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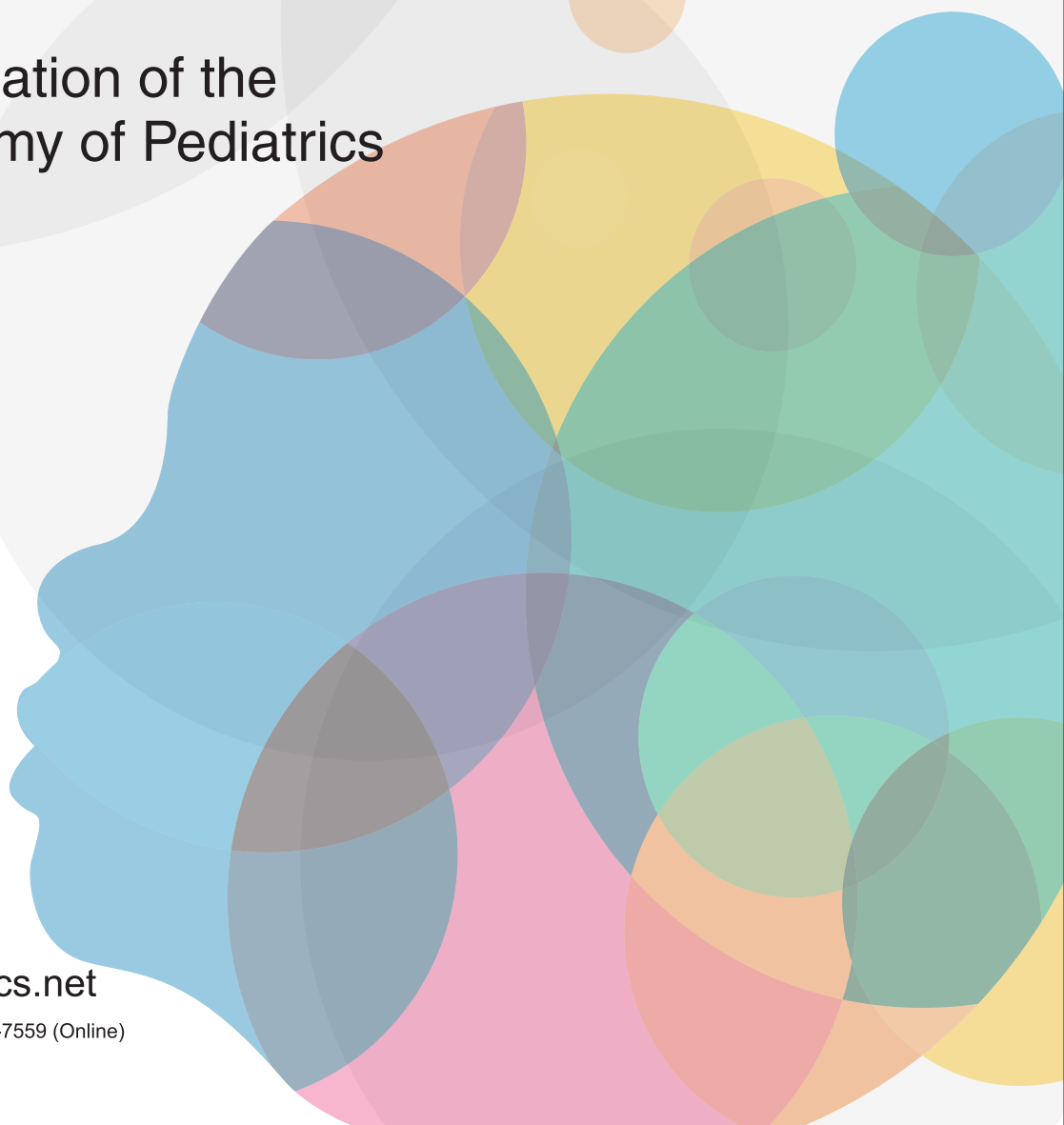

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IAP Guidelines for pediatric skincare state that ideal care of newborn skin comprises of:[1]

- 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]

RA/IB/8Mar2021/05

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

References: 1. Madhu R, et al. Indian Academy of Pediatrics Guidelines for Pediatric Skin Care. Indian Pediatr. 2021;58(2):153-161. 2. Data on File. 3. DOF 3 Capone AAD 2017. 4. Johnson & Johnson Consumer Products Worldwide. Claim support and data summary for Johnson's Cottontouch Baby Oil. 5. Anwar S, et al. A scoring method to assess the gentleness of cleansers. Presented at the American Academy of Dermatology Annual Meeting, March 20–24, 2020, Denver, CO, USA. 5. Data on file. 6. Capone K, et al. Effects of Emollient Use on the Developing Infant Skin Microbiome. Presented at the American Academy of Dermatology Annual Meeting, March 1-5, 2019, Washington, DC, USA.

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CONTENTS

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INVITED COMMENTARY

Amplitude of Care for the Neonatal Brain

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Neonatal encephalopathy is still a significant problem worldwide with an incidence estimated at 3 per 1000 live births [1]. It is a clinical condition encountered in the very early days of life of a newborn, characterized by depressed level of consciousness and/or seizures, often associated with abnormal tone and reflexes, and autonomic dysfunction [2]. This condition can be secondary to a plethora of etiologies during prenatal, intrapartum to postnatal period that can lead to cerebral injury [3]. There can be a variety of adverse short term and long term neurodevelopmental outcomes of neonatal encephalopathy, based on the etiology and severity of injury. In the last couple of decades, there has been a growing interest in developing accurate physiological, radiological and biochemical markers for a reliable prediction of outcome in patients with neonatal encephalopathy [4].

Amplitude-integrated EEG (aEEG) is one such biomarker that is widely used in neonatal intensive care unit (NICU) as a simple clinical tool to assess neonatal encephalopathy as it provides a real time and continuous monitoring of the cerebral activity. In addition to its use in detecting neonatal seizures, it is also helpful in predicting neurodevelopmental prognosis. aEEG represents a processed version of cerebral activity as recorded from limited electrodes on the neonatal scalp, which is derived by filtering frequencies below 2 Hz and above 15 Hz, semilogarithmic amplitude compression and time compression [5]. aEEG is a reliable and highly sensitive diagnostic tool that can be used in NICU especially when there is limited availability of conventional full array video-EEG (cEEG), which is considered the gold standard test for neuro-monitoring. Additional advantage of aEEG is the easy interpretation of recording by simple pattern-recognition, which can be particularly useful to healthcare providers in intensive care units without neurological background or formal electrophysiology training.

In the current issue of *Indian Pediatrics,* Sharma, et al. [6] have published a prospective observational study to evaluate the diagnostic utility of aEEG in predicting the short term neurodevelopmental outcome in term neonates with encephalopathy regardless of the cause. Per the authors, the need for conducting this study is the dearth of data regarding the utility of aEEG in neonatal encephalopathies other than hypoxic ischemic encephalopathy (HIE). Although the sample size was relatively small with 58 subjects, the study commendably included with a fairly wide spectrum of etiologies for encephalopathy with HIE being the major cause followed by infection. The authors' decision to exclude neonates with major congenital malfor-mations, chromosomal abnormalities, neuronal migration disorders was reasonable, probably due to inherently high risk of global developmental delay and/or death in this subset of patients due to systemic, non-neurological issues. The definition of abnormal aEEG used in this study were compliant with the standard definitions of abnormal patterns reported in the routine aEEG monitoring. The aEEG correctly identified the encephalopathy (abnormal aEEG in 86% of the encephalopathic neonates). Similar to the prior studies mostly done in HIE subjects, this study demonstrated the statistically significant association between abnormal aEEG (abnormal background, immature or absent sleep-wake cycling and seizures) and the primary outcome measure (abnormal neurological exam at discharge and/or death) with a very high sensitivity at 100%. The current study with its simple design elegantly corroborates and highlights the utility of aEEG in monitoring newborns to potentially enhance the neurological care and hopefully improve outcome.

Similar to the current study conducted by Sharma, et al. [6], there are several prior studies that corroborated the significance of aEEG as a predictive tool of neurological outcomes in neonatal encephalopathy, especially in neonates with hypoxic ischemic encephalopathy. Naqeeb,

et al. [7] demonstrated a close relationship between the aEEG and subsequent neurodevelopmental outcome. In their study, 91% of neonates with a normal aEEG were normal on follow up at 18-24 months of age, while 77% of infants with moderately abnormal or suppressed aEEG and/or seizures died or developed neurologic abnormalities [7]. Osredkar, et al. [8] demonstrated that early onset of sleep-wake cycling (within 36 hours) and a normal sleep wake cycle pattern in neonates with hypoxic ischemic encephalopathy were associated with a favorable Griffith developmental quotient between 1-5 years of age. A systematic review published by Rio, et al. [9] confirmed that aEEG back-ground activity during the first 72 hours of life has a strong prognostic value in infants with HIE, in terms of predicting neurological outcomes such as death or moderate/severe disability.

The current study adds more evidence on the utility of aEEG in all encephalopathic newborns. Despite this interesting result, it is worth mentioning that aEEG has an innate limitation due to the high occurrence of artifacts which can alter the interpretation, especially for seizures [10,11]. It is always useful to review the raw EEG data to confirm, given the high occurrence of seizures in this study (74%). While the short term prognosis at discharge is very useful, it is also important to compare with long term data in infancy at 18-24 months where more sophisticated developmental testing could be performed, and these are no effect of hypothermia or sedative medications.

In summary, aEEG is a simple non-invasive monitoring tool that could provide important data regarding cerebral function during the critical postnatal course for newborns with encephalopathy. More studies are needed to evaluate the changes in aEEG trends with treatments and interventions during the NICU course in relation to the short and long term outcomes.

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RESEARCH PAPER

Diagnostic Accuracy of WINROP, CHOP-ROP and ROPScore in Detecting Type 1 Retinopathy of Prematurity

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Background: Algorithms for predicting retinopathy of prematurity (ROP) requiring treatment need to be validated in Indian settings to determine if the burden of screening can be reduced without compromising the sensitivity of existing gestation and weight-based cut offs.

Objective: To evaluate the performance of the available algorithms namely, WINROP (Weight, Insulin-like growth factor I, Neonatal ROP), CHOP-ROP (Children's Hospital of Philadelphia ROP) and ROPScore in predicting type 1 ROP and time from alarm to treatment by each algorithm.

Study design: Ambispective observational.

Setting: Tertiary care neonatal intensive care unit in India.

Participants: Neonates less than 32 weeks or less than 1500 g born between July, 2013 to June, 2019 (*N*=578), who underwent ROP screening.

Primary outcome: Sensitivity, specificity and time from alarm to treatment by each algorithm.

Results: The sensitivity and specificity of WINROP was 85% and 36%, for CHOP-ROP it was 54% and 71%, and for ROPScore it was 73% and 67%, respectively in detecting type 1 ROP. A total of 50/51 (98%) of neonates with type 1 ROP underwent treatment at median gestation of 9 weeks and median time from alarm to treatment by WINROP, CHOP-ROP and ROPScore was 7, 7 and 3 weeks, respectively.

Conclusion: WINROP, CHOP-ROP and ROPScore were not sensitive enough to replace the gestational age, weight and risk factor-based screening criteria for type 1 ROP.

Keywords: *Neonatal intensive care unit, Premature, Sensitivity, Specificity.*

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Low- and middle-income countries are currently facing the third epidemic of retinopathy of prematurity (ROP) on account of higher rate of preterm birth and wide variations in neonatal care provided. Blencowe, et al. [1] estimated that approximately 98077 neonates in India would require screening for ROP amounting to nearly three lakh examinations every year. National guidelines recommend screening of all the neonates <34 weeks or <2000 gram or neonates with gestational age between 34-36 weeks with risk factors for ROP such as prolonged oxygen support, cardiovascular instability, and sepsis [2]. When compared to screening criteria in developed countries, these guidelines are much higher, as bigger babies also develop severe ROP in developing countries, and this further increases the screening load [3,4]. Given the paucity of skilled ophthalmologists for screening; gestation and weight-based screening criteria increase the burden on existing health systems, leading to poor quality of services being provided and eventually leading to missing out on cases requiring close follow up and treatment.

Current conventional screening method for ROP is a painful procedure. It leads to physiological changes like hypertension and decrease in oxygen saturation [5]. In addition, this is an additional burden on the fragile health system. Many screening algorithms have been developed and are in place for more than a decade now. However, due to their inability in providing 100% sensitivity (assuming gestation and weight risk factor-based screening criteria as standard), none of the algorithms have been able to replace existing protocols. These algorithms have shown high sensitivity and negative predictive value in many countries; however, they have not been widely validated in Indian settings [6-8]. Due to lack of sufficient literature in Indian settings, this study was planned with the aim to evaluate the diagnostic performance of all the three algorithms, namely WINROP (Weight, Insulin-like growth factor I, Neonatal ROP), CHOP-ROP (Children's Hospital of Philadelphia ROP) and ROPScore in predicting type 1 ROP in an Indian setting [9,10]. We also evaluated time from alarm to treatment by each algorithm.

METHODS

This study was conducted as an ambispective observational study with a retrospective phase collecting data from 1 July, 2013 to 30 June, 2018 and a prospective phase comprising of data collected from 1 July, 2018 to 30 June, 2019 at a tertiary care hospital. The policy of our unit is to screen all neonates less than 32 weeks gestational age (GA) or neonates with a birthweight less than 1500 g or bigger neonates (32-34 weeks GA or bithweight 1501-2000 g) with risk factors (respiratory or hemodynamic instability, anemia requiring transfusion or culture positive sepsis). Our unit has a strict pulse oximetry monitoring policy for preterm infants care in the NICU. Since only neonates less than 32 weeks GA can be entered in WINROP and ROPScore, the neonates less than 32 weeks or birthweight less than 1500 g who underwent retinopathy of prematurity screening were included in the study. Neonates with congenital malformation, hydrocephalus and hydrops fetalis were excluded.

Records of all the neonates who underwent ROP screening in the retrospective phase were retrieved from ROP registers maintained in the unit. In addition, all the demographic details, and antenatal, intrapartum and postnatal course details were retrieved from the medical records department. Birthweight, gestational age and weekly weight (weight on postnatal day 8, 15, 22, 29 and so on) of these infants till discharge was noted. Neonates on invasive ventilation were weighed on alternate days after disconnecting from ventilator for a brief duration as per the unit policy. The appropriateness of birthweight for gestational age was assigned by the AIIMS intrauterine growth chart [11] for neonates ≥32 weeks of gestation or Lubchenco growth charts [12] for neonates less than 32 weeks of gestation.

