelines.

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NEWS IN BRIEF

Autism - The silent grabber of children

Autism and Developmental Disabilities Monitoring (ADDM) Networkconducts active surveillance of ASD among children living in the areas under 11 ADDM sites across United States.In a recently published report, according to ADDM Network one in 44 children aged ≤8 years were identified to have ASD, the incidence of which has increased markedly from 1in 54 children over two years period. Other important findings - ASD was 4.2 times more prevalent among boys as compared to girls while 35% children were having an intelligence quotient (IQ) score ≤70. Children having ASD with IQ score ≤70 were diagnosed at an earlier age compared to those with IQ score >70.

Is this rise is a result of the early screening and referral or industrilization?As a primary care provider to the children / society we have to think about it.
(*Surveillance Summaries 03 December, 2021*)

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Update to Perinatal-Neonatal Management of COVID-19 Guidelines

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The guidelines for diagnosing and managing perinatal SARS-CoV-2 infection for the Indian context were last updated in May 2020. Newer evidence, the evolution of the pandemic, and its significant impact on mother-infant dyads led us to review and revise the guideline. This article summarizes the salient changes inthe perinatal-neonatal management of COVID-19.

Keywords: *Newborn, Pregnancy, SARS-CoV-2.*

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India witnessed the second surge of COVID-19 in March 2021 due to the SARS-CoV-2 double-mutant strain B.1.617 [1]. During this period, the test positivity rate was more than 20%, and pregnant women were noted to experience severe illness [2].The initial guidelines on diagnosis and management of perinatal SARS-CoV-2 infection in India were published in April 2020 [3] and updated in May 2020. The guideline development group (GDG) updated the systematic review to evaluate new evidence and used the GRADE methodology to develop recommendations [4]. We, herein, summarize the updates on managing pregnant women and neonates exposed to COVID-19. Readers may refer to the version 3 of the complete recommendations for more details [4].

Recommendations for the Management of COVID-19 in Pregnancy and Labor

COVID-19 in pregnancy is associated with an increased risk of severe disease and pregnancy-related compli-cations such as preeclampsia/eclampsia, gestational diabetes, and thrombosis [5,6]. Pregnant women with COVID-19 have a two-fold higher risk of needing intensive care, mechanical ventilation, extracorporeal membrane oxygenation, and higher mortality [7]. Increased maternal age, obesity, pre-existing comorbidity, chronic hyper-tension, diabetes, and preeclampsia are associated with severe illness [7]. The risk of stillbirth, intrauterine growth restriction, and preterm birth is increased twofold. The updated recommendations are listed below:

i) The updated COVID-19 testing strategy for pregnant women (**Table I**) is based on the Indian Council of Medical Research (ICMR) recommendations [2].

ii) The decision to manage a COVID-19 positive pregnant woman at home or in a health facility depends on obstetric risk factors, comorbidities, the severity of COVID-19 illness, and social conditions. Women with obstetric complications, moderate or severe COVID-19 illness, unsuitable social conditions, and situations where telemonitoring is difficult should be admitted to a health facility. Home quarantine is cost-effective, but tele-consultation services are mandatory for monitoring.

iii) Maternity care services and other specialty services are available at Dedicated COVID Health Centers (DCHC) and Dedicated COVID Hospitals (DCH). All suspected or confirmed COVID-19 pregnant women should deliver at DCHC or DCH as per disease severity and availability of obstetric and neonatal services.

iv) The use of steroids in pregnant women with COVID-19 depends on fetal and maternal indications (**Table II**). Dexamethasone given for ten days or until discharge to hospitalized patients with moderate to severe COVID-19 on oxygen or respiratory support has been shown to reduce mortality by 30% [8]. For fetal lung maturity, dexamethasone is given 6 mg IM every 12 hours for four doses. When used solely for maternal indications, alternate steroids (methylprednisolone, prednisolone, or hydrocortisone) can be considered based on availability, cost, and individual preference [9,10].

v) In asymptomatic/mild disease, pregnancy should be continued until term or based on obstetric indications. The mode of delivery should be guided by obstetric indications, cardiorespiratory stability, and oxygenation. COVID-19 itself is not an indication to terminate a

Table I Updated Recommendations for COVID-19 Testing Among Pregnant Women

Testing situation	*Surveillance in containment zones and screening at points of entry*	*Surveillance in non-containment zones*	*Hospital Settings*
Indications for testing	Test irrespective of symptoms	Test if a history of travel to a high-risk area in the last 2 wk Symptomatic Direct contact with a laboratory-confirmed case	All pregnant women in or near labor and hospitalized for delivery
Preferred test in order of priority	RAT RT-PCR or TrueNat or CBNAAT	RT-PCR or TrueNat or CBNAAT RAT	RT-PCR or TrueNat or CBNAAT RAT

Note: No emergency procedure (including deliveries) should be delayed for lack of test. Pregnant women should not be referred for lack of testing facilities. All arrangements should be made to collect and transfer samples to testing facilities.

Table II Recommendations for the Use of Steroids in Pregnant Women With COVID-19

Indication for steroids		*Setting*	*Dose schedule*
Fetal lung maturation	*Maternal COVID-19 illness*		
Yes	No	All settings	Dexamethasone 6 mg IM every 12 hours for four doses, irrespective of maternal COVID-19 status.
No	Yes	Resource limited	Dexamethasone 6 mg/day PO/IV for ten days or until discharge, whichever is earlier.
		Resourceful (available, affordable, and maternal preference for dexamethasone alternatives)	Methylprednisolone or Prednisolone or Hydrocortisone in equivalent doses for ten days or until discharge, whichever is earlier.
Yes	Yes	Resource limited	Dexamethasone 6 mg IM every 12 hourly for four doses (2 days) followed by 6 mg/day PO/IV for eight more days or until discharge, whichever is earlier.
		Resourceful (available, affordable, and maternal preference for dexamethasone alternatives)	Dexamethasone 6 mg IM every 12 hours for four doses (2 days) followed by Methylprednisolone or Prednisolone or Hydrocortisone in equivalent doses for eight more days or until discharge, whichever is earlier.

pregnancy or perform a caesarean section. However, a caesarean section may be indicated to manage respiratory failure in critically ill pregnant women with refractory hypoxemia.

vi) Symptomatic pregnant women with fever >39°C despite the use of antipyretics, moderate or severe COVID-19 illness, or comorbid conditions (poorly controlled hypertension or diabetes, preeclampsia, pre-labor rupture of membranes, bleeding per vaginum) should be admitted to a DCH having an intensive care unit with multidisciplinary support. Management of COVID-19 illness in pregnancy is provided in **Box I**.

vii) COVID-19 vaccines can be offered at any gestational age in pregnancy, but the second dose should preferably be completed before the third trimester. Physicians should inform pregnant and lactating women of the risks of COVID-19, the benefits of vaccination in the local epidemiological context, and limited safety data and assist them in the informed decision-making process.

Recommendations for the Management of Neonates With COVID-19

Among neonates born to COVID-19 positive mothers, the proportion with a positive test ranges from 0.5% to 13% (median 2%) [5,6]. The NNF COVID-19 registry observed a 10% positivity rate [11]. This variability is explained by the variation in testing policy and the population profile.

i) Neonatal resuscitation should follow standard guidelines, and providers should use appropriate personal protective equipment (PPE). Delayed cord clamping and skin-to-skin care at birth should be practiced for all stable neonates born to COVID-19 positive women. The risk of postnatal COVID-19

Box I Updated Management of COVID-19 During Pregnancy and Labor

Asymptomatic or Mild illness

Home isolation with active surveillance by telemonitoring or admission to a health facility based on obstetric risk factors, comorbidities, and social conditions

Indications for hospitalization: Worsening dyspnea, unremitting fever >39°C despite antipyretics, inability to tolerate oral hydration and medications, persistent pleuritic chest pain, confusion, or obstetric complications.

Home care comprises supportive measures, e.g., hydration, adequate rest, and frequent ambulation with increased activity as tolerated.

The use of ivermectin or doxycycline is contraindicated.

Vitamin C, Vitamin D, and Zinc are not recommended for the treatment of COVID-19.

Moderate or severe illness

Admit to a dedicated COVID hospital with a high dependency unit or intensive care unit

Oxygen therapy: Maintain SpO2>94%. Awake-prone positioning if feasible and acceptable.

Remdesivir: Remdesivir should not be withheld from pregnant patients if indicated (patients requiring oxygen therapy, especially early in the disease course). Guidelines issued by the government about rationale use of remdesivir should be followed

Venous thromboembolism prophylaxis: All pregnant women with COVID-19 should be assessed for the risk of venous thromboprophylaxis and prescribed prophylactic anticoagulation with low molecular weight heparin/ unfractionated heparin (e.g., enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) and continued for ten days following hospital discharge unless there is a contraindication.

Tocilizumab: The use of tocilizumab (interleukin-6 receptor antagonist) should be considered for women meeting the criteria, i.e., hypoxia and systemic inflammation. During pregnancy, decisions about tocilizumab administration must include shared decision-making between the pregnant woman, family, and the healthcare provider.

Monoclonal antibody: Monoclonal antibody therapy such as bamlanivimab-etesevimab and the casirivimab-imdevimab combination should not be withheld from pregnant patients if they qualify for its use (non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and hospitalization) after a discussion of the potential benefits and risks.

Convalescent plasma therapy: There is no role for convalescent plasma therapy

transmission can be reduced if mothers wear a triple layer mask and strictly adhere to respiratory etiquettes. The use of filters with T-piece/bag-mask devices and aerosol boxes forintubation is not recommended.

ii) Mother-infant dyads should room-in, and exclusive breastfeeding should be encouraged regardless of maternal COVID-19 status. When direct feeding or rooming-in is not feasible, the mother's expressed milk should be provided.

iii) Kangaroo care is recommended for low birthweight neonates regardless of the COVID-19 status of the mother or neonate.

iv) Symptomatic neonates with suspected COVID-19 should be isolated in a COVID designated area. The suspect and confirmed COVID-19 cases should be segregated.

v) All forms of respiratory support are at risk of generating aerosols, and healthcare providers must wear appropriate PPE. The area providing respiratory support should preferably be a negative air pressure area.

vi) The updated testing strategy for various scenarios is provided in **Table III**. Serologic testing (total, IgM, or IgG antibody levels) is not recommended to diagnose COVID-19 in neonates.

vii) Neonates with asymptomatic or mild COVID-19 require no additional routine laboratory tests. Those with moderate or severe COVID-19 illness should undergo relevant biochemical, hematologic, and coagulation tests to assess the complications and rule out alternate diagnoses. Neonates with severe COVID-19 requiring mechanical ventilation, in whom alternate causes such as neonatal sepsis have been ruled out, may benefit from dexamethasone, 0.15 mg/kg once daily for 5-14 days. Specific anti-COVID-19 treatment (remdesivir, lopinavir/ritonavir, chloroquine/ hydroxychloroquine, ivermectin, or interferon) and adjuvant therapies (intravenous gamma globulin) are not recommended.

viii) Stable mother-infant dyads may be discharged from the health facility after 24-48 hours of delivery if discharge criteria are met, and birth vaccination is completed. All COVID exposed neonates should be followed up for at least 14 days and preferably till 28 days of life.

ix) The GDG recommends using the WHO case definition for MIS in children for the neonatal age. A 2-tiered approach – proposed by the American College of

Table III Updated Recommendations for SARS-CoV-2 Testing Among Neonates

Scenario	*Recommendations*	
	Timing of first test	*Repeat testing*
Suspected perinatal transmission: (Mother with COVID-19 detected within 14 days before or within 2 days after delivery)	Between 24-48 hours of age. Rooming-in should not be postponed if testing is delayed. In case of early discharge, take a pre-discharge sample.	A repeat test is desirable at 5-7 days of age (or earlier if the neonate becomes symptomatic). Repeat testing can help to prevent transmission from the neonate (who is likely to be asymptomatic even if infected) to other family members.
History of exposure to personnel with COVID-19 (including mother or family member or healthcare provider)	Asymptomatic high-risk contacts to be tested once between day 5 and day 10 of coming into contact (if symptomatic, see below)	-
Symptomatic neonates (irrespective of history of exposure) with onset at or beyond 48 hours of life and presenting with acute respiratory (respiratory distress or apnea with or without cough, with or without fever) or sepsis-like illness (fever, lethargy, poor feeding, seizures or diarrhea).	At the time of the first evaluation. Immediate RAT, if available, can help decide the transfer of the neonate to an appropriate area.	If negative, repeat the test in 24-48h if the index of suspicion is high. If the neonate requires ongoing hospital care because of prematurity and its complications, documentation of negative RT-PCR is desirable before shifting to a non-COVID area.

CBNAAT: cartridge-based nucleic acid amplification test; COVID-19: novel Coronavirus disease; RT-PCR: reverse transcriptase-polymerase chain reaction, SARS-Co-V-2: severe acute respiratory syndrome coronavirus 2, TruNat: chip-based RT-PCR test.

Rheumatology is recommended for evaluation of a suspect case. Treatment options include intravenous immunoglobulin, methylprednisolone, and aspirin (Web Fig 1). Neonates with suspected MIS should be managed at tertiary care hospitals where multidisciplinary and cardiology support is available.

CONCLUSION

The updated perinatal COVID guideline addresses the use of antenatal steroids, COVID vaccination for pregnant and lactating women, testing and treatment of COVID-19, and the multisystem inflammatory syndrome in neonates.

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The paper attempts to capture the development of the Department of Pediatrics, Safdarjang Hospital, New Delhi, from a historical perspective in its founding years in late 1950s, showing the progress from its nascent state as a part of adult medicine to a full-fledged independent department with state-of-the-art advances in the 2020s. From an ordinary Pediatrics Department, it was reorganized radically to expand clinical facilities as well as education and research by innovative methods, developing subspecialties including an upgradation of the neonatology division, simultaneously establishing linkages with community level centres. The pioneering workshops for training obstetricians and pediatricians paved the way for initiation of multiple such national workshops across the country, by the Government of India, for establishment of neonatal care units countrywide. It was instrumental in the formulation of 'Essential Newborn Care' as the first national newborn care program and later a new concept of 'Mother and Neonatal Care Unit (M-NICU)' for perinatal care, apart from many other contributions for shaping national policies.

Keywords: *Child health programs, Iconic institution, M-NICU, Pioneering, Workshops.*

The time period between 1940 and 1960, of the last century, was one of the most challenging periods for child health in the country. The infant mortality rate was over 150 and the neonatal mortality rate over 100 [1]. A few cities in the country like Mumbai, Chennai, and Delhi had pediatric care facilities, with only a handful of pediatricians. The country had no specific child health program, and the child was considered and treated as a mini adult. Pediatrics was not even recognized as a specialty and was part of general medicine. The transition of pediatrics began in the sixties and the seventies. It formally separated from medicine and became an independent subject, and newborns became the domain of pediatricians. Subsequently, pediatric sub-specialties developed, and child health found its place in the national five-year plans, with dedicated health policies and programs.

The Department of Pediatrics, Safdarjung Hospital, was an integral part of this historic journey. The distinctive innovative clinical services and the path-breaking pioneering research carried out at this institution has influenced national policies, thereby creating an indelible footprint in the history of pediatrics in India.

The Initial Years: 1950-1960

The hospital was established in southern Delhi in 1942, and was rebuilt in the fifties as a multi-specialty hospital. The pediatrics department had three pediatric and one pediatric surgery unit, each with 50 beds, and was headed by a pediatrician and a pediatric surgeon, respectively. The outpatient department functioned from a barrack, while emergencies were attended to in the hospital's emergency department.

The Department of Obstetrics and Gynecology included an outpatient department (OPD) and casualty, and two separate labor rooms, one for aseptic cases and the other for infected cases. In the instance where a newborn had delayed cry at birth, the traditional custom of slapping the buttocks was performed by the obstetrician. Pediatricians attended deliveries done by caesarean section, but not normal deliveries, unless called for.

The newborns were transferred to their mothers/special care nursery, after initial observation. Two separate large rooms without ancillary facilities functioned as Special Care Nursery. The status of newborn care during this decade is summarized in **Box I**.

1960-1978

The author (SKB) joined the Department in 1965. Dr. Shanti Ghosh, who joined as Head, Department of Pediatrics in 1966, radically reorganized the Department along with Dr. S Vaishnava, Dr. GP Verma, and SKB.

Clinical Services

General Pediatrics: While the three-unit system continued as before, a unique OPD service was established with the concept of 'under-five clinics.' Separate sections designated for anthropometry, immunization, nutrition, and consultation were introduced for the benefit of each patient. The nutrition section visually explained the needs of a young child utilizing a typical Indian *thali*, common in

Table I Status of Newborn Care (1956-66)

No of Births	: 7064
Neonatal mortality rate	: 43
Pediatrician	: Visiting
Residents	: Shared with General Pediatrics
Nurses	: Shared with Obstetric wards
Newborn-hospital status	: None
Newborn Care	
• At Birth	• LSCS and emergencies when called • Ambu bag, but no warmer or O2 hood
• Primary level	• Initially in one room for observation • Later rooming in with mother • First clinical examination 24-48 hrs • One round and examination per day • No pre-written protocols, case records

every Indian household. Every child received a 'Road to Health Card', adapted from David Morley's 1974 Health Record, detailing his/her visit.

Sub-specialties: The Department established sub-specialties of pediatric nephrology and juvenile diabetes headed by Dr Sarla Vaishnava, and pediatric cardiology led by Dr SK Sanyal, trained at prestigious institutions abroad.

Neonatology services, which till then were in a primitive state and relatively neglected, were organized as an independent neonatal unit by Dr. Ghosh, with SKB as head. The task to reorganize it was extremely challenging.

Meeting the Challenge

The challenges were met head-on with innovation and collaboration with allied specialties, chiefly obstetrics. The first innovation was creating and implementing a mandatory orientation and training in basic newborn care, imparting skills like resuscitation at birth, to all the staff at the beginning of their postings. Alongside, we proactively communicated with our obstetric colleagues to discuss common clinical problems and devise solutions. This led to increasing mutual trust and resulted in the unexpected gesture of transferring two unused labor rooms to the neonatal unit by Dr. Pinto, Head of obstetrics and gynecology department. This helped reorganize and establish the newborn unit by creating two 25-bedded special care nurseries **(Fig. 1)**.

Lack of equipment in our nurseries was overcome by improvising techniques like using electric light bulb lamps as infant warmers, ordinary needles modified to be used as scalp vein needles, and large bore needles (liver biopsy needle) with standard catheters for exchange blood transfusion, and infant carrying baskets for transporting newborns (**Fig. 2)**.

Regular interdepartmental meetings were started, which included monthly obstetric-neonatology meeting to discuss monthly audit, perinatal mortality conferences with pathology department, interaction with microbiology department for infection surveillance, with radiology, clinical pathology departments and blood bank. In addition, there were daily morning review meetings within the unit to discuss the past 24 hour events, which provided the faculty and trainees a multi-dimensional learning environment well beyond just case management.

All these changes enabled us to introduce the innovation of protocol-based pediatric and neonatal care. Our neonatal unit protocols became representative of the institution and formed the basis of national guidelines.

Problem Focused Approach

The reorganization described above brought striking improvement in the quality of newborn care. But to deal with continuing high mortality in very low birth weight (preterm, IUGR), infections, birth asphyxia, and extreme weather, we adopted a problem-focused approach grounded in research.

Fig. 1 Safdarjang Hospital (a) Obstetric and Newborn wing, and (b) the rooming in practice.

Some such strategies included classification of newborns at birth as appropriate for gestation (AGA), small for gestation (SGA), and large for gestation (LGA) so as to identify high-risk infants [2,3]. A critical review of admissions in extreme weather lead to the diagnosis of Primary Cold and Heat Injury of the newborns [4,5]. These conditions were described for the first time in the country and led to the use of low temperature reading thermo-meters in nurseries, and eventually to air conditioning of labour rooms, nurseries, and postnatal wards. Studies on gastric aspirate cytology helped in the early diagnosis and treatment of intrauterine infections and pneumonias [6]. The study regarding early discharge versus standard discharge of low birth weight newborns from special care nursery, established early discharge of low birth weight infants at 1.3-1.4 kg weight, to be as safe as standard practice and prevented deaths by overcrowding and nursery acquired late infections [7].

These and other studies carried out by the Safdarjang Hospital team changed established practices, improved the outcome of newborn babies, and were adopted nationally.

1979 -1985

Newborn Care Comes of Age

Dr Shanti Ghosh and Dr Vaishnava retired by 1979 and SKB took over the department as Head with a young team. In 1980, in response to a concern raised by the then medical superintendent, Dr NL Pramanik, regarding static neonatal mortality rate and the need for upgrading the neonatal unit to a tertiary level intensive care facility, a detailed proposal was formulated after diligent review and deliberations amongst the clinicians and experienced nurses. The proposal included servo-controlled warmers (open-infant-care systems against standard Isollet incubators for visibility, ease of nursing care, maintenance, lower infection rates, and being user friendly), pulse oximeters, portable transcutaneous vital sign monitors (as opposed to fixed monitors), blood-gas analyzers, oxygen analyzers, and flux meters for measuring phototherapy light intensity. This resulted in the establishment of a state of the art neonatal intensive care unit in 1980 (**Fig. 3**). These measures changed the administrators' viewpoint about newborn care in India.

Intensive Care to Primary Care

The hospital-based newborn care at Safdarjang Hospital highlighted the country's primary need for all three levels of care from primary to tertiary level, to provide affordable, quality newborn care for every infant, irrespective of his/her birth weight, gestational age, place of birth, and the person conducting the delivery.

We, therefore, devised an Indian Council of Medical Research (ICMR) pilot study, "A concept of regionalization of perinatal care." which required establishing primary care at a Primary Health Care Centre at Bhorakala and Secondary Care Centre at Government Civil Hospital, Gurugram, Haryana and Tertiary Care Centre at Safdarjang Hospital, New Delhi in a radius of 70 km. This community-based study involved a primary health centre, a district hospital, and an apex hospital with linkages and referral systems without dedicated, supportive transport and tele-communications services but with a referral available to a higher centre.

Fig. 2 Indigenous improvised equipment.

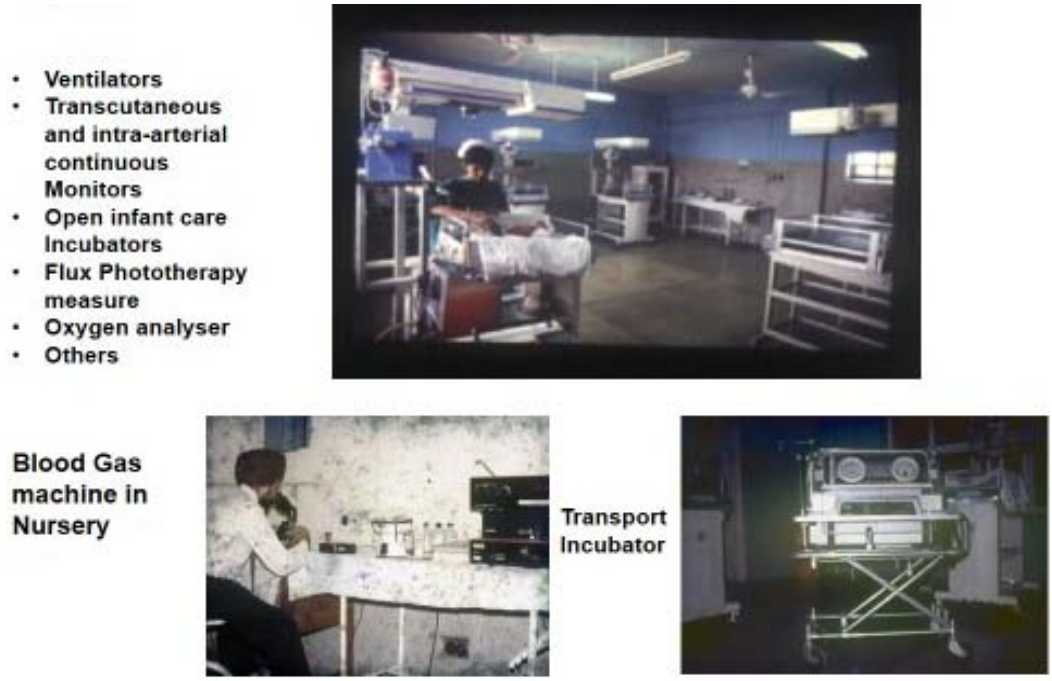

Fig. 3 Neonatal intensive care unit, Safdarjang hospital, 1980.