All the infants satisfying the inclusion criteria were screened for ROP as per the unit protocol at 4 weeks of postnatal age with the exception of those <28 weeks whose first screen was done at 2-3 weeks postnatal age. ROP was described as per International Classification of Retinopathy of Prematurity and was classified into treatment group as per Early Treatment of Retinopathy of Prematurity Classification [13,14]. The worst stage of ROP and the presence of plus disease (when present) was recorded. In cases where both eyes were affected, worst stage of the ROP of either eye was taken. Postnatal age of development of type 1 ROP as defined by any ROP in Zone I with plus disease or stage 3 ROP in zone I without plus disease or stage 2 or 3 ROP in Zone II with plus disease was noted and the treatment provided was also recorded. The infants with type 1 ROP findings who were lost to follow up were contacted telephonically to know their ophthalmological outcome and intervention done (laser photocoagulation/anti-VEGF injection). Similar data collection was performed for the prospective phase after informed parental consent. Ethical clearance was obtained from institute's ethics committee.

Data obtained from included neonates was entered into the following three predictive algorithms according to the eligibility criteria:

WINROP: All the neonates less than 32 weeks of gestation at birth irrespective of the BW were eligible to be entered into WINROP, which is available online (*www.winrop.com*) [15]. Birthweight, gestational age and weekly weight were entered till 35 weeks of postmenstrual age or discharge, or till the alarm signals in the algorithm, whichever was earlier. WINROP algorithm requires that the weight of neonate be entered till 35 weeks of postmenstrual age (PMA) to classify a neonate to be at low risk.

CHOP-ROP: Neonates less than 31 weeks of GA or less than 1501 g birthweight were eligible to be evaluated by CHOP-ROP [16]. Birthweight, gestational age and daily weight gain rate was entered into the algorithm to calculate the risk score from 2nd week onwards. CHOP-ROP requires documentation of neonatal weight at end of second week to be included in the algorithm. Weight change in the first week was disregarded as per the original study. Daily weight gain rate was calculated by weekly measurements (difference between current weight and previous week's weight divided by 7). For neonates with gestation >28 week, only birth weight and weight gain rate was used for calculation. Alarm cutoff of ≥0.010 was used to identify neonates at risk of type 1 ROP.

ROP score: Neonates less than 32 weeks or <1500 g whose weight at end of 6th week postnatal age was available before discharge or at follow up were eligible to be included in the ROPScore algorithm proposed by Eckert, et al. [17]. This score required data on use of oxygen in mechanical ventilation (invasive or non-invasive ventilation including CPAP upto sixth completed week), requirement of blood transfusion up to sixth completed week of life, neonate's weight at sixth completed week in addition to birthweight and gestational age: ROPScore excel sheet was used for calculation of the score. Cutoff for risk of type 1 ROP was taken as ≥14.5.

Primary outcomes were to evaluate the specificity and the sensitivity of three screening algorithms namely, WINROP, CHOP-ROP and ROPScore, in predicting type 1 ROP. Secondary outcome was time from alarm to predict type 1 ROP by these algorithms to the time the neonates underwent treatment for the same.

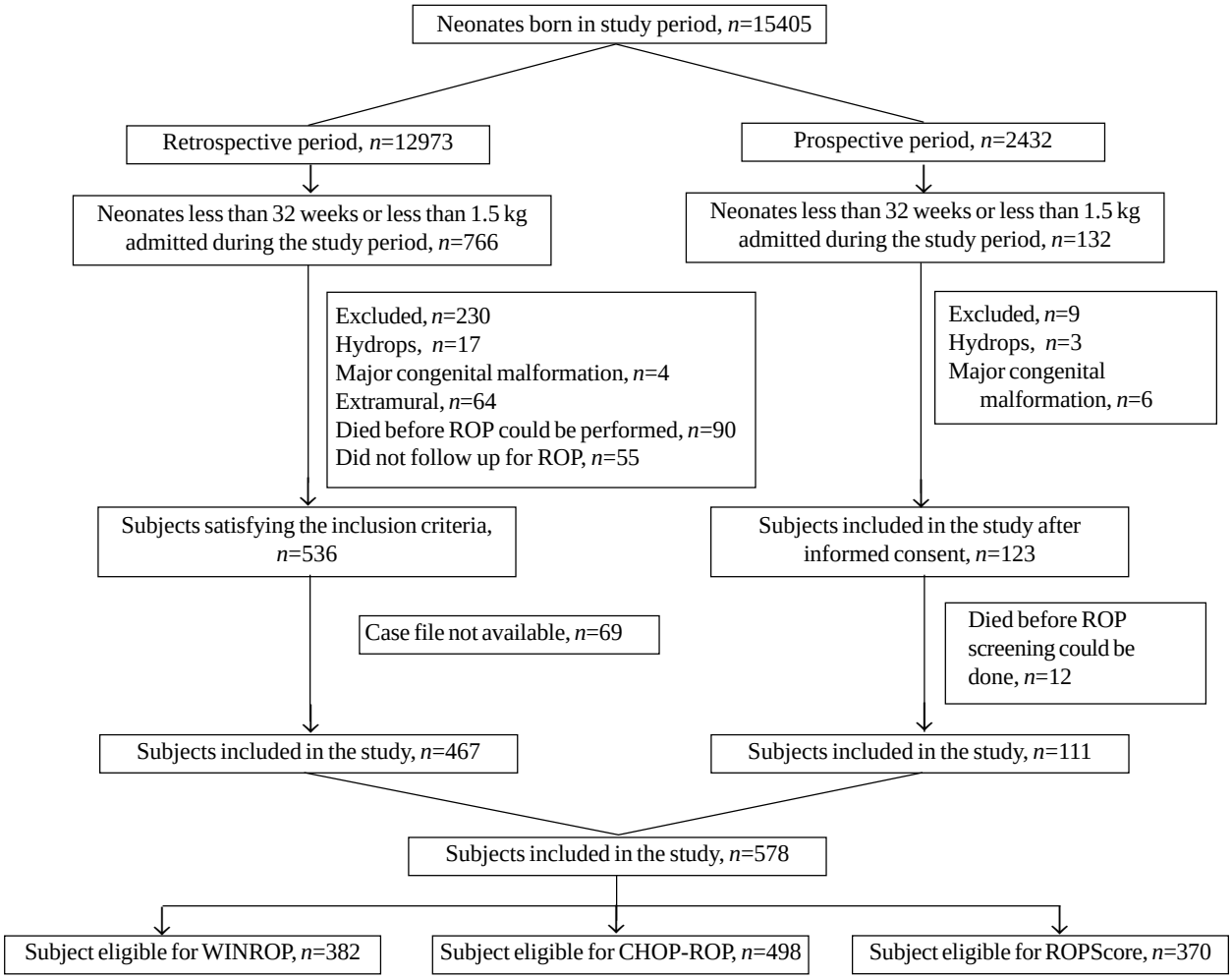
The reported specificity for CHOP-ROP was 51%, for ROPScore 57%, and for WINROP was 60% [6-9,18]. To detect a similar magnitude of difference (i.e. absolute difference of 9%) between CHOP-ROP and WINROP algorithms, with a power of 80% and alpha error of 5%, a total of 473 neonates had to be enrolled.

Statistical analysis: Statistical analysis was done using Stata 12.0 (StataCorp). Diagnostic performance of all the three algorithms was described by calculating sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio along with 95% confidence interval for predicting the risk of type 1 ROP using Open Epi ver 3.01. The receiver operating characteristics (ROC) curve was constructed, and the cutoff of ROPScore and CHOP-ROP with 100% sensitivity and maximal specificity was calculated.

RESULTS

Out of 15,405 neonates born during the study period with 898 neonates were less than 32 weeks GA or birth weight <1500 g. The records of 578 neonates who underwent at least one ROP screening satisfying the inclusion criteria were available. A total of 382 out of 578 (66%), 498 out of 578 (86%) and 370 out of 578 (64%) neonates could be analyzed for their risk of developing type 1 ROP using WINROP, CHOP-ROP and ROPScore algorithms, respectively. **Fig. 1** describes the study flow and reasons for exclusion from the study.

Neonates included in the study had a mean (SD) GA and birth weight of 30.3 (2.4) weeks and 1184 (308) gms, respectively. Other demographic details have been provided in **Table I**. One third of the neonates were noted to have any ROP with a quarter of them requiring treatment



ROP: Retinopathy of prematurity; WINROP: Weight, Insulin like growth factor-1, Neonatal ROP: CHOP-ROP: Children's hospital Philadelphia ROP.

Fig. 1 Study flow.

Table I Baseline Characteristics of the Study Population (*N*=578)

Characteristics	*Value*
Gestational age (wk)[a]	30.3 (2.37)
Birthweight (g)[a]	1184 (308)
Small for gestational age	234 (40.5)
Male	306 (52.9)
Singleton	414 (71.6)
Complete antenatal steroid coverage	350 (60.5)
Resuscitation (more than initial steps)	181 (31.3)
Apgar score at 1 min[a]	6.1 (2.02)
Apgar score at 5 min[a]	7.5 (1.3)
Respiratory distress requiring surfactant	176 (30.4)
Bronchopulmonary dysplasia	81 (14)
Invasive ventilation	150 (26)
Invasive ventilation duration (d)[b,c]	6 (3-19)
Grade III or IV intraventricular hemorrhage[d]	18 (3.2)
Periventricular leukomalacia[d]	67 (11.6)
Hemodynamically significant ductus arteriosus	61 (10.5)
Hypotension requiring inotropes	60 (10.4)
Sepsis requiring antibiotics	182 (31.4)
Day of regaining birth weight[a]	11.9 (5.3)
Anemia requiring transfusion	112 (19.4)

Data expressed as no. (%) except [a]mean (SD) or [b]median (IQR). [c]among those who received it; [d]among those screened.

Table II Retinopathy of Prematurity in the Study Population

Characteristics	*Retrospective Cohort (n=467)*	*Prospective Cohort (N=111)*	*Combined (n=578)*
Any ROP	183 (39.2)	25 (22.5)	208 (36)
Type of ROP			
Type 1	42 (8.9)	9 (8.1)	51 (8.8)
Type 2	18 (3.8)	1 (0.9)	19 (3.3)
Mild ROP	123 (26.3)	15 (13.5)	138 (23.9)
Identification of any ROP (wk)[a,b]	6 (4-8)	7 (6-9)	6 (4-8)
Identification of type1 ROP (wk)[a,b]	9 (7-10)	9 (7-12)	9 (7-10)
Number of screenings[a]	3 (2-5)	3 (2-4)	3 (2-5)

Data represented as n (%) or [a]median (IQR). [b]time to identification. ROP-retinopathy of prematurity.

(**Table II**). No neonate less than 32 weeks having type 1 ROP was missed by the existing screening protocol; amounting to sensitivity of 100% in this age group. Around 70 (12%) neonates were lost to follow up from the screening protocol out of which 5 neonates had type 1 or 2 ROP on last screen available and were contacted telephonically to know their final ophthalmological outcome. All but one neonate with type 1 ROP underwent treatment for the same at a median postnatal age of 9 weeks or 36 weeks postmenstrual age. Only one baby received anti- VEGF injection during the study period.

Diagnostic performance of the three screening algorithms has been provided in **Table III**. WINROP had the maximum sensitivity (85%) to identify neonates with type 1 ROP followed by ROPScore and then CHOP-ROP. Specificity followed the reverse order with CHOP-ROP being most specific (71%). Decreasing the cutoff point of ROPScore to 10.79 gave 100% sensitivity with a specificity of 16.5% (12.8%-20.9%) and avoided screening in 61 neonates. WINROP and CHOP-ROP identified type 1 ROP earliest at 2 weeks of postnatal age, around 7 weeks before conventional screening method where the neonates with type 1 ROP were identified and treated at 9 weeks of postnatal age. ROPScore identified neonates at risk of type of type 1 ROP at 6 weeks of postnatal age, by which time 3 neonates were already treated for type 1 ROP by conventional screening method. ROC curve of CHOP-ROP and ROPScore for identifying type 1 ROP among 334 neonates showed area under curve of ROPScore [0.75 (0.66-0.83)] to be more than that of CHOP-ROP [0.66 (0.58-0.95)] (**Fig. 2**). Since WINROP gives only binary output to signify the risk of developing type 1 ROP unlike a continuum of scores provided by CHOP-ROP and ROPScore, an ROC curve for the same was not constructed.

DISCUSSION

The study was conducted at a level III neonatal intensive care unit on intramural neonates. The unit caters mainly to high risk neonates who are referred in utero from many parts of North India early in gestation and where gentle ventilation guided by pulse oximetry along with antibiotic stewardship is the norm.

Our rates of ROP and type I ROP were higher than the literature [19], possibly due to the smaller gestational age and lesser birthweight of our neonates. Sensitivity of WINROP in our cohort was 85.42% which was slightly lower than the recent study by Sanghi, et al. [10] (90%). Low sensitivity (65%) of WINROP was observed in a study in Taiwan where older and larger neonates developed ROP requiring treatment which were missed by the WINROP [20]. The specificity (36%), positive predictive value (16%) and high negative predictive value (94%) in our study was in accordance with the previously reported literature [8,21,22].

CHOP-ROP performed poorly in our cohort with a sensitivity of 54%. This was lower than that reported by

Table III Diagnostic Performance of WINROP, CHOP-ROP and ROPScore

Parameter	*WINROP (n=382)*	*CHOP-ROP (n=498)*	*ROPScore (n=370)*
Sensitivity (%)	85.4 (72.8-92.7)	54 (40.4-67.0)	72.9 (59-83.4)
Specificity (%)	36.2 (31.3-41.5)	71.4 (67.1-75.4)	67.3 (61.9-2.2)
PPV (%)	16.1 (12.1-21.2)	17.4 (12.3-24.2)	25 (18.6-32.8)
NPV (%)	94.5 (89.1-97.3)	93.3 (90.1-95.5)	94.3 (90.5-96.6)
Positive LR	1.3 (1.3-1.4)	1.9 (1.7-2.0)	2.3 (2.1-2.3)
Negative LR	0.4 (0.3-0.5)	0.6 (0.6-0.7)	0.4 (0.3-0.5)
Diagnostic OR	3.3 (1.4-7.6)	2.9 (1.6-5.3)	5.5 (2.8-10.9)
NNS	9.4 (5.9-21.4)	9.6 (6.2-21.1)	5.2 (3.8-7.9)

95% CI in parenthesis. ROP-retinopathy of prematurity; WINROP-weight, insulin-like growth factor I, neonatal, ROP; CHOP-ROP-Children's Hospital of Philadelphia ROP; PPV-Positive predictive value; NPV-Negative predictive value; LR- likelihood ratio; OR-odds ratio; NNS-Number needed to screen.

Doshi, et al. [9] (67%) in 2019 Indian infants in spite of their cohort dealing with bigger neonates. They used the nomogram provided by Binenbaum, et al. [16] for manual calculation of alarm limit. This method was not considered feasible in our setting due to large sample size and hence the original formula provided by Binenbaum, et al. [16] was used. In the study by Doshi, et al. [9] decreasing the cutoff from 0.014 to 0.010 gave 100% sensitivity. However, in our study the cutoff had to be decreased to 0.001 to give 100% sensitivity, which in turn decreased the specificity to unacceptable levels (2.23%).

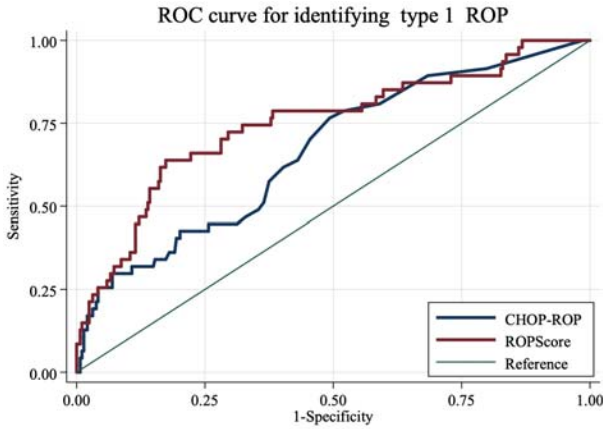
The sensitivity of ROPScore was 73% which was lower than previous studies (95-100%) [6,23]. When the cutoff of ROPScore was decreased to 10.79, the sensitivity approached 100% and this cut off potentially would avoid screening in 16.5% of neonates and thus has clinical implication. ROPScore showed better diagnostic performance with an area under curve of 0.75 vs 0.66 of CHOP-ROP. However, ROPScore has inherent disadvantages as it gives an alarm at 6 weeks of postnatal age when most of the neonates with aggressive posterior ROP are already identified by conventional screening methods and treated. In addition, many neonates with risk factors who are discharged before six weeks of postnatal age cannot be evaluated using ROPScore thereby missing out on cases with type 1 ROP.

The median time from alarm to treatment in our study for WINROP, CHOP-ROP and ROPScore was 7, 7 and 3 weeks, respectively which was lower than those previously estimated [24], where it was 11.1, 9.1 and 5.1 week, respectively.

An ideal algorithm for identifying type 1 ROP is the one with 100% sensitivity and a reasonable level of specificity so as to reduce the unwanted ROP screenings being done currently. None of the algorithms were sensitive enough in our setting probably due to a higher saturation target of 90-95% being followed in the unit. A similar decrease in sensitivity of WINROP from 87.5% to 48% was noted by Lundgren, et al. [25] when the saturation targets increased from 88-92% in 2011-2012 to 91-95% in 2015-2016.

Strengths of our study are its large sample size, and using registers maintained by the staff and doctors of the unit containing data of neonates who underwent ROP screening to retrieve the files of neonates who underwent screening, and this was cross-checked with the electronic discharge data of the unit. Three rounds of file retrieval from medical records department was conducted before classifying a file as non-available. Our study has some limitations as well. The weight was not available at 6 weeks completed age in 196 out of 467 (42%) neonates enrolled in retrospective phase. None of the algorithms could accommodate all the neonates included in the study, thereby true comparison of diagnostic performance of the various algorithms with the existing weight and gestation-based criteria could not be performed.

In conclusion, none of the screening algorithms with their recommended cutoffs was able to provide 100% sensitivity as provided by the weight, gestational age and



ROC: Receiver operating characteristics curve; CHOP-ROP- Children's Hospital of Philadelphia ROP; ROP-retinopathy of prematurity.

Fig. 2 ROC curve of CHOP-ROP and ROPScore for identifying type 1 ROP.

WHAT IS ALREADY KNOWN?

- Gestational age, weight based as well as risk factor-based criteria are generally followed to screen neonates at risk for developing type 1 ROP.

WHAT THIS STUDY ADDS?

- None of the three screening algorithms examined in the study was able to provide 100% sensitivity as provided by the weight, gestational age and risk factor-based screening protocol.

risk factor-based screening protocol being currently followed in the unit. Although ROPScore with a modified cutoff of 10.79 looks promising since it has 100% sensitivity, it has a poor specificity of 16.5% and it gives an alarm at 6 weeks completed age, a time at which few of the neonates would already have been identified by conventional screening method.

Ethics clearance: Institutional ethics committee of Post Graduate research (clinical sciences), AIIMS, New Delhi; No. IECPG-280 dated 28 June, 2018.
Contributors: DT: prepared the first draft of the protocol and had the prime responsibility of data collection, data analysis and compilation of results; SM: collected data, cross checked data entry and contributed to the manuscript; AT: conceptualized the study, supervised data entry and provided input in preparation of protocol and final manuscript; MJS: contributed to protocol formation, helped in statistical analysis and contributed to final manuscript; PC: valuable suggestion during protocol formation and provided input to final manuscript; RA: critically reviewed the protocol of the study, ensured timely progress of the study via departmental meetings and provided input to final manuscript; AD: input in protocol of the study and critically reviewed the final manuscript. All the authors in principal agreed to the final manuscript of the study.
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CLIPPINGS

Theme: Gastroenterology and Hepatology

Relationship between quantitative sonographic measurements and serum biochemical parameters in childhood obesity (Pediatr Gastroenterol Hepatol Nutr. 2021;24:470-82)

Childhood Obesity is global public health problem affecting not only the adolescents but also the young children, and its prevalence is increasing day by day. According to WHO, in 2016 over 340 million children and adolescents aged 5-19 were overweight or obese; 39 million under-five children were overweight or obese in 2020. Obesity is closely related with the development of metabolic syndrome and excessive fat accumulation in hepatocytes leading to the development of non-alcoholic fatty liver disease (NAFLD) in children. In this study published from Turkey involving 174 overweight or obese children aged between 3-18 years (mean age of 10.6 year), the relationship between various indicators of obesity [e.g., BMI *z*-score, abdominal wall fat thickness, serum biochemical markers (AST, ALT, HDL, LDL, total cholesterol, Insulin and HOMA-IR levels)] and sonographic measurements of fatty liver was assessed. Authors found a positive correlation between liver-kidney echogenicity ratio (LKER) and serum transaminase and glucose levels in obese children. A positive correlation was also found between BMI *z*-score and abdominal wall fat thickness (AWFT) with fasting insulin level and HOMA-IR value. Authors concluded that due to the wide availability of the ultrasonography, it can be used as an effective tool in the management of the childhood obesity. **Celiac disease in children: An association with drug-resistant epilepsy (**Pediatr. Neurol 2021;120:12-17)

Seizures are one of the neurological manifestations in children with celiac disease. In the present study published from University of Utah, authors did a retrospective chart review to compare the children having epilepsy and celiac disease (*n*=56) with 168 age- and sex-matched controls having only epilepsy, to analyze the effect of gluten-free diet on seizure burden. Study results showed that the children with celiac disease had a significantly higher percentage of drug-resistant epilepsy compared to control group, but comparable to the general population. Adherence to the gluten free diet along with the medications reduces the disease burden in children with celiac disease having drug resistance epilepsy.

Neutrophil to lymphocyte ratio and gastrointestinal involvement among Henoch Schonlein purpura patients: A systematic review and meta-Analysis (J Pediatr Gastroenterol Nutr. 2021;73:437-43**)**

Recently the Neutrophil to lymphocyte ratio has attracted much attention as a marker of systemic inflammation. A very simple investigation which is easily available and does not add to the cost of routine investigations and has been tested in various clinical conditions. In the current study the authors does the meta-analysis of the studies published on Henoch Schonlein purpura (HSP), to evaluate the difference in the neutrophil to lymphocyte ratio among the HSP patients presenting with and without gastrointestinal manifestations. They have analyzed 6 studies with low heterogeneity, and found that the patients of HSP with gastrointestinal involvement have higher neutrophil to lymphocyte ratio compared to those without gastrointestinal involvement [mean difference of 0.88 (95% CI 0.55, 1.22)]. Authors concluded that the neutrophil to lymphocyte ratio in cases with HSP could serve as the marker of gastrointestinal involvement.

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RESEARCH PAPER

Preterm White Matter Injury: A Prospective Cohort Study

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Objective: To determine the incidence and risk factors of preterm white matter injury [WMI; periventricular-intraventricular hemorrhage (PIVH) and/or periventricular leukomalacia (PVL)].

Design: Prospective cohort study.

Setting: Level-3 neonatal intensive care unit.

Patients: Inborn preterm neonates (*n*=140) delivered at <32 weeks gestation or birthweight <1500 g.

Methods: Serial cranial ultrasounds were performed at postnatal ages of 3 days (±12 hour), 7 (±1) days, 21 (±3) days and 40 (±1) weeks postmenstrual age (PMA). PIVH and PVL were graded as per Volpe and De-Vries criteria, respectively. Univariate followed by multivariate analysis was done to evaluate risk factors for PIVH and PVL.

Outcome measures: The primary outcome was the incidence of preterm WMI. The secondary outcomes were evaluation of risk factors and natural course of WMI.

Results: The mean (range) gestation and birth weight of enrolled neonates were 29.7 (24-36) weeks and 1143 (440-1887) g, respectively. PIVH occurred in 25 (17.8%) neonates. PVL occurred in 34 (24.3%) neonates. None of them were grade III or IV PVL. Preterm WMI (any grade PIVH and/or PVL) occurred in 52 (37.1%) neonates. Severe PIVH (grade III) and cystic PVL occurred in 7 (5%) and 5 (3.6%) neonates, respectively. On multivariate analysis, none of the presumed risk factors were associated with PIVH. However, hemodynamically significant patent ductus arteriosus, and apnea of prematurity were significantly associated with increased risk of PVL.

Conclusions: Significant WMI occurred only in one-third of the cohort, which is comparable to that described in literature from the developed countries.

Keywords: *Outcome, Periventricular- intraventricular hemorrhage, Periventricular leukomalacia, Risk factors*.

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Survival of very low birthweight (VLBW) neonates has improved over the last decade; survival rates being more than 90% in most centers [1]. This is largely due to improved obstetric and neonatal care practices, in particular, use of antenatal steroids and gentler non-invasive modes of ventilation [2]. Preterm white matter injury (WMI) and its associated neurological sequelae are of important concern to the neonatologist.

Periventricular-intraventricular hemorrhage (PIVH) and periventricular leukomalacia (PVL) are the two major forms of preterm WMI. PIVH originates in a highly active zone of cell proliferation in the preterm brain called as subependymal zone or germinal matrix, and later spreads into the ventricular cavity. PVL is characterized by foci of necrosis in periventricular white matter (focal component) and more diffuse glial response in the form of reactive gliosis and microglial activation in the surrounding white matter (diffuse component). Cranial ultrasound (CUS) is the screening procedure of choice for preterm WMI, especially PIVH [3].

Initial studies done in the 1980s showed a high incidence of PIVH (up to 40-50%) [4-6]. This has decreased to about 20-25% in developed countries in the last two decades [7,8]. In a study from our own center in 2004, the incidence of preterm WMI was about 32% [9]. No recent data is available from low-middle income countries like India. Hence, we planned this prospective cohort study to determine the incidence of WMI and its associated risk factors in VLBW neonates. The primary objective of this study was to determine the incidence of PIVH and PVL (i.e., preterm WMI) in neonates born at less than 32 weeks gestation or birth weight <1500 g. The secondary objectives were to evaluate the risk factors and natural history of PIVH and PVL till discharge from Neonatal intensive care unit (NICU) or 40 weeks postmenstrual age (PMA) using serial CUS.

METHODS

This prospective cohort study was conducted at a level-3 NICU, All India Institute of Medical Sciences, New Delhi from March, 2018 to June, 2019. Inborn preterm neonates born at <32 weeks gestation or birth weight <1500g were enrolled. Neonates with major CNS malformations (antenatally diagnosed or diagnosed at birth) or dying before the first cranial ultrasound were excluded. The

neonates were followed until 40 weeks PMA or discharge from NICU, whichever was later (**Fig. 1**).

The study was approved by the institutional ethics committee. Before enrolment an informed consent was obtained from parents.

Protocol for cranial ultrasound: Serial cranial ultrasounds (CUS) were performed on: Day 3±12 hours; Day 7±1 day; three weeks ± 3 days and 40 weeks/at discharge. If any CUS other than the last one was abnormal, clinical team decided frequency of next ultrasound. All initial CUS (within the first week) were performed bedside using Philips CX-50 (Philips). Subsequent CUS were done bedside wherever feasible (neonate in level 3 unit) or in the Radiology department (for neonates admitted in step down unit after stabilization) using Supersonic imagine (Aixplorer) or Antaris (Siemens).

Using a small footprint curvilinear probe with 2-5 MHz or higher frequency, CUS was performed using anterior fontanelle as an acoustic window. Standard views were obtained in the coronal and sagittal planes. Ventricular index (VI) was measured in coronal plane as the distance between falx and lateral end of anterior horn of lateral ventricle [10]. Thalamo-occiptal distance (TOD) was measured in oblique parasagittal view as distance between the outermost point of thalamus at its junction with choroid plexus and outermost extent of occipital horn [10].

An experienced pediatric radiologist performed the cranial ultrasound (CUS) in first 40 cases. Subsequently, CUS were done by the first author with a simultaneous review of all images done by the pediatric radiologist. There was < 10% discrepancy in the reported findings and in all such cases, report of the radiologist was considered final. PIVH was graded as per Volpe classification and PVL as per De Vries criteria [11,12]. Transient periventricular flare was defined as periventricular echogenicity not lasting for more than 7 days. The reference values of VI and TOD, were from the study by Brouwer, et al. [10].

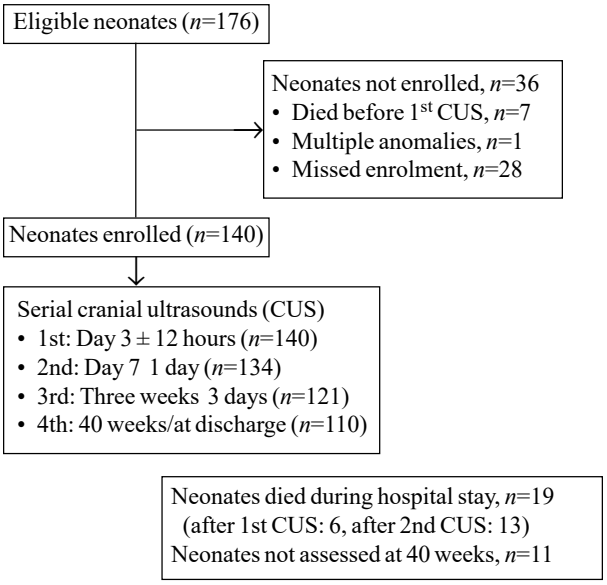

Fig. 1 Study flow chart.