It was a successful project, demonstrating the feasibility and cost-effectiveness of establishing the three levels of newborn care, equipping them appropriately and training the staff from the dais and traditional birth attendants to auxiliary nurse midwives (ANM), medical officers, nurses and pediatricians, obstetricians to create a functional and practical two-way referral system between community level and apex centers **(Fig. 4)** [8].

Education, Training and Continuing Medical Education

The department firmly believed that in addition to ongoing academic programs, training workshops and continuing medical education was needed across the country. One of the first such training courses was the Government of India – WHO 'Neonatology Orientation Course' by Prof Beryl Corner from Bristol, UK and Prof. Ghosh in 1969.

The success of this initial workshop paved the way for initiation of multiple National Neonatology Training Workshops across the country, in 1979, by the Government of India, in collaboration with WHO. SKB became the first Indian WHO Consultant for the workshops, organized at SAT Hospital and Medical College, Trivandrum, Kerala (1979), SCB Medical College, Cuttack, Odisha, (1980) and the Safdarjang Hospital, New Delhi (1980) for the purpose of training pediatricians and obstetricians to establish such units in their respective states. The department also organized the first pediatric intensive care workshop in 1983, by Government of India, for 22 Heads of the departments of pediatrics across the country.

The department participated in national and international conferences. It progressed from an occasional paper initially to wider publicity with each passing year. Our presentations graduated from an era of epidiascope transparencies to black and white slide projection to innovatively designed colored graphic data presentations.

Research and Publications

Some of the notable research contributions from the department include the development of the Indian Cognitive Development assessment scales; new understanding of common childhood infections and their treatment modalities in the Indian environment, feasibility of mass immunization campaigns [9] and modifying immunization schedules like the efficacy of three doses of the oral polio vaccine [10], need for a BCG booster dose [11], and early measles vaccination.

In neonatology, research accomplishments began with Dr Ghosh's classic paper on questioning the rationale for the international definition of low birth weight [12], describing undetected severe hypothermia causing cold injury and death [4], longitudinal studies from birth to adulthood to assess long-term effect of low birth weight [13], a landmark perinatal mortality study in over 27 000 births with autopsies in 50% of the perinatal deaths, feasibility of regionalization of perinatal care at national

Fig. 4 The triage system of newborn care.

level [14], demonstrating efficacy and safety of Low solute ORS solution in 0-3 months infants and risk of significant hypernatremia with standard WHO ORS solution [15], mid-arm-circumference (MAC) as a marker of low birth weights in community where infant weighing scales are not available [16], identification of high risk families and mothers and outcome of their off springs in rural and urban slum communities [17] and many others.

But, the landmark research milestone was the founding of 'The New Delhi Birth Cohort' (NDBC) in 1968 by Dr S. Ghosh, Dr IM Moriyama, and SKB in a 12 sq. km South Delhi community with 8181 cohort born to ever-married women followed from pre-pregnant state to pregnancy and childbirth. Our book [13] describes the five-decade incredible journey of this birth cohort, which is now a four-generation family cohort, and its enormous contributions to national and international research with respect to fertility, impact of child mortality on family planning, child survival, growth and cognitive development, the long-term effects of birth weight, gestation, fetal growth and childhood growth on adult health, cardio-metabolic disorders and human capital.

THE 21ST CENTURY: THE YEARS 2001- 2020

The current century saw rapid state-of-the-art advances in the department and its subspecialties, with physical restructuring, diagnostics, and adoption of standard evidence-based operating procedures aimed to reduce duration of hospitalisation and hospital acquired infections. A multidisciplinary comprehensive Early Intervention Child Development Assessment Centre (CDAC) was also established.

Emergency Triage and Pediatric Intensive care Unit (PICU): In 2017, the Department established the Emergency and Triage services in the New Emergency Block of the hospital, with the latest facilities, including continuous electronic monitoring, point of care diagnostic microbiology and biochemistry laboratories, blood bank, and supportive super-specialties like Paediatric Surgery, Neurosurgery, and Intervention Radiology. The paediatric emergency services are located on a separate floor with facilities to stabilize and monitor the critically ill. A unique feature is the provision of optimum care facilities for extramural neonates, which comprise almost 30% of pediatric admissions. Besides these, the Department has well equipped 20-bedded Paediatric Intensive Care Unit (PICU) for critically ill patients. Introduction of the concept of emergency assessment, triage and PICU services has significantly decreased the mortality within the first 24 hours of admission.

The department now has a dedicated hemato-oncology unit providing day-care based chemotherapy as well as a leukemia ward. In addition a separate thalassemia day-care unit is present, supported by a point of care lab.

Neonatology: A sharp (75%) increase in annual deliveries including a substantial proportion of high-risk pregnancies, led to the development of the novel concept of 'Mother in Neonatal Care Unit' (MNICU) (**Fig. 5**), a first of its kind model in Asia, in 2017. It created the concept of 'zero separation' involving couplet care, with the mother staying 24×7 in MNICU with the baby, actively partici-pating in the care from birthing till discharge.

The M-NICU concept brings a paradigm shift in the institutional management of small and sick neonates, especially relevant for the developing world. It opens out the possibility of introducing a four tier newborn care system with primary, secondary and MNICU and tertiary intensive care nursery. M-NICU is likely to be most practical, affordable, cost effective, humanised, mother incentive-based care resulting in significant reduction in nursery overcrowding and infections, successful establishment of breast feeding (Kangaroo care) and improvement of survival. The Government of India is also contemplating creation of such units across the country [18-20].

National and International Child Health Programs

With an active participation in the public health initiatives of Government and Non-Government programs, the department became a primary centre for scaling up child health interventions across the country, and the nodal centre for the Delhi Newborn Birth Defect Surveillance. The Ministry of Health and Family Welfare and the Ministry of External Affairs has also given the department the responsibility to prepare a module of Facility Based Newborn care (FBNC) and expand the mother, newborn, and child health programs, including immunization through the SAARC platform in SAARC countries.

It became a centre for WHO fellowship in Basic and Advanced Neonatology and Adolescent Medicine and established the country's first adolescent training centre at Safdarjung Hospital Adolescent Health Network (SHAHN). Multi-centre collaborative studies with the support of national and international organizations including DeNIS study, randomized controlled trials on probiotics, vitamin D and immediate Kangaroo Mother Care are some of the research activities of this century [21-24].

Fig. 5 Mother with her newborn in a maternal-neonatal intensive care unit (MNICU)

IMPACT ON CHILD HEALTH POLICIES

The department of pediatrics at Safdurjung hospital has had a huge impact nationally and internationally from its early days by its ever-evolving multifaceted clinical and research contributions. Nationally relevant researches led to revised national schedule of five doses of Oral Polio vaccination in UIP in 1985, inclusion of Low birth weight in Child Survival and Safe Motherhood program (1992), the formation of the national "Essential Newborn Care" program at the district level for the Government of India and its inclusion in the National Child Survival and Safe Motherhood program 1994. The Essential Newborn Care Program remains the pivot for all subsequent national newborn care programs from RCH I in 1997 to Newborn Action Plan 2014. The introduction of Dakshita 2015 and LaQshya 2017 is the fallout of the perinatal autopsy study's findings. The low solute ORS for oral rehydration is now universally accepted. The most recent 'Zero Separation' policy in creating MNICU, has given the developing world a much needed wholesome concept in perinatal and neonatal care.

The finding of 'the first 1000 days' in a child's life as the golden period for nutrition intervention in 'The New Delhi Birth Cohort' studies, has resulted in 'POSHAN,' the national nutrition program. The NDBC iconic magnetic data storage tapes in ASCII coded format 2400 Ft. spooler are a part of Indian Council of Medical Research (ICMR) Museum and are displayed as national treasure.

Awards and Honors

The distinctive contributions by the members of the Department earned them numerous accolades from national and international organizations. Prof Shanti Ghosh and SKB became President of Indian Academy of Pediatrics (IAP) and were honored by Medical Council Of India, ICMR, National Academy of Medical Sciences (NAMS), Indian Academy of Paediatrics (IAP), National Neonatology Forum, India (NNF), and the APPSEAR. SKB also became the Editor-In-Chief, *Indian Pediatrics* and Founder President NNF, India.

Several pediatricians of the country including Late Prof MK Bhan, Dr Soumya Swaminathan, Prof Vinod Bhutani, Prof Vinod Paul, Prof HPS Sachdev, Dr Panna Choudhary, Prof S Ramji and many others worked in their early formative years in the Department, imbibing the spirit, work ethics, philosophy and commitment to public health, and became well known nationally and internationally for their outstanding contributions [25].

WHAT EMBODIED THE DEPARTMENT?

The department became known for its invigorating academic and progressive environment. It had a cordial and

lively atmosphere, not only by providing freedom to learn and explore in academics and research, but also by the 'coffee club' culture where staff could interact informally with each other. The annual Diwali and Christmas celebrations, the movies, puppet, and magic shows for in-patients added to boost the team spirit and staff morale.

The presence of the offices of Indian Pediatrics and NNF housed in the department, and multiple on-going collaborative research work motivated the young physicians for research. The department believed in identifying young talent and providing opportunities to them. A crucial factor promoting progress was the congeniality between doctors and the nursing staff and para-clinical departments which enabled the department to accomplish its intended goals and objectives and attain enviable heights.

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Survival Analysis: Where, Why, What and How?

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Durations of any event, such as duration of hospitalization, is usually found to have a highly skewed distribution and incomplete values due to dropouts and limited follow-up. The usual methods of statistical analysis are, therefore, not applicable. The method of survival analysis is a nonparametric method and is designed to overcome these problems. Survival is a generic term and is used for any time-to-event data. The entire survival pattern at different points in time is studied by the Kaplan-Meier method under certain conditions. Log-rank method is used to compare survival pattern in two or more groups. Hazard is the rate of occurrence of an event per unit of time and studied by Cox method. The concept of survival and all these methods of survival analysis are briefly discussed in this short note in a non-mathematical format for medical audience.

Keywords: *Hazard rate, Kaplan-Meier method, Log-rank test.*

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Survival analysis is an important concept in biostatistics with extensive usage in medical research. This is a multi-faceted technique and has evolved as a full subject. For medical researchers, we herein discuss, in brief, where and why survival analysis is needed, what it is, and how it is done in practical settings.

WHERE AND WHY?

A special quantitative measurement in medicine is the time taken for the occurrence of an event. This requires that the time of beginning and the time of the end, both, are well defined. Duration of hospitalization is a commonly studied duration, measured from the time of admission to the time of discharge or death. The effect of oxygen saturation targets on the duration of respiratory support, oxygen therapy, and hospitalization in extremely preterm infants [1] and continuation duration after contraception insertion among adolescents and young adults [2] have been recently studied using the method of survival analysis. Such durations have two special features that make them distinct from other quantitative measurements and render the usual statistical methods inapplicable.

Censoring

Quite often, the full duration is not observed such as duration of hospitalization in the case of a patient who left against medical advice (LAMA) or when a patient is transferred. Such incomplete observations more commonly happen when a follow-up of patients is planned for, say, two years, but the patient becomes untraceable or uncooperative after one year, or when the event under consideration, such as death, does not occur within the two-year period. The latter would mean that the survival is known for at least two years, but the full duration is not known. Such truncated durations are called 'censored', meaning thereby that the observation is incomplete.