Gestational age was assessed from the last menstrual period or first trimester ultrasound scan. If both were not available or a discrepancy of 1 week or greater was noted between the two, expanded New Ballard score was used [13]. Steroid coverage was considered 'complete', if the mother received 4 doses of dexamethasone 12 hours apart or 2 doses of betamethasone 24 hours apart, with last dose given at least 24 hours before delivery. Small for gestational age (SGA) was defined as birth weight less than 10th percentile on Lubchenco charts 14]. Birth asphyxia was defined as 5 minute Apgar score ≤5. Respiratory distress syndrome (RDS), sepsis, hemodynamically significant PDA (hs-PDA), shock, preterm premature rupture of membranes (PPROM) and prolonged rupture of membranes (PROM) were defined as per standard definitions [15]. Arterial blood gases (ABG) done by the NICU team for clinical monitoring were checked for PaCO2 values in first 72 hours of birth. Hypocapnia was defined as $PaCO_2$ <35 mmHg and hypercarbia as PaCO2 >45 mmHg. Hypotension was defined as BP < 5th centile [16].

The antenatal details like demographic data, obstetric history and current pregnancy details including antenatal steroid status, gestational age, cause of preterm delivery, duration of rupture of membranes, etc. were collected by principal investigator from mother's hospital records after the baby was enrolled. The details of delivery room resuscitation and NICU course like sepsis, hypotension, shock, hypocapnia, hypercarbia and acidosis in first 72 hours, were recorded in a predesigned proforma.

Based on the available literature, we assumed the prevalence of preterm WMI as 20%. With 95% confidence limit and an absolute precision of 7%, the sample size was calculated to be 126. Anticipating a loss to follow up at 40 weeks PMA, we decided to enroll 140 neonates.

Statistical analysis: A database was created in Microsoft Access 2016 (Microsoft) for recording the variables. Data analysis was done using STATA 15.1 version (Stata Corp). The incidence of PIVH and PVL along with 95% confidence intervals (95% CI) were calculated. For risk factors, we did univariate analysis followed by multivariate logistic regression with PIVH or PVL as dependent variable and identified risk factors as independent variables. Data analysis was done separately for PIVH and PVL.

RESULTS

During the study period, 176 eligible neonates were born, of which 140 were enrolled (**Fig. 1**). The mean (range) gestation and birthweight of enrolled neonates were 29.7 (24-36) week and 1143 (440-1887) g, respectively. The baseline characteristics of enrolled neonates are summarized in **Table I**.

Table I Baseline Characteristics and Hospital Course of Preterm Neonates Enrolled in the Study (*N*=140)

Characteristics	*N (%)*
Maternal characteristics	
Hypertension	30 (21.4)
Diabetes	30 (21.4)
PPROM	52 (37.1)
Antenatal steroids	130 (92.8)
Complete course	89 (63.6)
Vaginal delivery	24 (17.1)
Delivery room details	
5-min Apgar score ≤5	26 (18.6)
Delivery room CPAP	101 (72.1)
Delivery room intubation	36 (25.7)
Chest compressions	3 (2.14)
Neonatal characteristics	
Male gender	79 (56.4)
Small for date	50 (35.7)
Gestational age[a]	29.7 (24-36)
< 28 wks	26 (18.6)
28-31 wks	79 (56.4)
≥ 32 wks	35 (25)
Birthweight (g)[a]	1143 (440-1887)
<500	2 (1.4)
500-749	15 (10.7)
750-999	36 (25.7)
1000-1499	70 (50)
≥1500	17 (12.1)
RDS requiring surfactant	40 (28.6)
CPAP in NICU	121 (86.4)
IMV in NICU	49 (35)
Hypocapnia within 72 h[b]	9 (6.4)
Hypercarbia within 72 h[b]	15(10.7)
Acidosis within 72 h[b]	19(13.6)
Shock within 72 h[b]	8 (5.7)
Shock at any time	22 (15.7)
hsPDA	28 (20)
Sepsis	51 (36.4)
Meningitis	6 (4.3)
Necrotizing enterocolitis	4 (2.9)

Data presented as no. (%) or [a]mean (range). [b]Hours of life. PPROM: Preterm premature rupture of membranes; CPAP: Continuous positive airway pressure; RDS: Respiratory distress syndrome; IMV: Invasive mechanical ventilation; hsPDA: Hemodynamically significant patent ductus arteriosus; NICU: neonatal intensive care unit.

PIVH occurred in 25 (17.8%; 95% CI 12.3–25.2%) neonates-grade I, II, III, and IV in 17 (12.1%), 1 (0.7%), 6 (4.3%), and 1 (0.7%) neonates, respectively. Severe PIVH (grade III) occurred in 7 (5%) neonates. PIVH was bilateral in 15 neonates. PVL occurred in 34 (24.3%; 95% CI 17.8–32.2%) neonates-grade I and II in 29 (20.7%) and 5 (3.6%) neonates, respectively. Transient periventricular flares occurred in 7 neonates. We did not detect any grade III or IV PVL. Cystic PVL occurred in 5 (3.6%) neonates. PVL was bilateral in all our neonates. Preterm white matter injury (any grade PIVH and/or PVL) occurred in 52 (37.1%; 95% CI 29.5-45.5%) neonates (**Table II**).

PIVH was detected in first three days of life in 22 (88%) neonates and in all cases by day 7. Progressive ventricular dilation occurred in one-third of patients with grade III PIVH. Periventricular white matter echogeni-cities appeared in 33 (97%) cases within the first 7 days of life. Periventricular cysts were detected in 5 cases of cystic PVL by 3 weeks of age. Additional three neonates had ventricular dilation in CUS done at term gestation with no abnormality detected in previous scans, indicating likely periventricular white matter loss.

On univariate analysis, female gender, vaginal delivery, hypercarbia, acidosis and shock in first 72 hours of life were associated with increased risk of PIVH. However, on multivariate analysis none of these factors were significant. Similarly, delivery room endotracheal intubation, hypocapnia in first 72 hours of life, apnea, anemia requiring transfusion, hsPDA, sepsis, meningitis and BPD were associated with PVL on univariate analysis. However, on multivariate analysis, only hsPDA (OR 3.09; 95% CI 1.02–9.39; *P*=0.04) and apnea (OR 2.81; 95% CI 1.04-

Table II Profile of Preterm White Matter Injury Among the Study Cohort (*N*=140)

Characteristic	*No. (%) [95% CI]*
Peri-intraventricular hemorrhage	
Any grade	25 (17.8) [12.3-25.2]
Worst grade	
I	17 (12.1)
II	1 (0.7)
III	6 (4.3)
IV (PVHI)	1 (0.7)
Periventricular leukomalacia (PVL)	
Any grade	34 (24.3) [17.8-32.2]
Worst grade	
I	29 (20.7)
II	5 (3.6)
IIIIV	00
Cystic PVL	5 (3.6)
Preterm white matter injury[a]	52 (37.1) [29.4-45.5]

7.56; P=0.04) were found to be significantly associated with increased risk of PVL (**Table III**).

DISCUSSION

In this cohort of 140 neonates, PIVH occurred in 25 (17.8%) neonates. Severe PIVH occurred in 7 (5%) neonates. PVL occurred in 34 (24.3%) and cystic PVL occurred in 5 (3.6%) neonates. Preterm WMI (any grade PIVH and/or PVL) occurred in 52 (37.1%) neonates. However, most neonates had low-grade lesions (grade I PIVH/PVL). Severe PIVH and cystic PVL occurred in less than 5% of neonates which is comparable to what is described in literature from developed countries.

Comparing our findings to a previous study done from our own center 17 years back by Maria et.al [9], the incidence of any grade PVL and cystic PVL decreased from 36.2% and 12.4% to 24.3% and 3.6%, respectively. The incidence of cystic PVL in our cohort is similar to that reported in data from developed world [17-18]. Studies from 1980s reported the incidence of PIVH in premature neonates up to 40-50% [4-7]. The incidence decreased to 20-25% in studies done in late 1980s and 1990s [8,19]. The incidence of PIVH has remained almost the same in the last decade i.e., 20-25% in VLBW and up to 40% in neonates born at d" 28 weeks gestation [17,20]. However, there has been an increase in the survival of ELBW neonates who are at even higher risk of PIVH, which may mask a true decline in incidence of PIVH.

Multiple studies have implicated the role of pressure passive cerebral circulation of preterm neonates in causation of PIVH; [18] the classic setting being severe RDS requiring mechanical ventilation [21-22]. Hypercarbia also increases the risk of PIVH [23]. However, in our study, none of these risk factors were associated with PIVH. In our cohort, vaginal delivery was not associated with increased risk of PIVH. Earlier studies had shown that VLBW neonates born vaginally were at higher risk of PIVH [24]. However, more recent studies have contrary results [25]. In a study on periventricular hemorrhagic infarction (PVHI) by Bassan, et al. [26], fetal distress, need for emergency cesarean section, low Apgar scores, and need for respiratory resuscitation were strongly associated with PVHI. Another interesting study in which 95 VLBW infants underwent amplitude- integrated EEG monitoring for first 72 hours of life found high incidence (48%) of seizures which increased the risk for IVH and white matter injury [27]. Our study failed to show any association of delivery room resuscitation or birth asphyxia with PIVH. In this study, hsPDA and apnea were associated with increased risk of PVL. We, however, did not find any significant association of PVL with low APGAR scores, RDS, hypocapnia, acidosis, PPROM or meningitis, contrary to what is described in literature [28-31].

In our study, PIVH was detected in first three days of life in 22 (88%) cases and in all 25 (100%) cases by day 7. Most cases of PIVH were clinically silent. Approximately 90% of cases of IVH occur within the first 72 hours of life, with 50% occurring in first 6 hours [5,32,33]. The lesion progresses in about 10-20% cases over 3-5 days [34].

We had 3 neonates with apparently normal first 3 CUS scans, but showed ventriculomegaly in CUS done at term equivalent age. Data suggests that presence of persistent echo-densities for >7 days is significant and may actually represent non-cystic PVL [35,36]. In a study by Inder et.al, on 96 VLBW neonates, 10 neonates who had either normal CUS or transient echodensity had subsequent evidence of WMI on MRI at term. Further, 22 neonates with overtly abnormal CUS as persistent echo-density had normal MRI

Table III Risk Factors of Periventricular Leukomalacia (PVL) Among the Study Cohort (N=140)

	PVL (n=34)	*No PVL (n=106)*	*Adjusted OR(95% CI)*	*P value*
Male gender	19 (55.9)	60 (56.6)	1.07 (0.47-2.48)	0.86
Small for gestational age	16 (47)	34 (32.1)	2.48 (0.94-6.54)	0.06
Prolonged rupture of membranes	4 (1.2)	19 (17.9)	0.32 (0.07-1.47)	0.15
Preterm premature rupture of membranes	14 (41.2)	38 (35.8)	2.69 (0.79-9.14)	0.11
Antenatal steroids	20 (58.8)	69 (65.1)	1.31 (0.50-3.39)	0.58
Vaginal delivery	8 (23.5)	16 (15.1)	0.72 (0.17-3.05)	0.65
5-min Apgar score <5	8 (23.5)	18 (6.9)	1.57 (0.50-4.94)	0.43
Respiratory distress syndrome	10 (29.4)	30 (28.3)	0.47 (0.13-1.47)	0.18
Apnea	23 (67.6)	39 (36.8)	2.81 (1.04-7.56)	0.04
Shock requiring inotropes	8 (23.5)	14 (13.2)	1.01 (0.29-3.57)	0.73
Hemodynamically significant patent ductus arteriosus	12 (35.3)	16 (15.1)	3.09 (1.02-9.39)	0.04
Meningitis	4 (11.8)	2 (1.9)	2.05 (0.24-17.4)	0.50

WHAT IS ALREADY KNOWN?

- The incidence of preterm white matter injury (any grade) and severe peri-intraventricular hemorrhage (PIVH) /cystic periventricular leucomalacia (PVL) is 20-25% and below 5%, respectively in the developed countries.
- Incidence of any grade PVL and cystic PVL in India 15 years ago was 36.2% and 12.4%, respectively.

WHAT THIS STUDY ADDS?

- Severe PIVH and cystic PVL occurred in less than 5% of neonates.

at term gestation. Therefore, the sensitivity and specificity of transient and persistent echodensity on CUS for predicting abnormal MRI findings at term may not be good [35]. Therefore, while periventricular cysts are sensitive and specific for abnormal MRI correlates and poor neurodevelopmental outcomes, transient and persistent echodensities/flares are variably predictive of WMI on MRI at term gestation. We decided to follow PVL using CUS only because of the ease of doing bedside CUS and the risks involved in doing MRI under anesthesia.

The strengths of this study are its prospective cohort design and meticulous follow up of VLBW neonates till term gestation. About 80% of enrolled neonates underwent at least four CUS. All CUS images were reviewed by an expert pediatric radiologist. Data analysis was done separately for PIVH and PVL.

Our study has some limitations too. The study was not powered to evaluate the risk factors of WMI. We chose a relatively larger margin of precision (7%) primarily due to feasibility considerations. In addition, MRI brain would have been a better modality for characterization of PVL. However, literature does suggest acceptable agreement between serial CUS and MRI done at 40 weeks' gestation [37]. We also could not assess the impact of the CUS abnormalities on subsequent neuromotor development.

In conclusion, most VLBW neonates in our cohort had low-grades of preterm WMI (grade I PIVH and PVL). The incidence of severe PIVH and cystic PVL in our setting is low and is comparable to data from developed countries. We also noticed a decrease in the incidence of preterm WMI over the last 15 years in our setting.

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

Ethics clearance: Institutional ethics committee, All India Institute of Medical Sciences, New Delhi; No. IECPG-457, dated November 29, 2017.

Contributors: MRM: principal investigator; reviewed literature; prepared the initial protocol and this manuscript; collected data; performed cranial ultrasounds of enrolled neonates with images reviewed by MJ; AKD: framed the idea and rationale of this study; reviewed the protocol; supervised this study throughout its course; critical revision and finalization of this manuscript; MJ: Framed the cranial ultrasound (CUS) protocol; performed CUS in first 40 cases and reviewed all CUS images; RA,JS,AS: helped in preparation of initial protocol and this manuscript; supervised the study and critical revision of this manuscript.

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RESEARCH PAPER

Prognostic Value of Amplitude-Integrated Electroencephalography in Term Neonates With Encephalopathy

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Objective: To evaluate the prognostic value of amplitude-integrated EEG in term neonates with encephalopathy. **Methods:** In this prospective observational study we enrolled 58 term neonates with encephalopathy from March, 2019 to March, 2020. Level of alertness was ascertained as per Volpe's classification and tone as per Amiel-Tison scale of tone assessment. Abnormal aEEG was defined as background activity other than continuous normal voltage, or immature or absent sleep-wake cycle, or presence of electrical seizure. Primary outcome was abnormal neurological examination at discharge and/or death prior to discharge. **Results:** Out of 58 neonates, aEEG was abnormal for 50 (86.2%). There was a statistically significant association between abnormal aEEG findings and primary outcome (*P*=0.04). The aEEG score cut-off of >2 had satisfactory sensitivity (88.8%) and specificity (79.5%) to predict primary outcome. **Conclusion:** Abnormal aEEG had good sensitivity but low specificity to predict the primary outcome in term neonates with encephalopathy.