This censoring is of three types. The example we have cited is for 'right censoring' where the endpoint has not reached at the time of the last observation. In rare cases, it could be 'left censoring' also where the beginning point is not known but the end point is known. This can happen when the interest is in the duration of disease, but the day of onset is not known or cannot be assessed. This has happened for many COVID-19 cases. The third could be 'interval censoring' where the exact duration is not known but only the interval is known. If surgery patients are followed quarterly for any complication, the only information available in the case of complication is that it occurred somewhere between, say, 9 and 12 months when no complication was reported at 9-month follow-up but reported at 12-month follow-up. Thus, the exact time of complication is not known. The present communication is restricted to only the right-censored data because that is the predominant type of censoring in medical research.

Skewed Distribution of the Durations

The second distinctive feature of durations is that the duration is generally relatively small for most cases but long or very long in some cases. For example, the duration of hospitalization in most heart surgery cases could be around 7 days but some develop complications and stay for 30, 40, or even 90 days. Thus, the statistical distribution of most

durations is highly skewed to the right. This makes the usual Gaussian based parametric analysis inapplicable and either logarithmic transformation or non-parametric methods are needed for analysis. In the case of highly skewed distribution, mean and standard deviation are misleading, and recourse to median and inter-quartile range (IQR) is taken.

Due to these two special features of data - censored values and highly skewed distribution - the usual statistical methods for quantitative measurements are not applicable to durations and a special method, called survival analysis is required. This is a nonparametric method and can be used for any kind of duration data. Yet, the method requires a reasonable sample size, at least 30 in each group, preferably 50 or more.

WHAT IS SURVIVAL ANALYSIS?

The method of survival analysis is needed when the study requires survival experience at different points in time. The term 'survival' in this case is generic and could mean any event such as discharge from the hospital or occurrence of a complication. Survival analysis tells us the percentage survived at different points in time – one year, two years, etc. - even when some of the durations are censored. It plots the survival pattern over time, called the survival curve, which can be used to draw inferences. An example is given later that would fix the idea.

If the interest is not in survival pattern but only in the percentage of patients who survived for, say, at least 3 months or at least 1 year, and if the duration is available for all (no censored values), there is no need of the method of the survival analysis. This percentage can be calculated in the usual manner and the inference regarding it being a prespecified value or for difference between two groups (such as one with treatment A and the other with treatment B) can be drawn as usual for proportions. This can be done even when the distribution of the duration is highly skewed. However, if some values are censored, survival analysis would be needed even for this proportion. Similarly, median survival time can be directly obtained without going through the process of survival analysis when the duration for all the subjects is known but this too would require the method of survival analysis if some durations are truncated (censored). Survival analysis is also needed if the entire survival pattern at different points in time is under study, whether the observations are censored or not.

Survival analysis requires that the duration for the occurrence of the event under investigation is recorded for each subject and the censored durations are marked. Consider the survival of children living with human immunodeficiency virus (HIV) [3]. Suppose these are followed up for 12 months after start of the antiretroviral therapy (ART). The duration of survival for 10 patients may be as shown in **Table I**.

The plus sign is for censored values. The third patient migrated and lost to follow-up after 4 months but was alive at that time. Patient numbers 5, 8, and 9 were alive at 12-month follow-up visit but were not followed-up thereafter. Their duration of survival is known at least 12 months but not beyond. Note in this case that mean or median duration of survival and percentage surviving 12 months or at any other time cannot be directly computed because of censored values.

Two extensions of survival analysis are commonly used. First, to compare the survival curves of two or more groups such as duration of hospitalization in mild and severe cases, and second, to find risk factors that affect the survival pattern such as the effect of age and time the antibodies are administered on the duration of survival in pediatric septic shock patients. The first requires log-rank test (discussed later) and the second is Cox regression, which also is briefly discussed later in the context of hazard rates. The Cox regression is also used to estimate hazard ratio relative to a reference base. Other aspects are not discussed here and available in the literature [4].

HOW SURVIVAL ANALYSIS IS DONE?

Kaplan-Meier Method

The method of survival analysis is quite mathematical, but we explain it here in simple terms. The primary method of survival analysis is the Kaplan-Meier (K-M) method. This method gives the proportion surviving at different points in time such as at 6 months and one year. Survival at time *t* in this case is the proportion surviving longer than *t* and the method considers the censored observations only till the time the subjects were last seen alive. After that they are ignored. This proportion is an estimate of the chance of survival at time *t* in the target population after due consideration of censored values. This can be easily obtained for each time-point with the help of an appropriate statistical package.

Table I Duration of Survival of Children With HIV on ART

Patient number	*Duration (mo)*
1	7
2	3
3	4+
4	10
5	12+
6	5
7	9
8	12+
9	12+

The estimated survival proportion can be plotted for different time-points *t*. This plot is called the survival function or survival curve. Only the unique time points are considered. If a time point is applicable to two or more subjects, it is counted only once. This method requires the calculation of as many survival rates as there are events unless several events occur at the same time. The more the number of time-points, the smoother the survival curve. This means that a smooth survival function is obtained when many time points are observed. In case the survival durations are not arranged in increasing order in your data, these should be arranged in ascending order before the calculations. The survival function can be used to find the mean and median duration of survival along with their confidence interval, which can easily be done using a computer program. This is explained with the help of an example.

Example – Wainstock, et al. [5] studied neurological morbidity in children born to severely anemic (Hb <7 mg/dL) women. The follow-up time varied in their study from child to child, but we assume it to be fixed 10 years for our example. The incidence of neurological morbidity is generally low, but suppose the following duration was observed in 20 children for developing neurological morbidity.

Duration (y) elapsed for occurrence of neurological morbidity in children born to severely anemic women:

10+	7	3	9	10+	10+	8	7	7	5+
7	9	5	4+	2	1	9	4	10+	10+

where + denotes that the observation is censored. Five children with 10+ did not develop any neurological morbidity till the age of 10 years, and two children with values 5+ and 4+ were lost to follow-up when their age was 5 years and 4 years, respectively. These durations are arranged in increasing order in **Table II** along with the other details of the K-M procedure.

The K-M method requires that the time, such as 'years' in this example, is considered as a continuous variable. This can be in decimals. Yet, for clarity, first column in **Table II** is the beginning time when, in our example, the start is from 20 cases. One case developed morbidity at 1 year so that only 19 remain at risk for developing morbidity at the beginning of the second year. Similarly, the number at risk at other time points is obtained. The K-M method calculates the proportion surviving at each point in time based on cases dying at each point in time after excluding the censored values. Subsequent proportion is obtained by multiplying with the previous proportion. The method is explained in the calculations shown in **Table II**. The event under study is developing neurological morbidity in our example in place of death.

The other important requirements for valid results from the K-M methods are: *i*) The censored values do not belong to special subjects so that the distribution of the censored duration is the same as of complete values; *ii*) The subjects are independent. That is, the survival duration of one does not affect the survival duration of the other; *iii*) The rate of the event is the same in early recruiters as in the late recruiters; *iv*) In general, the number of censored values should not exceed the number of complete values.

The plot of the survival function against time gives the survival curve (**Fig. 1**). This is based on the data in **Table II** on time for the occurrence of neurological morbidity in children born to severely anemic women. This shows how the numbers at risk are declining with time. The censored values are shown by a "+" sign (there are five overlapping plus signs at 10 years). The plot can be used to find median time to develop neurological morbidity by drawing a horizontal line at proportion = 0.50 and projecting it down from the point of intersection to the x-axis. This is the time when half of the patients remained at risk and the other half had the event. In this figure, the median duration of developing neurological morbidity is nearly 8 years. The survival table (**Table II**) gives a more exact median value, which is between 7 and 8 years where the survival proportion is 0.5.

The complimentary of survival (1–proportion survived) is called the hazard since it depicts the proportion of deaths at different points in time, where 'hazard' again is a generic term for any outcome of interest.

Table II illustrates that the computations for K-M survival function are tedious and a statistical package is usually used. The software also calculates the confidence intervals for each survival probability. The estimates for the

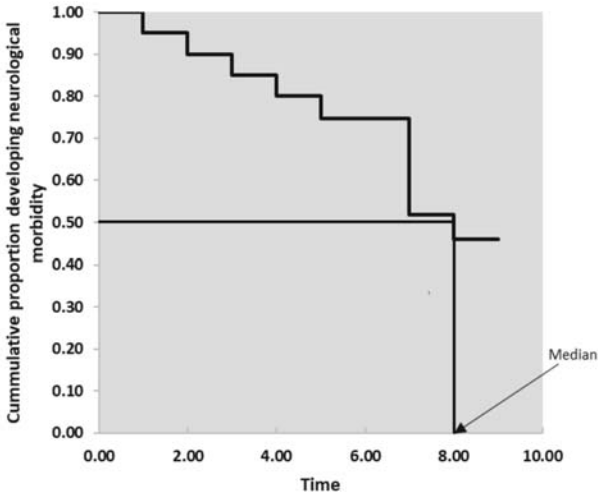

Fig. 1 Survival curve and the median survival time.

Table II Survival Analysis by K-M Method

Beginning time (year) t	Number at risk $n_{t+1} = n_t - d_t - c_t$, $n_0 = 20$	Developed morbidity at time t d_t	Censored c_t	Survival function (proportion with no morbidity) at time t $s_0 = 1$, $s_t = s_{t-1}(\frac{n_t - d_t}{n_t})$
1	20	1	0	$1 * \frac{20-1}{20} = 0.950$
2	19	1	0	$\frac{19}{20} * \frac{19-1}{19} = 0.900$
3	18	1	0	$\frac{18}{20} * \frac{18-1}{18} = 0.850$
4	17	1	1	$\frac{17}{20} * \frac{17-1}{17} = 0.800$
5	15	1	1	$\frac{16}{20} * \frac{15-1}{15} = 0.747$
6	13	0	0	$\frac{16}{20} * \frac{14}{15} * \frac{13-0}{13} = 0.747$
7	13	4	0	$\frac{16}{20} * \frac{14}{15} * \frac{13-4}{13} = 0.517$
8	9	1	0	$\frac{16}{20} * \frac{14}{15} * \frac{9}{13} * \frac{9-1}{9} = 0.459$
9	8	3	0	$\frac{16}{20} * \frac{14}{15} * \frac{8}{13} * \frac{8-3}{8} = 0.287$
10	5	0	5	

probability of survival are relatively unreliable for the time points towards the end because of fewer surviving subjects at those time points. The area under the curve is the same as mean surviving time but that is rarely used.

Estimation of the survival function or median survival time by itself may not be of much value unless it is compared with another group to find where the survival is longer. A plot of survival curves of different groups gives an indication of which group has better survival experience and the statistical significance can be checked with log-rank test.

Log-Rank Test

In place of comparing just the median survival time or the proportion surviving at specific time *t*, the log-rank test is used to compare the overall survival pattern of one group with other groups. The median may be nearly the same, but the pattern could be different (**Fig. 2**). In this figure, survival is better in one group at initial time points but worse at later time points, with survival curves shown as smooth curves for illustration. The right kind of survival pattern for comparison by log-rank test is shown in **Fig. 3**.

For example, the interest might be in comparing the pattern of duration of hospitalization of cases on a new regimen with those on the existing regimen. Another example is the time to return to school by students with and without attention-deficit/hyperactivity disorder (ADHD) following concussion [6]. Each of these can be compared using log-rank test.

Log-rank test also is a non-parametric procedure based on chi-square and used to check whether two or more survival curves are statistically significantly different. The null hypothesis is that the difference between the survival curves is due to sampling of cases and not real. For simplicity, we describe this test for two groups. The test requires that all the conditions mentioned earlier for the K-M method are met. That is, the sample size must be large and representative, censored values are random and not related to survival, early recruiters have the same survival as the late recruiters, and the survival time is recorded exactly and not in intervals. In addition, the survival curves should not cross each other – one should be lower than the other at most time points. Thus, the curves of the type shown in **Fig. 2** cannot be compared with log-rank test but those in **Fig. 3** can be compared. Also, the two groups must be independent – the survival of the patients in one group should not have any relationship with the survival of patients in the other group.