Keywords: *Hypoxic-ischemic encephalopathy, Prognosis, Seizures, Sleep-wake cycle.*

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Multi-channel electroencephalography (EEG) is considered as the 'gold standard' for evaluating background activity and detecting seizures, but continuous video-EEG monitoring and its interpretation is not feasible in the majority of neonatal intensive care units (NICUs), so amplitude-integrated EEG (aEEG) is used for real time monitoring of brain function and early detection of neonatal seizures [3]. In aEEG, the raw EEG signals are filtered, amplified and compressed for time to get a simplified aEEG waveform by which we can monitor long term trends in electro-cortical background activity [4].

Usefulness of aEEG in neonatal encephalopathies other than hypoxic ischemic encephalopathy has not been well studied and there is paucity of Indian data regarding the utility of aEEG monitoring in neonates. This study was planned to evaluate prognostic value of aEEG in term neonates with encephalopathy.

METHODS

This prospective observational study was conducted at a tertiary care NICU in India from March, 2019 to March, 2020 after institutional ethics committee clearance and informed consent from parents of all participants. Term neonates between 37^{+0} to 41^{+6} weeks of gestational age with encephalopathy were included. Babies with major lethal congenital malformations, chromosomal anomalies, neuronal migration disorders and myopathic disorders were excluded.

Invited Commentary: Pages 913-14

Encephalopathy was defined as subnormal alert state/ altered neurological function which may be associated with seizures [5]. Etiology of encephalopathy was sub-grouped as hypoxic-ischemic encephalopathy (HIE), infective causes, transient metabolic causes, intracranial hemorrhage (ICH), dyselectrolytemia, and inborn errors of metabolism (IEM). A detailed neurological examination was performed, and level of alertness was defined as per the Volpe classification, and tone was assessed as per Amiel-Tison scale of tone assessment [6,7].

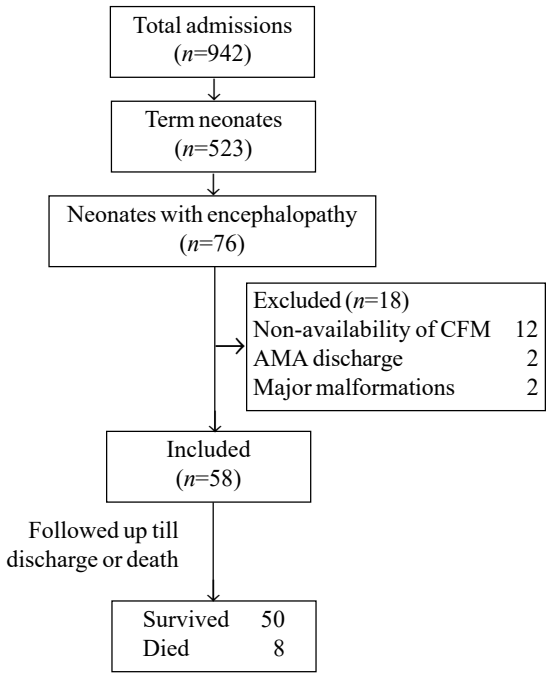
The aEEG monitoring was done by CFM Olympic Brainz Monitor (Natus Medical Inc.), with five biparietal hydrogel electrodes. Electrode impedance was main-tained below 10 ohms during monitoring. The aEEG was monitored for at least 24 hours for all enrolled neonates. A single investigator, trained for interpretation of aEEG findings in 10 aEEG recordings by a pediatric neurologist, noted the aEEG findings and scored as per the scoring used by Zhang, et al. [8].

Presence of any one of the following was defined as abnormal aEEG: any background activity other than continuous normal voltage, immature or absent sleep-wake cycle (SWC), and presence of any electrical seizure. Primary outcome was defined as subnormal level of alertness as per Volpe classification or any tone abnormality as per Amiel-Tison scale, at the time of discharge and/or death before discharge. Secondary outcomes were abnormal background activity, abnormal SWC, and electrical seizures, as defined above.

Statistical analysis: SPSS Software version 16 was used for data analysis. To determine the association between categorical variables, Chi square test was used as test of significance. $P<0.05$ was considered statistically significant. Diagnostic efficacy of aEEG background activity, aEEG sleep-wake cycle and aEEG seizures in predicting outcome at discharge was assessed by calculating specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio. Diagnostic efficacy of cumulative aEEG score in predicting outcome was assessed by ROC curve, suitable cut-off values were selected and AUC was calculated.

RESULTS

Of all the term neonates with encephalopathy, 58 were finally enrolled in the study and followed-up till discharge or death (**Fig. 1**). The baseline characteristics are given in



CFM, cerebral function monitor; AMA, against medical advice.

Fig. 1 Study flow diagram.

Table I Baseline Characteristics of Study Population (*N*=58)

Gestational age, wk[a]	38.5 (1.14)
Birthweight, g	2889 (360)
Male gender	35 (60.3)
Postnatal age	
1-3 d	36 (62)
4-7 d	8 (14)
8-14 d	5 (8.6)
15-28 d	9 (15.5)
Mode of delivery	
Vaginal delivery	24 (41)
Assisted vaginal delivery	6 (10)
Caesarean section	28 (48)
Resuscitation at birth	30 (52)
Antenatal risk factors	
Fetal distress	14 (24)
Pregnancy induced hypertension	6 (10)
Oligohydramnios	7 (12)
Polyhydramnios	6 (10)
Premature rupture of membranes	4 (7)
Etiology of encephalopathy	
Hypoxic ischemic encephalopathy	36 (62)
Infective	12 (21)
Transient metabolic	4 (7)
Intracranial hemorrhage	2 (3)
Dyselectrolytemia	2 (3)
Inborn error of metabolism	2 (3)

Variables are expressed as n (%) except [a]mean (SD).

Table I. Out of these, 50 (86.2%) survived. aEEG findings were abnormal for 50 (86.2%) of enrolled neonates. Out of these, 31 (62%) had normal outcome and 19 (38%) had abnormal outcome at discharge, or died prior to discharge. There was a statistically significant association between abnormal aEEG findings and primary outcome. Abnormal aEEG had 100% sensitivity, 20.5% specificity, 38% PPV, 100% NPV, positive likelihood ratio 1.26 and negative likelihood ratio 0, to predict primary outcome **(Web Table I).**

Out of 58 neonates, 38 (65.5%) had abnormal background activity. There was a statistically significant association between background activity and primary outcome (P=0.001). Out of 58 neonate, 19 (32.7%) had mature sleep-wake cycle and 39 (67.2%) neonates had immature or absent sleep-wake cycle, and there was a statistically significant association between sleep-wake cycle and primary outcome (P=0.001). A total of 43 (74.1%) neonates had electrical seizures, and aEEG seizures were significantly associated with primary outcome (P=0.002).

A cumulative aEEG score of 0-2 was seen in 32 (55%) neonates, and 26 (45%) had score >2. Out of 32 neonates with score of 0-2, 31 (97%) had normal outcome, ROC curve was plotted and cut-off value >2 was selected for high

sensitivity and low false positive rate. There was a statistically significant association between cumulative aEEG score >2 and primary outcome (P=0.001) **(Fig. 2).**

DISCUSSION

In this prospective observational study we assessed the characteristics of aEEG in 58 term neonates with encephalopathy and found that background activity, sleep-wake cycle and electrical seizures were significantly associated with primary outcome. In this study we also calculated cumulative aEEG scoring and we found that cumulative aEEG score of >2 was significantly associated with primary outcome. These results were largely consistent with previous studies.

In the present study we found that abnormal aEEG was significantly associated with abnormal outcome and it has high sensitivity, but low specificity to predict primary outcome. A meta-analysis by Chandrasekaran, et al. [9] showed similar results with pooled sensitivity of 87% and specificity of 36%. Similar to our findings, Van der Heide, et al. [10] noted significant association between aEEG background activity and neurologic outcome in neonates. Sewell, et al. [11] showed results opposite to our study with low sensitivity and high specificity. This may be due to inclusion of all grades of encephalopathy with various etiologies in our study, while they only included neonates with HIE. We found that aEEG cyclicity was significantly associated with primary outcome. Rhie, et al. [12] concluded in their study that delayed appearance of SWC was significantly associated with unfavorable neuroimaging in neonates with HIE, as was also seen in our study for all causes of encephalopathy.

Variane, et al. [13] showed that presence of recurrent aEEG seizures were associated with MRI brain abnormality and death, similar to this significant association with outcome was found in our study. Similar to this study, Luo, et al. [14] showed that aEEG scoring system has a higher specificity but low sensitivity as compared to individual components for abnormal outcomes.

Strengths of our study include enrolment of subjects with various causes of encephalopathy, albeit majority were HIE, and detailed study of the individual components of aEEG tracing and formulation of cumulative scoring cut-offs to predict short term neurological outcome.

Limitations of our study include a relatively small sample size, and inability to study long term neurological outcomes. Neonates admitted in the late stage of encephalopathy could have had different findings in aEEG if we had recorded aEEG at the onset of encephalopathy. Effect of ongoing drugs, and thera-peutic hypothermia were not taken into account, and the effects of postnatal age on aEEG findings were not studied.

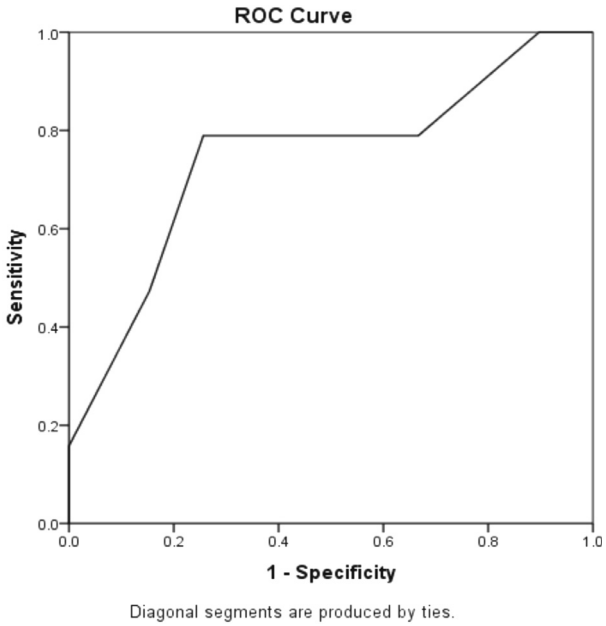


Fig. 2 Receiver operator characteristic (ROC) curve of cumulative aEEG scoring to predict abnormal neurological outcome (AUC=0.746).

To conclude, aEEG parameters such as abnormal background activity, absent sleep-wake cycling and presence of electrical seizures, either alone or in combination are associated with primary outcome of subnormal level of alertness or tone abnormality at discharge in term neonates with encephalopathy.

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

Ethical clearance: Institutional ethics committee, Kanchi Kamakoti CHILDS Trust Hospital Chennai; No. IEC-DNB/26/February2019, dated March 11, 2019.

Contributors: SGK: conceptualized the study, collected data, wrote the first draft of manuscript; NCK: study design, analysis, corrected manuscript and approved for final submission; HV: critical review of proposal, expert advice on data analysis and interpretation; SS: protocol development, supervising enrolment and outcome assessment; SSS: participated in planning of project and writing manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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WHAT THIS STUDY ADDS?

- Abnormal aEEG has high sensitivity but low specificity to predict primary outcome of subnormal level of alertness or tone abnormality at discharge, or death before discharge in term neonates with encephalopathy.

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CLIPPINGS

Theme: Gastroenterology and Hepatology

Do children with constipation have increased risk of asthma? Real-world data from a Nationwide population-based cohort study (Front Pediatr. 2021; 9:714406)

Research have shown that the alterations in the intestinal microflora have an important impact on the human body, and can be related to various chronic medical conditions. Recently it has been propounded that the alteration in the intestinal microbiota may have a profound effect on lung disease – gut-lung axis (GLA). In this nationwide population based cohort study, researchers have tried to assess the role of constipation as a risk factor for development of Asthma. In this equal number of matched children with and without constipation (10636 each) were enrolled from the Taiwan's National Health Insurance Research Database, and analyzed for the development of asthma. Results have shown that, after adjustment for sex, age, comorbidities, and use of medications, children with constipation had a 2.36-fold higher risk for developing asthma than non-constipated individuals. Also the severity of constipation was related to the increased risk of development of asthma in children. This study further highlights the important role of gut flora in development of disease.

Efficacy of polyethylene glycol 3350 as compared to lactulose in treatment of ROME IV criteria-defined pediatric functional constipation: A randomized controlled trial (Indian J Gastroenterol. 2021;40: 227-33)

Functional constipation constitutes up to ~ 30% of total cases coming to a pediatric gastroenterologist's outpatient department. Polyethelyene glycol (PEG) has been recommended as the first line of the management in cases of functional constipation. In the current study, to compare the efficacy of PEG 3350 (0.7–1.5 mg/kg/day) with lactulose (0.7–2.0 mg/kg/day); 100 children with functional constipation were randomized to receive either of the treatment. Results revealed that there was statistically significant increase in the median (min, max) stool frequency within 1 week in the PEG 3350 group as compared to the lactulose group [1 (0, 3) to 8 (3, 39) vs. 1 (0, 3) to 7 (1, 17)] (p-value < 0.01), which was maintained over a period of 4 weeks. There was a statistically significant reduction in the painful bowel movements in the PEG 3350 group as compared to the lactulose group at the end of first week. Thus, it concluded that the use of PEG 3350 is associated with faster symptom relief and the significant improvement in pediatric functional constipation.

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Web Table I Primary and Secondary Outcomes

Predictor	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Positive likelihood ratio*	*Negative likelihood ratio*
Primary outcome						
Abnormal aEEG	100%	20.5%	38%	100%	1.26	0.00
Secondary outcomes						
Background activity	94.7%	48.72%	47.3%	95%	1.85	0.11
Sleep-wake cycle	100%	48.72%	48.7%	100%	1.95	0.00
aEEG seizures	100%	38.46%	44.19%	100%	1.62	0.00
Cumulative aEEG score>2	88.8%	79.49%	50%	96.8%	4.33	0.14
Cumulative aEEG score>3	47.3%	84.62%	60%	76.7%	3.08	0.62
Cumulative aEEG score>4	31.6%	92.3%	66.7%	73.4%	4.11	0.74

PV, positive predictive value; NPV, negative predictive value

RESEARCH PAPER

Evaluating Maternal Discharge Readiness in Kangaroo Mother Care

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Objective: To develop and apply a tool for measuring hospital discharge readiness of mothers practicing continuous kangaroo mother care (KMC) in a tertiary setting. **Methods:** A 22-item questionnaire was adapted from an existing tool. After a pilot (*n*=20), the survey was administered to 200 mothers in the KMC unit, Kalafong Hospital, South Africa from 2017-2018. Two items which asked participants how confident and ready they felt overall were used to categorize women as 'ready' or 'less ready' for discharge. **Results:** Most women (*n*=168, 88.0%) were categorized as ready for discharge. The mean (SD) score for all 22 questions was 9.4 (0.7). Women categorized as 'less ready' scored lower overall (mean difference: 1.3) and within all four questionnaire categories compared to women who were discharge ready (*P*<0.05). **Conclusions:** Although most women in this study reported high levels of discharge readiness, further research is needed to see if results are comparable across settings.