The null hypothesis of identical survival curves in the two populations implies that the probability of survival (or of death) at *each* point of time is the same in one group as in the other. Under this null hypothesis, the expected number of

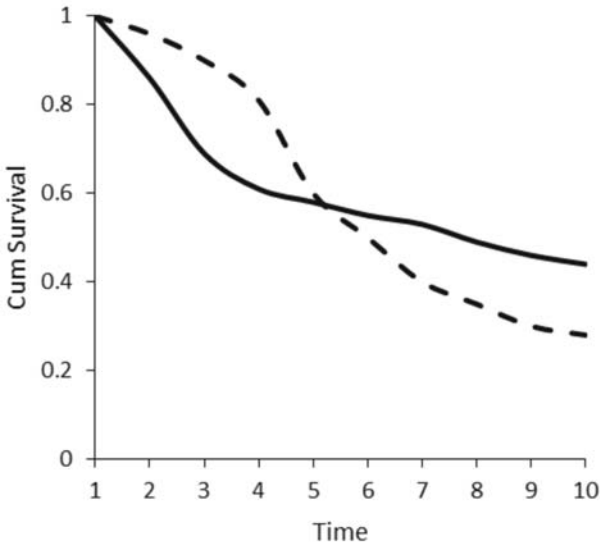

Fig. 2 Survival curves crossing each other.

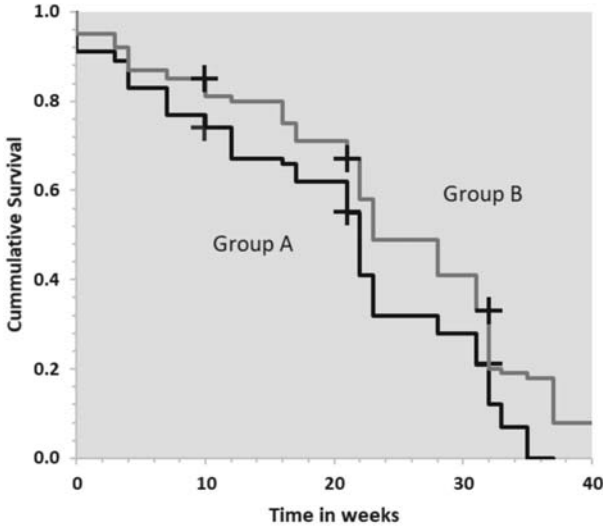

Fig. 3 Survival curves in two groups. The decline in survival in group A is steeper than in group B.

deaths is calculated for each time using the combined experience in the two groups.

For example, if there are 5 deaths in group-I at time *t* when 200 people are still at risk (after deaths and dropouts before time *t*), and 7 deaths in group-II where 100 people are at risk, the expected deaths under the null hypothesis in group-I are $\frac{100}{300}[5+7]=4$ and in group-II are $\frac{200}{300}[5+7]=8$. The sum of these kinds of numbers over different time-points are used to calculate the log-rank test.

The *P* value can be obtained in the usual manner using chi-square. This will only tell you that the difference is statistically significant or not, but would not tell you about the magnitude of the difference. For magnitude, hazard ratios at different points of time are calculated.

One subtle and difficult to understand limitation of the log-rank method is that statistical significance is mostly driven by the difference in survival at initial time points where the number of subjects is high. The number of available subjects declines at subsequent time points due to deaths and dropouts. To overcome this problem, Breslow test or Tarone-Ware test is used for comparing two survival curves when the number of subjects is large in the beginning but quickly declines and becomes small towards the end. That is, when the mortality and dropouts are high [7]. **Box I** lists when to use and when not to use survival analyses.

Hazard Ratio

Risk is the probability of occurrence of an event and is generally calculated at the end of the study irrespective of the time; whereas, the hazard rate is the risk per unit of time such as hazard of recurrence of papillary thyroid cancer per year in a high-risk population [8]. This can be different from year-to-year such as a low rate in the first year and progressively increasing each year. Hazard rate is especially used in survival studies because time is an important factor in these studies.

Box I Where to Use Survival Analysis

- For analyzing any duration (time-to-event) data if it has highly skewed distribution, particularly if some durations could not be fully ascertained (censored), but the subjects with censored values should not have special survival pattern.
- When the interest is in studying the complete survival pattern at different points in time even if no duration is incomplete.
- For comparing survival pattern in two or more groups (log-rank test)

Do not use

- When the number of censored values is more than the complete values because then the median survival duration and the area under the survival curve have poor reliability.
- The log-rank test can give misleading result when the two survival curves cross each other. Also, the groups under comparison must be independent.
- When the deaths or dropouts are fast, the numbers towards the tail become too small and the log-rank test loses its power.

The ratio of the two hazards called hazard ratio is used to compare hazard rate in one group with another, such as hazard of developing anemia per year in adolescent girls of low versus high socioeconomic (SE) status. A hazard ratio of 1.25 says that the hazard of developing anemia per year in girls of low SE status is 1.25 times (or 25% higher) of such a hazard in girls of high SE status. If this ratio remains the same over the period of the study, called proportional hazards, Cox [9] has shown that the factors affecting this ratio can be easily studied by a regression model. This analysis tells which factor is contributing how much and its significance towards difference in the hazard rates in the two groups under study. A more detailed explanation has been given by Kleinbaum and Klein [10].

CONCLUSIONS

A separate method of analysis is required for duration (time-to-event) data because durations generally have censored values and a highly skewed distribution. The method of survival analysis is nonparametric and takes care of both these 'aberrations' in the data. Survival is a generic term, and the method is applicable to any duration data. Kaplan-Meier is the method of choice to study the complete survival pattern when the duration is measured on continuous scale and when censored values are not related to the survival pattern. This can be used to estimate the median survival time despite censored values. Comparison of survival pattern in two or more independent groups is done by log-rank test.

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How to Improve the Efficacy of Student Feedback

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Context: Feedback processes are intricate, generally misunderstood, hard to execute efficiently, and often fail in their goals to influence students learning. Research highlights that students usually do not value the benefits of feedback. This paper reviews the literature on the definition, purpose, and models of feedback; and on exploring why some students do not value feedback, what factors are influencing the effectiveness of feedback, and how to improve the efficacy of feedback. **Evidence acquisition:** The relevant articles were searched through 'Google Scholar,' 'CINAHIL' and 'PubMed' using the key terms- "Student feedback," "Frameworks of feedback," "Barriers to effective feedback," and "Students' perspectives on feedback." The search criteria included: review and original research articles in the English language published in high-impact journals in the past ten years. **Results:** The results of different studies have illuminated diverse factors demanding the attention of educators to the effectiveness of feedback. Personal, relational, procedural, and environmental factors seem to affect the utility of feedback. To be effective, feedback should be actionable, non-judgmental, descriptive and specific, based on observable behavior, and should be given at a mutually agreeable time and place. **Conclusion:** The efficacy of feedback can be enhanced by creating students' feedback literacy, addressing students' perceptions and expectations, encouraging productive educational alliances, improving procedural elements of feedback, and environmental conditions.

Keywords: *Constructive, Effective, Performance, Self-assessment, Teaching.*

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Feedback is a crucial process in student learning. Constructive feedback offers insight into students' performance, accentuates the difference between the expected and the real results, and provides momentum for improvement [1]. Substantial evidence supports the importance of feedback in learning; however, several studies have reported its inefficiency in executing its intended function in real practice. Feedback processes are intricate, executed inefficiently, generally misunder-stood, and often fail in their goals to influence students learning [2,3]. Students often feel demotivated and demoralized after receiving feedback.

A National-level student survey reported a high degree of student discontent with the feedback process in England and Wales [4], similar to the Student experience survey in Australia [5]. These surveys have precisely identified feedback as among the highest complicated aspects of learners' training experience. Despite the mounting evidence to indicate that the students are not contented with feedback, educators justify the described discontent with the learners' inabilities [6]. The rationales in these discussions are that the students do not understand the concept of feedback [7,8], and they do not get satisfied with feedback despite the substantial degree of attention paid to them [9].

Researchers mention that inadequate student 'feedback literacy' is one of the significant obstacles to the effectiveness of feedback. Furthermore, the students respond differently to feedback within specific academic fields, curricula, circumstantial settings concerning their past experiences and personal attributes [10]. Some studies have identified the procedural elements of feedback, such as legibility and timeliness, as the issues demanding attention to improving student satisfaction with feedback. Reduction in motivation resulting from previous negative feedbacks has also been reported as a barrier to learners using feedback [11].

Results of different studies have illuminated diverse factors demanding the educators' attention to the efficacy of feedback. It is thus imperative to explicitly examine feedback from various perspectives. This article reviews the literature on the definition, purpose, and modes of delivery of feedback, the roadblocks to effective feedback, and the strategies to improve the efficacy of feedback.

DEFINITION AND PURPOSE

Feedback may be defined as "the process through which the students make sense of the information from various sources and use it to enhance their work on learning strategies [10]." This definition not only highlights the teacher's role in apprising students of their strengths and

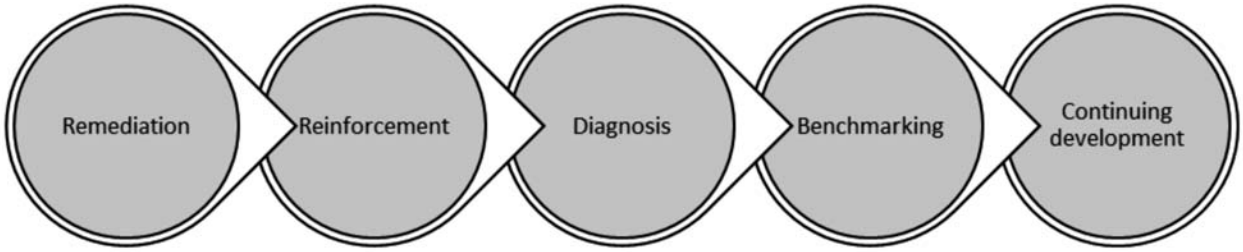

Fig. 1 The purpose of feedback- the roles ascribed to feedback create a nested hierarchy, and the constituent categories build on the direction provided by the preceding category.

areas for improvement but also includes the student's role in understanding and using comments to improve subse-quent performance.

Feedback emphasizes remediation, positive or negative reinforcement to behavior, diagnosing gaps between demo-nstrated and expected standards of performance, bench-marking (setting standards) and facilitating ways to fill the gaps, and addressing activities to support continuing development [12]. The roles ascribed to feedback create a nested hierarchy, and the constituent categories build on the direction provided by the preceding category (**Fig. 1**). Effective feedback targets three areas:

i) *Feed up*- "Where am I going?" The solution provides information about accomplishing learning goals associated with specific tasks or performance. Feedback can be ineffective if the goals are not clearly defined.

ii) *Feed back*- "How am I going?" This aspect of feedback provides information about progress and about how to proceed to attain learning goals.

iii) *Feed forward*- "Where to next?"- The answer provides specific information regarding more significant challenges, more information about what is not understood, more strategies to promote deeper understanding, and more self-regulation over the learning process [7].

These three questions do not work in isolation; instead, they work together; the answer to each question has the power to encourage further tasks relative to a goal.

HOW TO PROVIDE FEEDBACK?

Feedback can be formal (after a structured written or clinical assessment) or informal (in daily encounters between teachers and trainees, peers, or colleagues). It is directed at four levels for its effectiveness: feedback about the task, process of the task, self-regulation, and the self as a person [7]. Feedback should be actionable, non-judgmental, descriptive, specific, based on observable behavior, and given at a jointly settled time and location [1]. Several frameworks of providing feedback are mentioned in the literature. However, not every framework is applicable in all cases.