Keywords: *Hospital discharge, Outcome, Premature neonates, South Africa.*

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Kangaroo mother care (KMC) is one of the ten key interventions recommended by the World Health Organization [1] to improve the survival and health outcomes of premature neonates [2]. The majority of low birthweight (LBW) infants are born in low- and middle-income countries (LMICs) [3], where KMC has been shown to reduce the risk of mortality by 40% compared to conventional neonatal care [4].

There is a growing recognition of the importance of maternal self-reported discharge readiness [5], as research from high-income settings has identified that inadequate maternal discharge readiness is associated with increased health service utilization [6,7], low confidence in provi-ding infant care, and greater difficulty with stress, recovery, self-care and coping in the early postnatal period [8,9]. However, there is little evidence from LMICs of self-reported hospital discharge readiness in women after giving birth, especially in the context of KMC. This study aims to address this gap by piloting and implementing a tool for evaluating self-reported maternal discharge readiness among women practicing continuous KMC in a tertiary hospital setting in South Africa.

METHODS

Kalafong Hospital is a public teaching hospital with approximately 6000 deliveries per year. It serves women of predominantly low socioeconomic backgrounds, many of whom live in informal settlements. The KMC unit is one of the most well-established in the region, accommodating up to 20 mother baby dyads at any time.

Most LBW and premature babies receive intermittent KMC in the high-care neonatal unit before being transferred to the KMC unit for continuous KMC. A multidisciplinary team of medical and nursing staff, dieticians, and occupational and speech-language therapists provide extensive discharge preparation to mothers on feeding, KMC techniques, infant care, hygiene, medications, and follow-up arrangements. Evaluating correct feeding techniques for preterm babies and touching and handling are very important before making a decision on discharge from hospital. Most babies receiving continuous KMC tend to be discharged from hospital earlier [10], at a lower weight, and still on top-up expressed breast milk fed by cup.

The questionnaire used in the current study was adapted from the Parent Discharge Readiness Survey [11]. Face validity of the adapted questionnaire was evaluated by local health professionals and researchers, and a focus group discussion with five study-eligible women. It was then piloted with a sample of 20 women who met the study inclusion criteria. Average inter-item correlation was 0.16 (acceptable level 0.2-0.4) [12] and principal components

analysis (PCA) identified ten components with an Eigen value >1. As questions were clinically informed, with the intent of gathering information to improve clinical practice, no questions were removed. Cronbach's alpha of the questionnaire was 0.81 and was not improved if questions were removed to increase internal consistency.

The study population comprised all eligible women staying in the KMC unit between 1 November, 2017 and 30 April, 2018. Recruitment was conducted using convenience sampling. Of 212 women who were approached, 200 (94.3%) agreed to participate. Reasons for non-participation included: depression, previous bad experience with research, or disinterest.

The included women were aged 18 years or older who spoke any of the Sotho or Nguni languages, Afrikaans, or English, staying in the KMC ward for at least three days with an infant born prior to 37 weeks (preterm) or under 2500g at birth (LBW). Women with major social issues (e.g., alcohol or drug addiction), those exclusively formula feeding (as breastfeeding is a core component of continuous KMC), and mothers of infants admitted for palliative care were excluded.

Two trained research assistants administered the questionnaire on the day of hospital discharge through face-to-face interview of approximately 30 minutes duration, in the woman's preferred language. They recorded responses in English. Hospital records provided maternal and neonatal clinical information and socio-demographic data, which were complemented by data collected upon recruitment. In the case of multiple births, information from the twin with the poorest clinical indicators was used (e.g., lowest birth weight) and the twin pair considered one entity relating to the mother, as the condition of the poorer twin is the main criterion for discharge planning according to hospital protocol.

Maternal discharge readiness was treated as a dichotomous variable (ready/less ready). Two questions asking about overall discharge readiness were used to determine overall level of perceived readiness on a 10-point scale (Q18 and Q22). Women scoring ≤8 on either of these two questions were categorized as 'less ready' while women scoring >8 on both questions were categorized as discharge 'ready.'

Statistical analysis: Crude differences between discharge 'ready' and 'less ready' groups were evaluated with Pearson chi-square and Fisher exact test for categorical variables, and independent samples *t*-test for continuous variables. Crude differences between discharge 'ready' and 'less ready' groups on each item were investigated using independent samples *t*-test. All data were analyzed using IBM SPSS Statistics version 25 statistical software with level of significance set at $P<0.05$.

RESULTS

Of the 200 women who agreed to participate, 190 (95%) women were included in the analysis of discharge readiness. Women were excluded if they were transferred to another hospital (n=5), discharged prior to completing the questionnaire (n=4), or did not complete all questions (n=1).

Descriptive characteristics of the study participants are presented in **Table I**. Most women reported they were of South African citizenship (78.5%), were multiparous (68.0%) and with a singleton pregnancy (86.5%). For infants, the mean (SD) gestational age at birth was 32.8 weeks (2.7), and birthweight was 1703g (424g). The mean (SD) gestational age at discharge was 36.1 (1.9) week.

A sensitivity analysis of the outcome measure (ready/less ready for discharge) was undertaken by adjusting the cut-off score applied to Q18 and Q22 from 7 to 9 to assess the proportion of women being classified as ready/less ready. It was determined that a score of ≤8 (out of 10) on Q18 or Q22 allowed for reasonable discrimination between the two groups, and was also most consistent with the original tool [11]. In contrast, the mean of all 22 items with the cut-off score ≤8 resulted in 95% of participants categorized as 'ready' and therefore did not provide good discrimination between 'ready' and 'less ready' mothers in our study. The majority of women were categorized as discharge ready (n=168, 88%). Women who were considered less ready (n=22, 12%) were more likely to be younger, have a multiple pregnancy, and have an infant who was smaller at both admission to and discharge from the KMC unit ($P<0.05$).

The 'less ready' group scored lower overall and in each category of questions compared to women who were discharge 'ready'(**Table II**). Mean scores for the 'less ready' group were 1.2 points (12.6%) lower across feeding-related questions, 0.9 points (9.5%) lower across questions related to infant care, 1.3 points (13.8%) lower across infant health and medications questions, and 1.0 point (10.1%) lower across questions related to KMC.

Web Table I shows mean scores for each discharge readiness questionnaire item. Women who were 'less ready' scored significantly lower, on average, than women who were discharge 'ready' on all but four individual questions (Q4, Q7, Q9, and Q21; $P<0.05$). The greatest differences between the 'ready' and 'less ready' groups were seen in four questions: Question 18 'How confident/sure do you feel that you are ready for your baby to come home?' (mean difference: 2.6, $P<0.001$); Question 22 'Please tell us how ready you feel overall to take your baby home.'

Table I Descriptive Characteristics of Study Participants

Characteristic	*All (N=200)*	*Discharge readiness*	
		Ready (n=168)	*Less ready (n=22)*
Maternal			
Age, y[a,b]	28.8(6.0)	29.2 (6.2)	27.0 (4.5)
Country of citizenship			
South Africa	157 (78.5)	130 (77.4)	18 (81.8)
Zimbabwe	32 (16.0)	30 (17.9)	1 (4.5)
Malawi	6 (3.0)	3 (1.8)	3 (13.6)
Lesotho	2 (1.0)	2 (1.2)	0
DRC	1 (0.5)	1 (0.6)	0
Other	2 (1.0)	2 (1.2)	0
Rural home	20 (10.0)	16 (9.5)	3 (13.6)
Married or co-habiting	106 (53.0)	92 (54.8)	10 (45.5)
Maternal income[a,c] (*n*=102)	3104 (2691)	3057 (2738)	3740 (2543)
Paternal income[a,c] (*n*=97)	6401 (6516)	6645 (6814)	5398 (5020)
Primipara	64 (32.0)	51 (30.4)	10 (45.5)
Mode of delivery (*n*=195)			
Vaginal birth	91 (45.5)	76 (45.2)	12 (54.5)
Caesarean birth	104 (52.0)	87 (51.8)	10 (45.5)
Multiple pregnancy[c]	27 (13.5)	18 (10.7)	6 (27.3)
HIV-positive	46 (23)	43 (25.6)	2 (9.1)
Neonatal			
GA at birth, wk[a]	32.8 (2.7)	32.8 (2.7)	32.7 (2.3)
Birthweight, g[a]	1703 (424)	1719 (439)	1654 (308)
1500-2499 g	138 (69.0)	115 (68.5)	18 (81.8)
1000 to 1499 g	49 (24.5)	42 (25.0)	3 (13.6)
≤999 g	13 (6.5)	11 (6.5)	1 (4.5)
Males	114 (57.0)	96 (57.1)	12 (54.5)
Admission weight, g[a,c,e]	1769 (330)	1794 (343)	1684 (209)
Discharge weight, g[a,c,e]	2025 (304)	2059 (307)	1907 (222)
Days in high care prior to KMC unit[a]	13.2 (12.1)	13.4 (12.1)	13.3 (12.0)
Days in KMC unit[a]	10.2 (7.2)	10.4 (7.6)	9.6 (3.9)
Oxygen therapy[e]	57 (28.5)	49 (29.2)	6 (27.3)
Oxygen therapy (d)[a,e]	3.2 (6.8)	3.4 (7.1)	2.7 (5.0)
Breastfeeding	200 (100)	168 (100)	22 (100)
Medically complex	97 (48.5)	84 (50.0)	10 (45.5)

The sample for discharge readiness was 190. Values in no. (%) except [a]mean (SD). GA: gestational age, DRC-Democratic Republic of the Congo. [b]P=0.05. [c]P<0.05. [d]income per month in Rand;[e]in KMC unit.

(mean difference: 2.3, *P*<0.001); Question 14 'How confident/sure do you feel that your baby is strong enough to go home now?' (mean difference: 2.3, *P*<0.001); and Question 13 'How confident/sure do you feel that your baby's heart and breathing are stable and it is safe to go home?' (mean difference: 2.0, *P*<0.001).

Table II Mean Scores by Question Category

	All (n=190)	*Discharge readiness groups*	
		Ready (n=168)	*Less ready (n=22)*
Feeding	9.3 (0.9)	9.5 (0.7)	8.3 (1.1)
Infant care	9.4 (0.9)	9.5 (0.8)	8.6 (1.3)
Infant health and medications	9.3 (0.9)	9.4 (0.8)	8.1 (1.1)
Practising KMC	9.8 (0.7)	9.9 (0.4)	8.9 (1.3)
Overall	9.4 (0.7)	9.6 (0.5)	8.3 (0.9)

Values in mean (SD). For comparison between 'ready' and 'less ready' groups, P<0.001 for 'feeding' and for 'infant health and medications' categories, and P<0.01 for 'infant care' and 'practicing KMC' categories. Overall P<0.001.

DISCUSSION

To our knowledge, this is the first time a survey instrument has been used to empirically examine maternal discharge readiness in a LMIC setting. The questionnaire developed in the current study builds on an existing validated tool [11], focusing on those components appropriate in the context of facility-based continuous KMC.

Although babies in our study were discharged earlier than higher income settings, most women (88%) still reported high levels of readiness to return home with their infant(s) at the time of discharge. This may reflect the context of facility-based KMC where mothers are their infant's primary caregiver, and the strong focus on discharge preparation and education in the study setting. Women in the current study scored highly on questions specifically related to feeding, infant care, infant health/ medications, and ability to practice KMC. Even women who were categorized as 'less ready' for discharge, had a mean score >8 in each questionnaire category. This may indicate that although some mothers felt less ready for discharge in general, the quality of discharge preparation in the KMC unit ensures mothers have the skills to safely care for their infants. The high level of self-reported discharge readiness observed in the current study may also reflect the fact that the study hospital has one of the most well established KMC programs in South Africa.

Some limitations exist with this study. The generalizability of this study is limited by the small sample size, convenience sampling method, and the single-center setting characterized by maternity patients of predominantly low socioeconomic status, as well as early discharge from the KMC unit.

In conclusion, the maternal discharge readiness questionnaire is a useful tool for use among mothers in an established continuous KMC unit in a LMIC setting. Most

WHAT THIS STUDY ADDS?

- This study highlights the importance of quality preparation for mothers practising continuous kangaroo mother care prior to discharge from hospital.

women undertaking continuous KMC in the study setting reported high levels of perceived readiness at the time of discharge, including preparedness with feeding and caring for their infants, confidence in their infants' health, and their ability to continue KMC at home. Further research is needed in different LMIC contexts to see if results are comparable across settings.

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

Ethics clearance: Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (187/2017; 9 June, 2017), the Research Ethics Committee of Kalafong Hospital (KPTH 34/ 2017; 13 June, 2017), and the Human Ethics Committee, University of Western Australia (RA/4/1/9307; 25, July 2017).

Contributions: CG: data analyses and drafting the manuscript; TL,DBP: conceptualization of the study design, data analyses, substantial contribution to the manuscript; EvR, A-MB: conceptualization of the study design, data collection and preparing the dataset, substantial contribution to the manuscript. All authors approved the final manuscript.