Feedback Sandwich Model

Feedback begins and ends with appreciative and positive feedback (about what the student has done well); the crucial feedback component (constructive criticism or the area of improvement) is 'sandwiched' between the positive aspects [13] (**Fig. 2**). This approach is useful for learners with low esteem; however, if used frequently, its effectiveness can be lost, as the students start ignoring the crucial middle component of feedback. An example is depicted in **Box I**.

Pendleton Rules

Pendleton rules are so designed that the learner's strengths are discussed first, avoiding discussing weaknesses right at the beginning [1] (**Fig. 3**). The learner is encouraged to reflect on the positive areas (What was done well?). The facilitator reinforces those positive areas. Further, the weaknesses

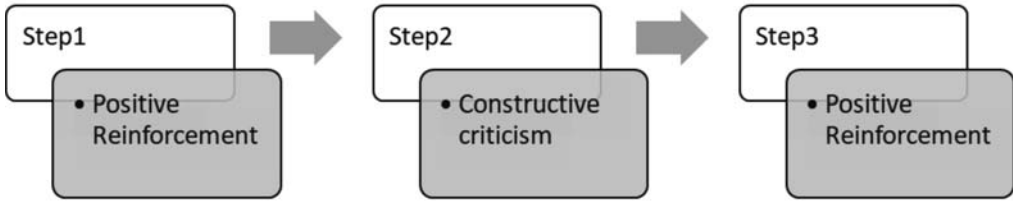

Fig.2 Sandwich model of feedback- The crucial component of the feedback (constructive criticism) is sandwiched between the positive aspects of the feedback.

(What could have been done differently?) and the strategies to overcome weaknesses are discussed (How can these be achieved?). Finally, an action plan is developed to fill the gap between the real and the intended results.

This method helps in creating a safe learning environment and prevents the defensive attitude of the learner. The student feels that he is valued, and his opinion is heard. Additionally, it encourages reflective behavior in the learner. However, it has been criticized for its rigidity, formulaic nature, insufficient time, and lack of opportunities for interactive discussions [14].

SET-GO Method

SET-GO is an *aide-memoire* for the sequence of actions while providing descriptive feedback [1,15]. A descriptive, non-judgmental, and outcome-based approach to facilitate a behavior change is employed in this model. The facilitator bases the judgment on:

What did I see? - Facilitator reflects to the learner, explaining what did he observe.

What else did you see? - The learner acknowledges the incident and reflects on it to identify the problem.

What do you think? - The learner is encouraged to solve the problem.

What goal would we like to achieve? - The learner is asked to identify the goals (an outcome-based approach).

Any offers of how we should get there? - The learner is asked to offer proposals, alternative skills, and rehearsals to accomplish the goals [1]

The agenda-led, outcome-based feedback method, illustrated below, underpins the SETGO method.

ALOBA (agenda-led-outcome-based analysis) model: The principle of the ALOBA model is to identify areas where the learner requires assistance (**Fig. 4**). Feedback starts with agenda-setting; the learner is asked to express his problems and determine the objectives to be achieved. This early acknowledgment of difficulties offsets defensiveness and allows the learner to emphasize the feedback itself rather than being apprehensive of the nature of the negative feedback. In the next step, the facilitator tries to determine the objectives that the learner intends to achieve. The learner is encouraged to self-analyze and make suggestions for improvement. The facilitator provides descriptive and non-judgemental feedback and suggests the skills to accomplish the objectives. The recommended skills are rehearsed, and a mutually agreed action plan is developed for improvement [16]. Contrary to Pendleton rules where the learner is a passive recipient of the recommendations from the facilitator, the learner in the ALOBA model is an active participant and equal contributor to the activities [1].

Box 1 Example of Sandwich Model of Feedback

- *Positive reinforcing statement:* "I liked the way you systematically examined Mr. G's abdomen using the flat of your hand."
- *Constructive criticism:* "I observed that you did not pay any attention to his facial expressions while palpating his abdomen to know whether you were causing him any inconvenience."
- *Positive reinforcing statement:* "You ended your case presentation very well by accurately and succinctly summarizing your findings."

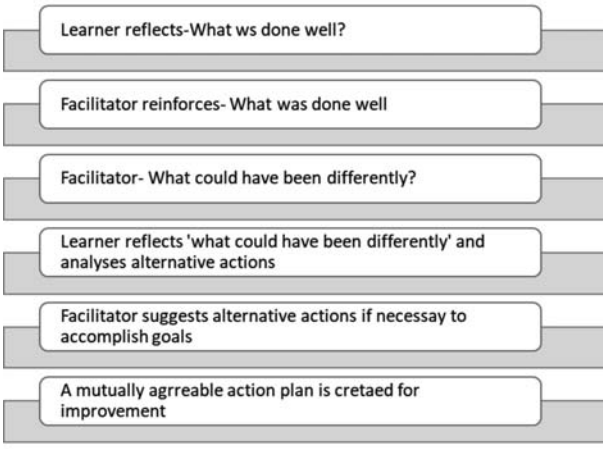

Fig. 3 Pendleton rules- the learner is encouraged to reflect on the positive areas first, later the weaknesses and the strategies to overcome the weaknesses are discussed.

Chronological Fashion Feedback

This model emphasizes reflecting observations sequentially, recapitulating the experience that occurred during the feedback session. For example, an observer can go through a

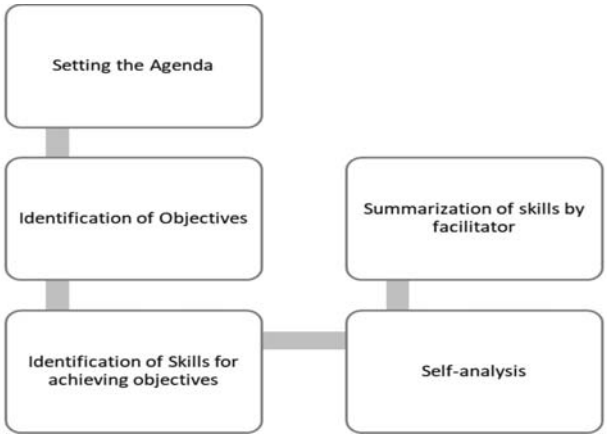

Fig. 4 ALOBA model of feedback-Agenda led outcome-based analysis.

learning session and give feedback for all the activities from beginning to end. This method is helpful only for short feedback sessions [17].

Alternative Models of Feedback

Several different models of feedback, such as One-minute preceptor [18], the Chicago Model [19], and the Six-step problem-solving model [20], are also in practice. These models are based on the principles of the ALOBA technique and Pendleton rules.

Learner-Centered Models

Learner-centered models promote the active participation of the learner in the feedback process. These models propose that the learners should take more responsibility for seeking (learner-centered) and responding (self-regulation) to feedback and for their own learning [21].

Educational Alliance Framework

Some authors have proposed a bidirectional educational alliance framework that emphasizes a cordial relationship between the learner and the educator [22]. This transformed feedback approach allows a collaborative understanding of performance objectives and a jointly settled action plan (**Fig. 5**).

Ask-Tell-Ask Model

The Ask-Tell-Ask model [23] is a simple, bidirectional, learner-centered model that fosters learners' self-assessment abilities and provides assessors with the opportunity to share constructive feedback with the learner (**Fig. 6**). This model increases students' accountability and can be used in diverse settings.

Using Ask-Tell-Ask, the assessor first asks the learner for their perceptions about strengths and weaknesses. Then the assessor tells them his impressions, supported by observations and specific examples, and then the assessor wraps up by asking the learner to help create a development plan.

These learner-centered models increase students' accountability, promote self-regulated learning, and are underpinned by adult learning principles [23].

WHY DO STUDENTS NOT VALUE FEEDBACK?

Feedback has been widely shown as an intervention to promote learning. However, a substantial body of research highlights that the learners do not value the potential of feedback. These findings have led the researchers to explore why some learners do not appreciate the received feedback and which aspects are essential in affecting students' feedback practices.

Learners' Characteristics

Studies have reported that the feedback approach, which is perceived to threaten the learner's self-esteem, can adversely affect performance and motivation [7]. Students tend to renounce or overlook comments if they raise adverse emotional responses [24,25]. Research highlights that the learners' attributes and how the learners perceive feedback substantially affect the outcomes of feedback [26]. The learners with a rigid perception of their caliber interpret negative feedback as a personal failure, and thus they feel demotivated. The feedback that focuses on the learner's personality rather than 'behavior' is likely to impact negatively on the motivation and performance of the learner [8].

A lack of dialogue between assessors and students about what is expected of them can result in the student ignoring to act on feedback [24]. Students are generally not skilled in interpreting or working on comments competently. Therefore, important information remains obscure [27]. Student's imperfection in deciphering feedback can lead to mutual resentment and misconception of the remarks [28]. The student's prior experience with feedback also determines the effectiveness of feedback.

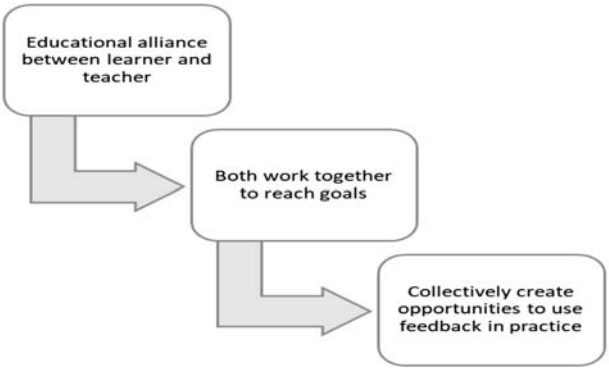

Fig. 5 Educational alliance framework emphasizes a cordial relationship between the learner and the educator.

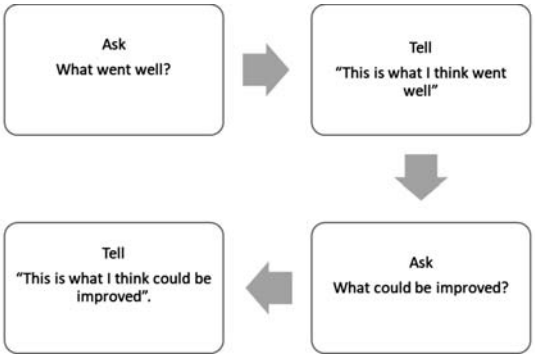

Fig. 6 The Ask-Tell-Ask model fosters learners' self-assessment abilities and provides assessors with the opportunity to share constructive feedback with the learner.

Some authors have mentioned that the students fail to use feedback provided in higher education because it may be dissimilar from the one they have previously received. Students are generally not familiar with what constitutes feedback at university against what they receive at school [29].

Assessors' Characteristics

The assessor's credibility [30] and authority [31] may also affect a student's use of feedback. Students prefer feedback from an experienced, competent, accomplished, and accessible teacher [30]; however, they feel reluctant and hesitant to seek feedback from the teachers in a hierarchical education system. Some authors have reported 'legibility' as a matter of concern; according to their results, 30% of students said that occasionally feedback that they get is not readable [29,32].

Feedback Process

Several researchers have mentioned the cultural factors that act as barriers to the effective use of feedback. Research shows that in some cultures, asking questions from older faculty is not an accepted practice; therefore, the students avoid seeking or using feedback [33]. Many researchers have identified 'improper timing' as a cause of the ineffectiveness of feedback. Feedback received after completing the module makes it problematic for the students to use it [34,12]. Literature also reveals that feedback dissatisfaction is a sign of enhanced capitalism, and that students now have higher expectations [35].

Studies [36] report that the fear of upsetting student or sabotaging the teacher-student relationship, fear of doing more damage than good, inability to handle emotional responses of students against the negative feedback, non-specific or generalized feedback, feedback without an action plan, lack of consistency of feedback, or the lack of respect for the facilitator are the common barriers to effective feedback (**Box II**).

IMPROVING EFFICACY OF STUDENT FEEDBACK

There are no prescriptive guidelines on how to give useful feedback. However, certain essential principles can help engender healthy educational practices in both learners and assessors.