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Web Table I Scores on Individual Maternal Discharge Readiness Items

Questionnaire Item	*All (n=190)*	*Ready (n=168)*	*Less ready (n=22)*
How prepared do you feel ...			
Q1. …to breastfeed your baby?[b]	9.2 (1.3)	9.4 (1.2)	8.1 (1.8)
Q2. …to express your own breastmilk for your baby?[d]	9.2 (1.4)	9.5 (1.1)	7.7 (2.0)
Q3. …to cup feed expressed breastmilk to your baby?[a]	9.1 (1.5)	9.2 (1.3)	7.6 (1.6)
Q4. …to know how much FM 85 powder to add to your expressed breastmilk?	9.0 (1.8)	9.1 (1.9)	8.5 (1.2)
Q5. …to bathe, change nappy and dress your baby?[c]	9.8 (0.8)	9.9 (0.7)	9.2 (1.3)
Q6. …about your knowledge of how many wet nappies and bowel movements your baby will have per day?[b]	8.8 (2.1)	8.9 (2.0)	7.6 (2.4)
Q7. …to know that your baby is warm enough?[e]	9.2 (1.6)	9.3 (1.5)	8.4 (2.1)
Q8. …on what medicines your baby will take at home?	9.6 (1.1)	9.6 (1.1)	9.1 (1.3)
Q9. …to give these medicines to your baby?[c]	9.6 (1.1)	9.7 (1.0)	8.7 (1.7)
Q10. …about what you must do when your baby has a fever or gets sick at home?[b]	9.1 (1.5)	9.3 (1.3)	7.9 (2.0)
Q11. …to practise continuous KMC at home?[b]	9.8 (0.7)	9.9 (0.4)	8.8 (1.5)
Q12. …to tie your baby in the KMC position?[c]	9.8 (0.9)	9.8 (0.8)	9.0 (1.4)
How confident/sure do you feel…			
Q13. …that your baby's heart and breathing are stable and it is safe to go home?[a]	8.9 (1.6)	9.2 (1.5)	7.2 (1.5)
Q14. …that your baby is strong enough to go home now?[a]	9.0 (1.4)	9.3 (1.2)	7.0 (1.7)
Q15. …that you will be able to breastfeed your baby at home?[b]	9.6 (0.9)	9.8 (0.7)	8.8 (1.5)
Q16. …that you will be able to cup feed your baby at home?[b]	9.4 (1.3)	9.4 (1.2)	8.7 (1.2)
Q17. …that you know when and how often to feed your baby during the day/night?[c]	9.7 (0.7)	9.8 (0.6)	9.0 (1.3)
Q18. …that you are ready for your baby to come home?[a]	9.6 (1.0)	9.9 (0.3)	7.3 (1.4)
Q19. …that you can carry your baby skin-to-skin at home?[b]	9.8 (0.7)	9.9 (0.3)	8.9 (1.4)
Q20. …that you will be able to take care of your baby at home?[c]	9.8 (0.5)	9.9 (0.3)	9.3 (1.1)
Q21. …to give your baby the daily medicine?	9.8 (0.7)	9.8 (0.7)	9.5 (0.8)
Q22. Please tell us how ready you feel overall to take your baby home[a]	9.7 (1.0)	10.0 (0.2)	7.7 (2.0)

Value in mean (SD). [a]P<0.001; [b]P<0.01; [c]P<0.05; [d]P=0.01; [e]P=0.05.

RESEARCH PAPER

Comparison of the Predictive Accuracy of Stool Color for Triage of Infants for Phototherapy (STrIP) Score With Transcutaneous Bilirubinometer in Predicting Serum Bilirubin in Neonates

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Objectives: To compare the agreement of stool color for triage of infants for phototherapy (STrIP) score and transcutaneous bilirubinometer values with measured serum bilirubin in neonatal hyperbilirubinemia. **Methods:** Babies more than 35 weeks of gestation, with clinical jaundice, and on exclusive breastfeeding were included in the study. Babies with who were clinically unstable or who had received phototherapy based on clinical assessment were excluded. The agreement was analyzed using Bland-Altman charts. Results of three non-invasive methods were further compared with the measured serum bilirubin levels. **Results:** There was a mean difference of 4 mg/dL of bilirubin between transcutaneous bilirubin and serum bilirubin levels, whereas the agreement between the STrIP score and Serum bilirubin shows a difference of only 2 mg/dL. On further analysis of Kramer, transcutaneous and STrIP score, method of bilirubin estimation against serum bilirubin, there was a mean difference 6 mg/dL, 4 mg/dL and 2 mg/dL, respectively. **Conclusion:** STrIP score has the best agreement with serum bilirubin in neonates compared to other non-invasive techniques such as transcutaneous bilirubinometry and clinical assessment using Kramer scale.

Keywords: *Hyperbilirubinemia, Estimation, Outcome.*

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Newborn jaundice is a common clinical problem in first week of life [1]. Timely intervention can prevent bilirubin toxicity leading to kernicterus with long term morbidity [2-4]. Serum bilirubin, an invasive test is the gold standard for determining bilirubin levels.

There are various non-invasive methods to predict the bilirubin levels, with each having its own advantage and disadvantages. Original Kramer scale was further improvised by the identification of five zones and its corresponding range of serum bilirubin [5]. Although this was considered a low-cost tool in screening the neonatal jaundice, it has limitations of observer variation and difficulty in visually assessing the jaundice in dark skinned babies [6].

Transcutaneous bilirubinometer are based on the principle of absorption of light by the skin at particular wavelength [7]. These devices were found to be inaccurate in severe hyperbilirubinemia, preterm and babies who received phototherapy [8,9]. Smart phone apps have also been developed using optical techniques for detection of newborn jaundice [10]. These apps have an added advantage of being detected at the earliest by the parents at home.

We previously demonstrated that the stool color in addition to clinical staging expressed as STrIP score can accurately predict SBR [11]. This is based on physiological plausibility of relation between entero-hepatic circulation, stool color and serum bilirubin. STrIP score is the sum of Kramer score and the matched stool color score, which predicts serum bilirubin. Unlike TcB, stool color is neither influenced by ambient light or skin color, and it does not need a sophisticated optical device. In this study, our objective was to compare the agreement of STrIP score and transcutaneous bilirubinometer values with measured serum bilirubin in neonatal hyperbilirubinemia.

METHODS

This prospective study was conducted between January and June, 2019 in the postnatal ward of JSS Hospital. All babies more than 35 weeks of gestation, with clinical jaundice, and on exclusively breastfeed were included in the study. Babies who were clinically unstable or who had received phototherapy based on clinical assessment were

excluded. Babies who did not pass stools during the observation time (10 AM to 1 PM) were not included in the study. Ethical clearance was obtained by the institutional ethics committee. Informed consent was obtained from the mother.

Blood sampling for serum bilirubin was done on day 3 of life as per unit protocol or when clinically indicated. Serum bilirubin estimation was done using the principle of diazotization method. Clinical assessment of jaundice was done using Kramer scale on the same day. STrIP weightage was calculated with the stool sample. Stool sample was collected within 3 hours of detection of clinical jaundice, and the color of the stool was compared by the same investigator with the stool color card (stool strip) and stool color weightage was determined. When there was a gradient of color, the darkest portion of the color was taken for determining the stool color weightage as per the STrIP card which ranged from 1 to 5. Matching of stool color with the stool color strip was done in day light between 10 AM and 1 PM beside the window. STrIP score was then calculated by adding the stool color weightage to clinical assessment by Kramer scale. At the same time, average of three bilirubin readings was taken at the forehead by transcutaneous bilirubinometer (MBJ 20, SAAG Medicare system) in a quiet child soon after assessing the STrIP score.

To estimate the agreement between two non-invasive measurements with the gold standard (serum bilirubin measurement), we defined the precision of 95% confidence of limit of agreement to be 40% of the standard deviation of the difference of two measurements based on our pilot study for sample size. A sample size of 84 subjects was calculated.

Statistical analysis: Statistical analysis was done using Microsoft Excel 2016 and Analyse-it version 4.3 for excel. Both the interventional measurements were compared with the measured serum bilirubin using Bland - Altman analysis for mean and the 95% limits of agreement along with their confidence interval.

RESULTS

During the study period, a total of 332 newborns were admitted to the postnatal ward, of which 252 were eligible. However, 94 were excluded as they met exclusion criteria or got transferred to special wards and another 75 due to non-passage of stools between the pre-decided time window. Finally, a total of 83 (53% males) eligible neonates were included in the study. Of these, 12% were 40 weeks and above, 15% had jaundice by 48 hours of age, and 51% between 48-96 hours. Among the neonates who had dehydration, the median (IQR) dehydration was 3% (2%-4%) above the expected for age (**Table I**). The mean difference between Kramer scale and SBR was –3.2 mg/dL, between TcB and SBR was 1.6 mg/dL, and that between STrIP score and serum bilirubin was 0.9 mg/dL.

Bland-Altman analysis was done for agreement for all the three non-invasive methods of prediction of bilirubin against SBR. Kramer scale underestimates serum bilirubin and 95% of the values assessed by Kramer scale lie between +0.1 to –6.4 mg/dL of serum bilirubin. 95% limits of agreement between TcB, STrIP and SBR is shown in **Fig.1**. TcB had a 95% limit of agreement between +3.9 to –4 mg/dL. In contrast, the limit of agreement between STrIP and SBR was between +2.2 and –2 mg/dL (**Fig. 1**).

Median (IQR) TcB value and STrIP were 11.9 (9.6-12.7) vs 11 (9-13) mg/dL (P= 0.82). The median (IQR) SBR was 11.2 (9.1-12.6) mg/dL.

DISCUSSION

The present study demonstrates that the STrIP score can predict serum bilirubin more accurately than the other non-invasive method like transcutaneous bilirubinometer, at three days of age. The mean difference between STrIP score and serum bilirubin was 0.9 mg/dL, much lesser as compared to other non-invasive methods.

The visual assessment using the modified Kramer score is the most widely practiced method of jaundice screening among neonates. Joan, et al. [12] demonstrated Kramer scale to be ineffective in screening jaundice with the sensitivity and specificity being 89% and 54%, respectively. Factors like skin color, birth weight, observer difference (nurse, treating physician) are factors contributing for its poor accuracy [13-15]. This further reinforces that the clinical estimate by Kramer scale alone is not sufficient to detect jaundice needing treatment. Transcutaneous bilirubinometer is another non-invasive

Table I Baseline Characteristics of the Neonates With Hyperbilirubinemia (N = 83)

Characteristic	*Value*
Age (d)	3 (2-5)
Gestation (wk)	37 (36-38)
Preterms[a]	21 (25.3)
Birthweight (kg)	2.9 (2.4-3.2)
No dehydration[a]	54 (65)
Kramer score	7 (7-10)
STrIP score	11 (9-13)
Transcutaneous bilirubinometer value	11.9 (9.7-12.7)

All values in median (IQR) or [a]no. (%). STrIP- Stool color for triage of infants for phototherapy.

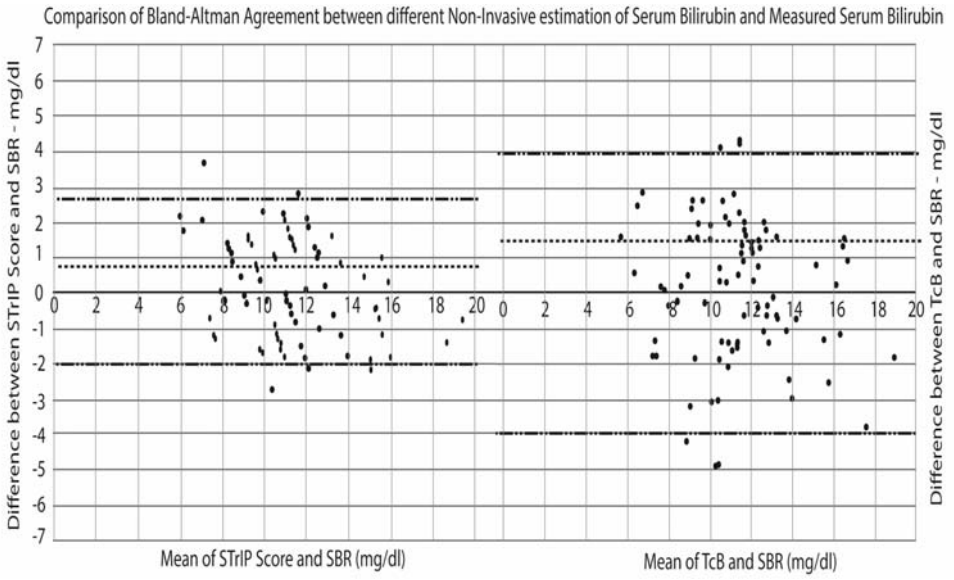

Fig. 1 Bland-Altman agreement between STrIP score vs SBR and TcB vs SBR.

method used in bilirubin assessment of newborn. Studies have concluded TcB to have better correlation with serum bilirubin levels than visual assessment [6,15]. Although transcutaneous bilirubin assessment was found to be better than the visual assessment of jaundice, bilirubin values were found to be inconsistent in different sites.

Our study has shown that the values of both STrIP score and TcB are very close to measured serum bilirubin and there was no statistically significant difference between them. Hence the comparison of agreement between STrIP score and TcB values against SBR serves as clinically useful information. The STrIP score values hover around +/- 2 mg/dL of SBR compared to TcB which hovers around +/- 4 mg/dL. The clinical implication of this wide variation with TcB is significant, as the margin of error in making management decision in neonatal hyper-bilirubinemia is very small. Among the three non-invasive clinical estimation of bilirubin, the close match with SBR is the STrIP score, throughout the range of clinical utility i.e., between serum bilirubin values of 5-20 mg/dL.

Modified Kramer scale and transcutaneous bilirubin method was developed with the intention of having a test which is simple, reliable, accurate and to avoid repeated blood sampling. STrIP score has all the benefits as above along with added advantage of promising predictive accuracy.

The limitation in this study is the possible bias of the observer as the same person had performed TcB measurement and STRiP score assessment.

To conclude, STrIP score, a simple, bedside, easy to use, reliable non-invasive method has the best agreement with serum bilirubin in neonates compared to other non-invasive techniques - transcutaneous bilirubinometry and clinical assessment using Kramer scale. Larger studies might further help in ascertaining its utilization at the community level in early detection of hyperbilirubinemia requiring phototherapy. More studies are needed to conclude the same for reliable use in larger population.

Ethics clearance: Institutional ethics committee, JSS Medical College; No. JSSMC/IEC/ 140120/19NCT/2020-21, dated 30 January, 2020.
Contributors: SK: study design, analyzing the data and preparing the manuscript; BJT: collected the data, did the literature search and contributed for preparation of the manuscript; DT: has helped in literature search, and manuscript preparation; SM: analysis of data, conceived the research question contributed to the study design, and helped in preparing the manuscript. All the authors have approved the manuscript in the present form.
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WHAT THIS STUDY ADDS?

- In neonates with clinical jaundice, STrIP score had a better agreement with serum bilirubin than transcutaneous bilirubinometer.

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RESEARCH PAPER

Serum IgG Titers Against *Toxoplasma gondii* in Uninfected Infants Exposed In Utero to Toxoplasmosis

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Objective: To describe the mean time of decrease of *T. gondii* IgG titers in uninfected infants exposed in utero to toxoplasmosis. **Methods:** A retrospective cohort study was conducted between 2008-2017, among infants under 12 months and exposed in utero to toxoplasmosis. Serial monthly monitoring of serum IgG titers were done till undetectable levels. **Results:** 240 infants with mean gestational age at diagnosis of 19.2 weeks were included in the study. The mean (range) time for IgG level to become undetectable was 7.9 (0.8-25.0) months. 14 infants became negative between 13-24 months. **Conclusion**: Majority of asymptomatic infants exposed in utero to T. gondii become seronegative before 12 months of age.