Feedback Content

Feedback should emphasize correction as well as future development. Literature shows that there are three essential features to improve the effectiveness of student feedback: the student should have cognizance of the goal of performance, should be able to identify the discrepancy between the expected achievement and the actual achievement, and should make efforts to fill the disparity using appropriate actions or strategies [37].

Therefore, if the feedback is not used to fill the gap between the current achievement and the expected achievement, it is not feedback; it is just 'dangling data' [37]. Furthermore, the language of feedback should be clear, free of jargon, and understandable [24].

Timing

Research highlights that feedback is highly effective when provided straightway after the activity [7]. However, delaying feedback on complicated tasks can give the learners time to self-evaluate and consider alternative approaches to improve future performance [38]. The educational environment and the learner's emotional state can also influence the time to provide feedback [2].

Qualities of the Assessor

The student's perceptions of the teacher's expertise and educational alliance with the assessor govern the feedback's effectiveness [39]. Some authors believe that the feedback from a teacher who has not built a learning relationship with the learner may be listened to but is not heard with an open heart and mind [40].

Creating Student Feedback Literacy

Feedback literacy has been described as the ability to read, interpret and use written feedback [41]. Some authors have

Box II Barriers to an Effective Feedback

Learner

Emotional response to feedback
Learner's rigid perspective
Lack of feedback literacy
Prior dissimilar experience
Higher expectations

Assessor

Lack of communication between learner and assessor
Lack of credibility and authority of the assessor
Lack of skills to give feedback
Fear of upsetting student
Fear of sabotaging the student-teacher relationship
Fear of doing more harm than good
Lack of respect for the assessor

Process

Feedback approach that targets learner's personality and self-esteem
Non-specific feedback
Feedback without an action plan
Lack of consistency of feedback
Improper timing

Environment

Cultural factors
Lack of privacy
Threatening environment

Box III Summary of the Principles of Providing Effective Feedback

Learner

- Feedback should target specific behavior or performance, not the personality of the learner.
- Feedback should provide opportunities for learners to seek, listen and respond with honesty to feedback.
- Learners should be apprised of the advantages of feedback.
- The learner should be engaged in critical reflection of the performance (self-analysis through reflection).

Assessor

- The assessor should be credible and experienced.
- Assessors should develop a concrete educational alliance with the learners.
- The assessor should protect the self-esteem of the learner.

Process

- Feedback should be given privately, especially if it is negative.
- Feedback should be given straightway after the activity except under specific conditions when feedback can be delayed.
- Feedback should include an emphasis on improving the self-regulatory ability of the learner.
- Feedback should not be provided in a threatening manner.

Content

- Feedback should inform the learner of performance goals, the discrepancy between the expected and the actual achievement, and the action plans to attain the desired goals.
- The language of feedback should be clear, free of jargon, and understandable.
- Feedback should be aligned with the learning objectives, clinical activity, or teaching session.

emphasized four elements of student feedback literacy viz., appreciating feedback processes, making judgments, managing affect, and taking actions to use feedback. 'Appreciating feedback' relates to students identifying both the importance of feedback as well as their active participation in the feedback process. 'Making judgment' is about students learning to evaluate judgment, developing capabilities to self-evaluate and assess the work of others. 'Managing affects' relates to controlling feelings, emotions, and attitudes; and avoiding defensiveness [10]. 'Taking actions' relates to understanding the essence of information and making use of it to improve performance [6].

The student feedback literacy can be improved by peer feedback or peer review. Peer review helps the students to compare their work with that of others, and through this exposure, students develop the competence of self-evaluation [42]. Studies have reported that the feedback-seeking behavior can be generated if the students are apprised of the benefits of feedback through appropriate activities and are offered opportunities to engage in meaningful tasks with peers or others [6]. Research shows that digitally-enabled peer feedback, because of its quick delivery and transportability, can help the learners to generate feedback and engage in peer review [10].

The student feedback literacy can also be improved using selected student work samples that illustrate the standard and coherence of feedback expectations [43]. However, sometimes assessors have reservations regarding the role of 'exemplars' in that they feel that students may consider them as models to be emulated [44]. Furthermore, feedback should be aligned with the learning objectives, clinical activity, or teaching session. A summary of guiding principles has been highlighted in **Box III**.

CONCLUSION

Feedback is a vital component of the learning cycle. Constructive feedback improves learning and sets the momentum for future development. To be effective, it ought to be actionable, non-judgmental, descriptive, and specific, based on observable behavior, and should be given at a collaboratively settled reasonable time and place. Adopting a constructivist approach to feedback, introducing qualitative changes in the feedback process, and improving student feedback literacy might help the learners to understand and make effective use of feedback.

The arena of student feedback is not well researched, and there has been little pragmatic research on students' beliefs, attitudes, perceptions, and expectations regarding feedback. More work is needed to explore the strategies to strengthen students' beliefs about feedback and improve their abilities to receive and use feedback.

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Risk of Sequelae of COVID-19 in Children Cared for by Primary Care Pediatricians

148 Italian children (*n=148*) suspected of and evaluated for COVID-19 infection during the first phase of the pandemic were followed-up for 6 months.During the follow-up period, no difference in the prevalence of new-onset respiratory, dermatological or neurological symptoms, nor in psychological distress,were observed in children who were positive and negative for SARS-CoV-2.

Keywords:*Outcome, Psychological distress, Respiratory problems, SARS-CoV-2.*

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Several studies have described the characteristics of pediatric coronavirus disease 19 (COVID-19) cases [1-3], but few were based in the primary care setting. An observational study was therefore performed with a group of Italian primary care pediatricians with the aim to describe the characteristics of children visited for a suspected severe acute respiratory syndrome 2 (SARS-CoV-2) infection and to monitor their health status in the 6 months after the first visit.

Information concerning children with suspected SARS-CoV-2 infection during the first phase of the pandemic (February, 2020–June, 2020) was collected by a group of 35 family pediatricians in the Lombardy Region, Italy, who voluntarily participated in the study. All pediatricians had a long-standing experience in out-of-hospital pediatric practice. Five of them were actively involved in designing the study, and in planning the questionnaire for data collection.

All Information related to demographics, symptoms, presence of any comorbidity, and diagnostic test results (molecular and/or serological test) was collected by using a pre-designed questionnaire. COVID-19 suspected cases were defined as children with flu-like symptoms and children with family members who had a suspected or confirmed COVID-19 infection. Molecular tests (real-time polymerase chain reaction on nasopharyngeal swab) were prescribed by the local health authorities, while serological tests (IgG anti-SARS-CoV-2 detection) were performed based on the parents' decision. Details concerning wheezing episodes, new onset of dermatological (e.g., rash, dermatitis, urticaria) or neurological (e.g., headache, seizures, neuropathies) symptoms, and symptoms potentially associated with psychological distress (e.g., sleep disorders, anxiety, irritability) in the 6-month period after the first consultation were collected by the family pediatricians to monitor the sequelae of the infection. Since the study was mainly descriptive, no *a priori* sample size calculation was made.

The study was approved by the Fondazione IRCCS Istituto Neurologico Carlo Besta's Ethics Committee. The characteristics of positive versus negative children were compared using the chi-square test.

Of a total of 349 children were suspected of SARS-CoV-2 infection; 148 (42%) underwent a diagnostic test and among these 41 (28%) tested positive. Symptom prevalence was slightly higher in SARS-CoV-2 positive children compared to negatives (71% vs 55%), with sore throat occurring less commonly in positive children (18% vs 51%; *P*=0.002).

Among those tested positive, three cases had pre-existing comorbidities (asthma, Duchenne muscular dystrophy, and Henoch-Schonlein purpura) as against nine negative cases. Four positive children were hospitalized: two infants (one of whom was an asymptomatic neonate delivered by a positive mother), a 6-year-old child, and a 12 year old adolescent. None had pre-existing comorbidities. The length of hospital stay ranged between 5 days to 1 month and, with the exception of the neonate, the hospitalizations were associated with COVID-19 pneumonia. The 12-year-old adolescent developed myocarditis and was admitted to the pediatric intensive care unit for cardiogenic and septic shock.

During the follow-up period of 6 months 107 of the 148 children (72%) had contacted or visited the pediatrician for a health issue (range: 1-8 visits), 38 (26%) had no health problems, and 3 (2%) were lost to follow-up. A total of 48 children had come into contact with a positive case during the follow-up. Thirty two of these underwent a molecular test, and only one tested positive (with no previous history of COVID-19).

The prevalence of respiratory, dermatological, and neurological symptoms were similar in positive and negative children during the follow-up period (**Table I**). In all, 24 children (17%) had psychological distress, which was not present before the epidemic; 16 developed sleep disorders, 14 anxiety and/or irritability, and 6 both.

To the best of our knowledge, this is the first study describing a series of pediatric COVID-19 cases cared for by primary care pediatricians. Despite the small sample size, some findings are worthy of consideration. During the first pandemic phase, less than half of potentially infected children underwent diagnostic tests, with a prevalence of 1 out of 3 suspected cases. As reported in other studies, fever and cough were the most common symptoms, while in our study a greater proportion of children with malaise were observed [5]. Except sore throat, the most common symptoms were similar in positive and negative children, as observed by Garazzino, et al. [3] in children attending a pediatric hospital for COVID-19.

During the first pandemic phase schools were closed and contagion occurred in the household setting. It is therefore not surprising that the number of potentially affected family members was associated with an increased likelihood of infection incidence. The number of hospitalized children was low; though, the prevalence of moderate–severe cases in children was not negligible.

Table I Characteristics at Follow-up in Children with Suspected COVID-19 (*N*=148)

	Positive (N=41)	*Negative (N=107)*	*Overall (N=148)*
Diagnostic test[a]			
Molecular	15 (15)	86 (85)	101
Serological	28 (38)	45 (62)	73
Male gender	19 (26)	55 (74)	74
Age (y)			
<1	3 (38)	5 (62)	8
1-5	15 (29)	37 (71)	52
6-11	14 (22)	49 (78)	63
12-16	9 (36)	16 (64)	25
Median (IQR)	7(4-11.5)	6 (3-10)	6.5(3.5-10.5)
6-month follow-up			
Visits	1.9 (1.7)	2.0 (1.3)	2.0 (1.4)
New-onset symptoms			
Wheezing	0	6 (6)	6 (4)
Dermatological[b]	1 (3)	6 (6)	7 (5)
Neurological[c]	2 (5)	5 (6)	7 (6)
Psychological distress	6 (15)	18 (17)	24 (17)
COVID-19 positive	0/8 (20)	1/24 (23)	32 (22)

Data is reported as no(%). 2 children were positive to both molecular and serological tests; [a]26 children underwent both diagnostic tests; [b]Psoriasis flare (n=1), dermatitis (n=3), rash (n=2), plantar wart (n=1); [c]Symptoms due to headache (n=4), Duchenne muscular dystrophy (n=1), Seizure (n=1), not specified (n=1).

No differences between positive and negative children were observed during the follow-up. The sample size may be too small to detect statistically significant differences, but the fact that the proportion in the two groups was very close suggests that a greater likelihood of sequelae in positive cases is unlikely. A few case series have reported and have suggested the occurrence of 'long covid' in the pediatric population [6,7]. A comparison with children who tested negative to COVID-19 may be needed, since it is likely that some symptoms may be strongly associated with the pandemic situation and with quarantine, and not only with COVID-19 infection [8]. Given the observational characteristic of the study, no additional diagnostic tests were done and therefore, we were not able to evaluate whether there were any cardiac or central nervous system sequelae in children with no clinical symptoms.

In our sample, psychological distress occurred in nearly 1 in 6 children, consistent with other reports [8-10] with no differences in incidence between positive and negative cases, suggesting that COVID-19 per se is not a risk factor. Despite the limitations of this study, it showed that children with COVID-19 do not seem to be at a greater risk of sequelae than children without.

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Lift the Lip: A Simple Visual Tool for Caries Risk Assessment

Early childhood caries (ECC) is the tooth decay present in the primary teeth of children under 6 years of age. ECC may begin soon after primary teeth erupt and white spot lesions are its earliest manifestation that can progress into cavitated carious lesions within a very short time. ECC management is demanding, requiring substantial cooperation from young children. Often due to the severity of the condition, comprehensive care under general anesthesia is required, which is expensive and carries an inherent risk [1].

Early identification and management of ECC can reverse the disease process and prevent further decay. The first oral examination is therefore recommended soon after the eruption of first tooth and no later than the age of one year. This early visit helps in evaluating the caries risk of the child, and imparting oral health education as well as anticipatory guidance to parents [2]. Most parents are not conscious of the benefits of this early oral examination and often see a dentist only when severe ECC has already set in. Infants and toddlers are likely to be seen by pediatricians more frequently. If these health professionals can spot children with a higher risk for caries and refer them to a dentist, early preventive measures can be initiated.

'Lift the lip' maneuver has been developed as a simple, visual screening tool for caries risk assessment [3]. It is particularly useful in young children because till 18 months of age, there is greater prevalence of white spot, non-cavitated lesions that can be arrested or reversed by preventive interventions. Beyond this age, cavitated lesions requiring surgical mediation become more common [4]. Timely detection and referral of high-risk children by pediatricians may be the key to control ECC through preventive, non- invasive measures that are pain-free.

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Leprosy Mimicking Carpal Tunnel Syndrome in a Child on Growth Hormone Therapy

A 16-year-old boy, operated for craniopharyngioma at 12 year was receiving thyroxine, hydrocortisone and desmopressin for last 4 years, and growth hormone (GH) at (0.25 mg/kg/week) for 1 year, He presented with increasing pain, numbness and tingling over right palm for 3 months. On examination, swelling involving right wrist and hand, and claw hand deformity were noted. Right hand was cooler than the left, and radial artery pulsations were feeble. As the child was on GH, with carpal tunnel syndrome (CTS) being a known adverse effect, this was the initial diagnosis. GH therapy was withheld and physiotherapy was initiated.

On the next visit, detailed clinical examination showed decreased sensory perception, a small hypopigmented macule over dorsal aspect of ring finger, and thickened ulnar nerve behind right medial epicondyle, raising the possibility of leprosy. Further review of history revealed that mother had been treated for leprosy 20 year back. Nerve conduction study showed right median and ulnar motor sensory neuropathy, and skin biopsy revealed perivascular lymphocyte infiltration with few epithelioid cells, confirming a diagnosis of tuberculoid leprosy. Multidrug therapy (MDT) for leprosy was initiated and GH was restarted. At follow-up after 12 months of MDT, there was complete resolution of symptoms.

In children, the commonest cause of CTS is lysosomal storage disorder [1]. It is reported in 35-45% of acromegalic patients and 5-30% of adults receiving GH therapy; however, it is rare in children [2]. The mechanism is related to salt and water retention by growth hormone, leading to edema of synovial tissue and compression of median nerve [2]. In leprosy, the neuropathy is due to chronic inflammatory granuloma [3]. In settings where leprosy is rare, the diagnosis may be missed. Koss, et al. [4] previously reported a young woman, who presented with recurrent CTS despite surgical decompression and was later diagnosed to have leprosy [4]. In our case also, the child being on GH therapy initially mislead us towards considering CTS. In clinical medicine, sometimes the most likely possibility may not be the correct answer.

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A Holistic Approach to Minimize the Negative Effects of Auditory Stimulation in the NICU is the Need of the Hour

We read with interest the article on effect of earmuffs on physiological parameters of preterm neonates by Kaur, et al. [1] in the recent issue of the journal. We would like to commend the authors on their effort. Herein, we would like to add our views on some of the issues raised in the article.

A systematic review on the effect of earmuffs on physiological parameters in preterm infants by Ozdemir, et al. [2] concluded that it is not clear that the use of earmuffs reduces stress or provides physiological stability in preterm infants born between approximately 28-32 weeks [2]. Other studies have also pointed out the potential for certain complications with the use of hearing protection devices such as damage to delicate preterm skin by the adhesive that keeps the hearing protection device in place, and damage to the developing ear structure if a tight seal is maintained around the ear for long periods of time [3].

We feel that it would be appropriate to explore other modalities to minimize the negative effects of auditory stimulation from the neonatal intensive care unit environment. An interesting study by Webb, et al. [3] suggested benefit by replicating uterine sounds for preterm babies, which attenuated loud peaks of sound, thereby reducing the negative impact of the additional volume [4]. A more holistic approach would be to create an individualized environment with a Newborn Individualized Developmental Care and Assessment Program (NIDCAP) [5], which may be more effective than trying to remove all negative sounds. Low-risk preterm infants who received individually based NIDCAP orientated care showed significant improvement in neurodevelopmental outcomes, including self-regulation and posture at 2 weeks of age [5]. Hence, while the use of earmuffs may have some potential for benefit, it would be more appropriate to focus also on other innovations to minimize noxious environmental noise and promoting and individualizing positive sounds.

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Congenital Anetoderma

A previously healthy 3-month-old preterm boy presented with guttering of skin over the left leg since birth. Examination revealed two well circumscribed, skin-colored, atrophic annular plaques (2-4 cm in diameter) with overlying wrinkled surface around the left knee joint (**Fig. 1**), with a distinct inward herniation on palpation. Antenatal history and family history were non-contributory. Screening for underlying immunodeficiency, connective tissue disease and thyroid profile were negative. Loss of dermal elastic fibers on histopathology confirmed the clinical impression of congenital anetoderma.

Fig. 1 Two well-circumscribed skin-coloured, atrophic plaques with wrinkled surface around the knee joint of left leg.

Anetoderma is rare cutaneous disorder characterized by circumscribed areas of atrophic lesions attributed to loss of dermal elastic tissue. It has been classified into following types: primary (no underlying associated disorder, lesions arise within clinically normal skin), secondary (associated with inflammatory dermatosis, cutaneous tumors, infections, drugs, and autoimmune diseases), familial, iatrogenic anetoderma of prematurity (over sites of monitoring leads, adhesives), and congenital. Differential diagnoses include morphea (sclerotic plaque with characteristic peripheral lilac rim), idiopathic atrophoderma of Pasini and Pierini (non-indurated depressed plaques with abrupt 'cliff-drop' border), localized lipoatrophy (inherited, acquired, idiopathic and iatrogenic due to injectables), and focal dermal hypoplasia (Goltz syndrome). Ablative and non-ablative fractionated laser have been used with variable success.

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Fordyce Spots in a Neonate

A term male newborn was born by spontaneous vaginal delivery with a birth weight of 2780 g. At about 48 hours of life, this exclusively breastfed baby was noticed to have a few small fluids filled lesions on the inner aspect of the lower lip. Examination of the oral cavity revealed a few vesicles containing clear fluid in the oral mucosa, especially on the inner aspect of his lower lip (**Fig. 1**). The vesicles were around 2-4 mm in diameter with no surrounding erythema. A diagnosis of Fordyce spots (intraoral sebaceous gland hyperplasia) was made based on the characteristic clinical findings. The neonate's mother was counseled regarding the benign and self-limiting nature of these lesions, and discharged from hospital. At follow-up visit on day 7 of life, all the lesions had resolved completely.

Fig. 1 Fordyce spots over mucosal surface of lower lip.

Fordyce spots are heterotopic hyperplasia of the sebaceous glands in neonates. These are essentially benign and self-limiting lesions, but often are not evident in neonatal period. These are slightly different from the typical sebaceous glands as these are not associated with hair follicles and their ducts open directly on the skin or mucosal surface. When present, Fordyce spot are believed to develop under the effect of maternal androgens. It is important to recognize this benign self-limiting mucosal condition to avoid unnecessary evaluation.

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Lipschutz Ulcer

An 8-years-old girl presented with complaints of acute onset, painful genital ulcer of 2 days' duration associated with high grade fever. There was no history oral ulceration, local trauma, prior drug intake or history suggestive of sexual abuse. Examination revealed febrile patient with axial temperature of 101^0F and round ulcer measuring 15X15mm, covered with pseudo-membrane over medial aspect of labia majora (**Fig. 1**). Complete blood count showed leukocytosis (14000/mm^3); with rest of the investigations including urine examination, pus swab and culture, ELISA for human immunodeficiency virus, VDRL, and IgM and IgG for herpes simplex virus 1 and 2 were negative. Patient was treated symptomatically with paracetamol, potassium permanganate soaks and topical mupirocin ointment twice a day. The pain reduced in 3 days and ulcer healed within a week.

Lipschutz ulcer, also known as ulcus vulvae acutum, is an acute painful ulcer that presents most commonly in adolescent girls, in absence of sexual contact and immunodeficiency. The exact etiology is not known but may be associated with viral infection such as Epstein- Barr virus and cytomegalovirus. It presents as acute painful ulcer involving labia minora or majora, introitus, fourchette and vestibule. The ulcer can be single or multiple, with sharply demarcated borders and overlying gray exudate (pseudo-membrane). Kissing ulcers over opposite surfaces are common. There may be associated systemic symptoms like fever, oral aphthae and diarrhea. The differential diagnosis includes sexually transmitted infections such as syphilis, chancroid, herpes simplex infection; Behcet disease, Crohn disease and trauma. Clinicians should be aware of this condition and should differentiate it from sexual abuse, so as to avoid unnecessary investigations and parental anxiety.

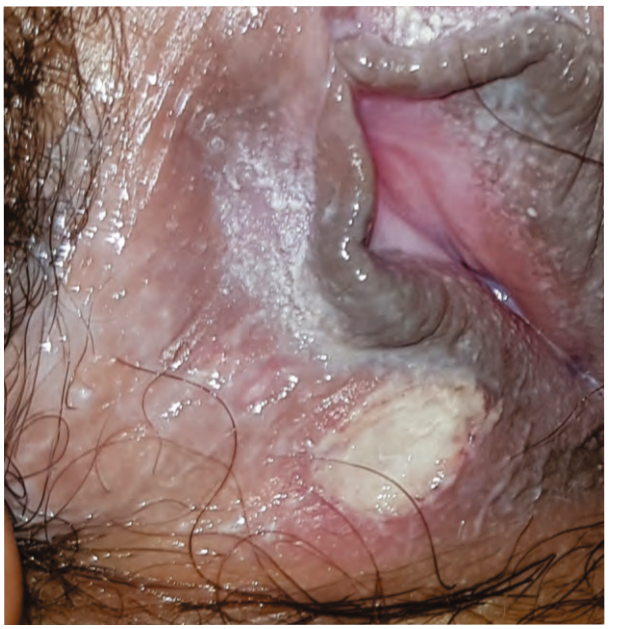

Fig. 1 Solitary, 15X 15 mm ulcer over medial aspect of labia majora covered with gray exudate (pseudo-membrane).

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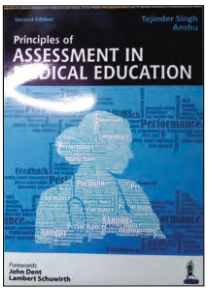

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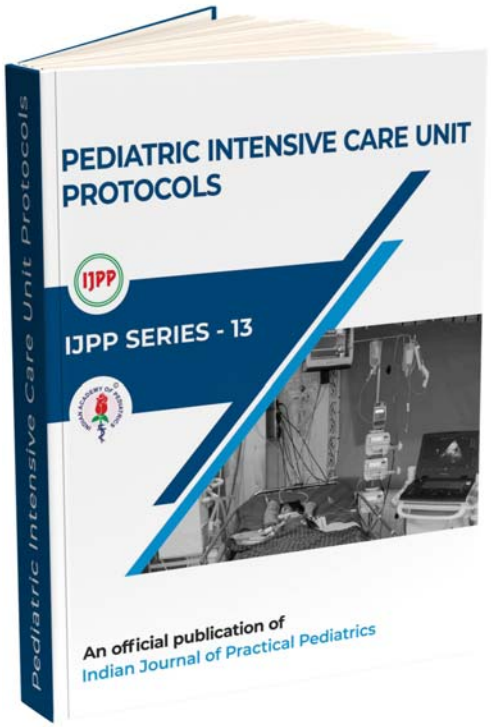

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