Keywords: *Chorioretinitis, Intrauterine infection*, *Maternal exposure, TORCH.*

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Toxoplasmosis is one of most prevalent infectious diseases in the World [1,2], with a prevalence of 60-80% in Brazil [3]. Approximately half of infected people are asymptomatic; however, infection during pregnancy can cause chorioretinitis and delayed psychomotor development in infants [4,5]. A congenital toxoplasmosis surveillance system was established in Brazil in 2016, which estimated rates between 0.3-1.3/1000 live births, one of the highest in the world [6,7].

Guidelines on management of infants exposed to toxoplasmosis in utero recommend screening paired blood samples from mother and baby and the target organs for disease at birth [8-10]. Infants are considered not infected if *Toxoplasma gondii* immunoglobulin IgM titers are negative and IgG titers are equal or lower than their mothers, with no evidence of congenital toxoplasmosis after complete clinical, radiologic, and laboratory evaluation. In these exposed infants monthly measurement of *T. gondii* IgG is recommended to exclude congenital infection. Levels of *T. gondii* IgG titers are expected to reduce by half every month until undetectable [2].

The follow-up of asymptomatic exposed infants can be time-consuming, and costly for health services and families. The aim of this study was to observe the time of decrease of *T. gondii* IgG titers of asymptomatic infants exposed in utero to toxoplasmosis.

METHODS

This retrospective cohort study was conducted at a reference pediatric infectious diseases center in a tertiary pediatric hospital, University of Rio de Janeiro, Brazil from 2008 to 2017. The study was approved by the institutional review board.

All infants up to 12 months of age referred with history of in utero exposure to *T. gondii* without infection at the end of follow-up were included. The study excluded subjects who were not followed up until the diagnostic definition, those who were referred after 12 months of life, those whose medical records were not available and those who were diagnosed with congenital toxoplasmosis during the follow up. The infant's vertical exposure to *T. gondii* was diagnosed by maternal acute infection during pregnancy defined by presence of serum IgM or reactive IgG for *T. gondii* in a woman with previously non-reactive IgG level. Additional criteria to define exposure without congenital toxoplasmosis were normal central nervous system (CNS) imaging by ultrasonography or tomography, normal fundoscopy, negative polymerase chain reaction test for *T.gondii* in amniotic fluid, negative *T. gondii* IgM, and undetectable IgG titers for *T. gondii* before one year of age [11]. IgA testing was not done as it was not available. The infant was considered as having congenital infection if any of these tests presented evidence of toxoplasmosis infection. The laboratory method used for the specific *T.*

gondii serology varied during the time of the study due to government supplies' availability. In most of them, the IgG was considered non-reactive if less than 1.0 IU/mL Nevertheless, every time there was a change in methods, another serology was ordered for the children, as soon as possible, to make sure that the titers were decreasing.

Obstetric, clinical, demographic, and laboratory data were obtained from the medical records and collected in a standardized form. All data were included in a database using Access 2016 and analyses were performed using STATA software (version 13.0; Stata Corp LP) statistical program. Categorical and continuous variables were described by frequencies, central (mean and median) and dispersion measures (IQR). The time between birth and the first non-reactive *T. gondii* IgG sample was calculated and described in median (IQR).

RESULTS

In this study, 432 medical records of newborns and infants with a history of in utero exposure to toxoplasmosis were collected. The selection of the participants is shown in **Fig. 1**. A total of 240 exposed infants with mean gestational age 39 weeks, and mean birth weight and head circumference as 3231 g and 34.3 cm, respectively were included. The mean maternal age was 24.7 years and the mean gestational age at the time of maternal diagnosis of *T. gondii* infection was 19.2 weeks (35.5% in the first and 42.7% in the second trimester of pregnancy). Treatment with spiramycin or sulfadiazine and pyrimethamine was performed in 76.3% of mothers. Only 9 (3.7%) mothers reported any specific symptoms of toxoplasmosis, one had non-specific flu-like symptoms, 78 (32.5%) were asympto-matic (diagnosed through prenatal screening) and 152 (63.3%) did not have any information about the symptoms.

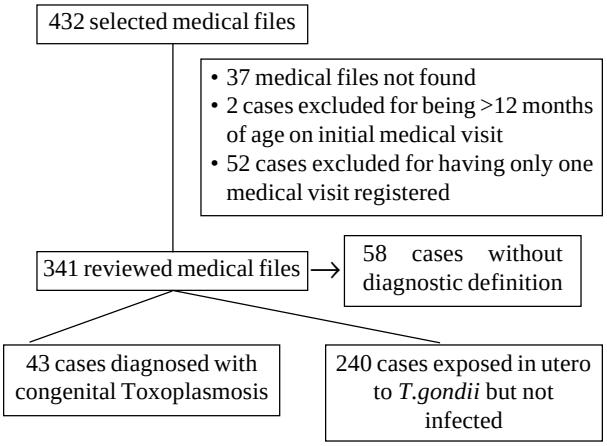

Fig. 1 Flow of the study.

The mean (range) time for toxoplasmosis IgG titers to become undetectable in the serum was 7.9 (0.8 to 25.0) months. The median (IQR) *T. gondii* IgG titers at the first visit were 115 (45, 223) U/mL. **Fig. 2** shows the time span to reach undetectable/ negative IgG titers in these patients, showing that 50% of uninfected infants took 7.3 (95% CI: 6.83-7.76) months to have a non-reactive serology. One infant had a positive IgM test after birth which was found to be non-reactive when tested after day five of life. The average age when the IgG levels became non-reactive did not change during the study period (data not shown).

Fourteen infants took more than 12 months (range 13 to 24 months), to present negative serology, 7 infants had a gap of more than 2 months between IgG titers measures near the 12 months mark. The remaining seven patients reached undetectable IgG titers between 14 to 19 months and remained asymptomatic throughout the follow-up, with normal target organ screening tests repeated a few times and a clear monthly drop in IgG titers.

DISCUSSION

In this study, we found that the mean age for IgG titer to become undetectable in newborn in utero exposed but not infected by *T. gondii* was 7.9 months.

A major limitation was missing data and medical records. The follow-up required frequent visits over a long period of time, which led some families to miss appointments or abandon the follow-up. The lack of standardized technique to perform *T. gondii* serology and change in laboratory techniques with time was another limitation.

The Brazilian guidelines recommend additional hematological and liver function tests in infants exposed in utero to *T. gondii* [9]. *T. gondii* IgG maternal antibodies passed to the newborn are expected to decrease by 50% each month until non-reactive between 6 and 12 months of

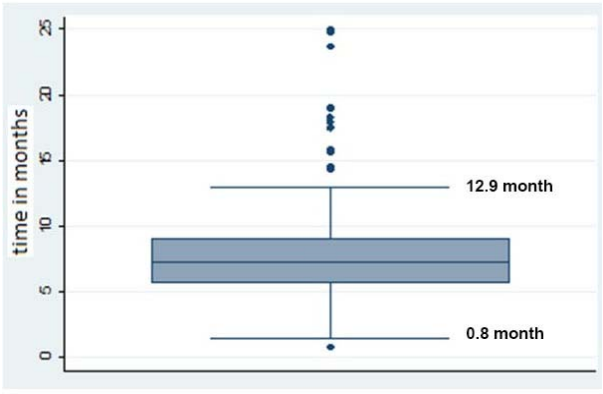

Fig. 2 Box-plot showing time span for toxoplasmosis IgG to reach undetectable levels.

WHAT THIS STUDY ADDS?

- Asymptomatic infants exposed in utero to toxoplasmosis may take longer than 12 months of age to achieve undetectable IgG titers.

life [2,12]. Therefore, a follow-up with monthly serological *T. gondii* tests until negativity of IgG is recommended [9,11]. Our results found a similar age range to reach undetectable specific IgG serology of 7.9 months.

In this study, the age for IgG titers to become undetectable ranged from 0.8 to 25.0 months unlike the range of 6 to 12 months described earlier [2]. Therefore, asymptomatic infants with low IgG titers should not be classified as infants with congenital toxoplasmosis at 12 months, and the presence of reactive IgG after 12 months as a diagnostic criterion for congenital toxoplasmosis should be re-evaluated. Asymptomatic infants with low IgG titers should be analyzed individually to serially monitor IgG decrease at 12 months of age. In such cases, patients may continue to be followed and be considered as only exposed in utero to toxoplasmosis but not infected when the serology is negative after 12 months of life.

Ethics clearance: IPPMG institutional review board; CAAE: 74564017.7.0000.5264, November, 2017.
Contributors: DV: data collection, analysis and manuscript prepration; MM: data collection, writing of the manuscript and was the responsible for its translation to English; ACF,TA: conceptualization study and manuscript review; CH: conceived the initial idea and the design of the study, data analyses, manuscript review. All authors approve the final manuscript.
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RESEARCH PAPER

Effect of Earmuffs on Physiological Parameters of Preterm Neonates Nursed in Incubators: *A Before-and-After Study*

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Objective: To determine the effect of earmuffs on stability of physiological parameters i.e. heart rate, respiratory rate, and oximeter saturation (SpO_2) in preterm neonates. **Methods:** Non-randomized, cross-over study. 60 stable preterm neonates observed without and with earmuffs for 2 hours each (control and intervention periods, respectively). The above parameters were recorded every 60 seconds. Spikes of parameters and fluctuation [by coefficient of variation (CoV)] were compared between periods. **Results**: Spikes of all parameters as a proportion of observations, were significantly less in intervention period. Median (IQR) spikes per subject were lower in intervention vs control: tachycardia [2.5 (2.5, 18) vs. 20.5 (2.2, 37.7); *P*<0.01]; tachypnea [11.5 (11.5, 25) vs. 18 (2, 40) vs; *P*=0.01] and hypoxia [0 (0, 0) vs. 0 (0, 1.75); *P*<0.01]. There was significantly less fluctuation of heart rate and SpO_2 with earmuffs. **Conclusion**: Earmuffs improve physiological stability of preterms.

Keywords: *Heart rate*, *NICU, Noise, Respiratory rate*.

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The American Academy of Pediatrics recommends noise levels of less than 45 A-weighted decibels (dBA) in neonatal intensive care units (NICU) [1]. High noise level adversely affects the physiological parameters, behavior, and sleeping patterns of neonate. In a pilot study, we found that the mean (SD) noise level in our NICU was 57.60 (3.95) dBA. There is a paucity of well-conducted studies evaluating the effect of earmuffs on noise reduction and stabilization of physiological parameters, such as heart rate (HR), respiratory rate (RR), pulse oximeter saturation (SpO_2), and blood pressure in preterm neonates, and the available studies have shown conflicting results [2-4].

A Cochrane review on the effect of noise reduction on very low birth weight infants could find only one single-center randomized controlled trial on 34 newborns [5]. The authors reported better weight gain and neuro-development among infants who were randomized to wearing silicone earplugs [6]. Some RCTs have included a reduction in both light and noise levels, making it difficult to assess the effect of noise reduction alone [7,8]. Previous studies have compared only the average values of the physiological parameters [2-4,7-11]. Relying solely on averages could be misleading because averages do not adequately reflect transient but harmful spikes nor do they capture fluctuation of the physiological parameters. We hypothesized that the application of earmuffs on preterm neonates, nursed in incubators in a NICU, would reduce spikes and fluctuations in their physiological parameters.

METHODS

We conducted a prospective, cross-over study in a level III NICU in a tertiary care institute in Northwest India. The institute ethics committee approved the study protocol. The study was done in accordance with the Helsinki declaration and with the Indian Council of Medical Research (ICMR) national ethical guidelines. We included preterm neonates (<37 weeks gestation) who required incubator care, but were otherwise clinically stable. Kangaroo mother care was intermittently provided but they were unable to consistently maintain body temperature outside an incubator. Infants who were ill, sedated, encephalopathic, had scalp electrodes, or had syndromes associated with deafness were excluded. Written informed consent was obtained from either parent. Baseline data included the demographic and clinical profile of enrolled neonates.

In the 'control' period, we recorded HR, RR, and SpO_2 at 60-second intervals for 2-hour duration by a multichannel monitor (IntelliVue MX800, Philips) without the application of earmuffs, thus providing 120 data points for each parameter. This was followd by a two-hour washout period. Following this, in the 'intervention' period, we recorded data on the same neonates for 2-hour

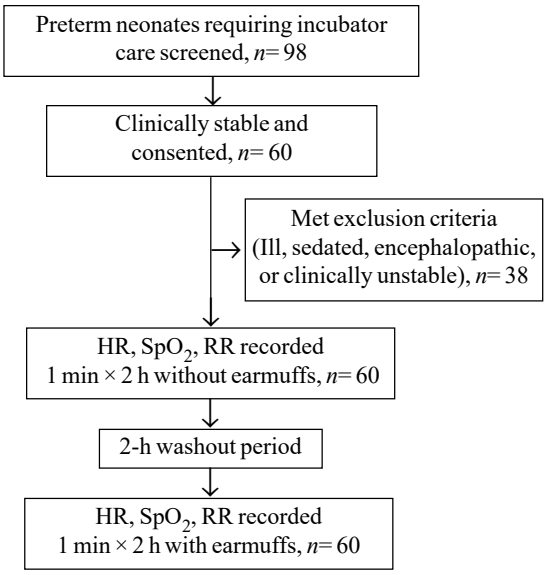

Fig. 1 Flow diagram of the study population.

duration with the application of earmuffs (Minimuffs, Natus Medical Inc.), which reduce noise by 7 dBA, as per manufacturer. Each subject acted as its own control.

At the start of the control and the intervention periods, we measured the sound level inside the incubator using the Bruel and Kjaer precision integrating sound level meter type 2230, fitted with microphone type 4155. We collected data at a time when we anticipated the least number of nursing/clinical activities so that other stressful conditions could be avoided.

We defined a 'spike of tachycardia' in two ways- either as any data point of HR ≥160 beats per minute (bpm) or any data point of HR ≥180 bpm; a 'spike of tachypnea' as RR ≥60 breaths per minute; and a 'spike of hypoxemia' as SpO_2<90%. We recruited a sample size of convenience of 60 consecutive eligible subjects.

Statistical analysis: Normality of distribution was determined by Shapiro-Wilk test and the QQ plot. We compared proportions between the periods by the McNemar test and distributions by the Wilcoxon signed rank-sum test for skewed distributions. Using the data point as the unit of observation, we compared the proportion of spikes between the two periods. Using the subject as a unit of observation, we compared the median number of spikes. We calculated the coefficient of variation (CoV) of each parameter for each subject and compared the median CoV. Using 120 data points for a given parameter, we calculated the area under the curve (AUC) using a differential function for each subject in each period, and compared the median AUC between the groups.

RESULTS

We enrolled 60 eligible subjects (31 males) (**Fig. 1**). The study population had a mean (SD) gestation of 31 (2.5) weeks, birthweight of 1348 (408.3) grams and current weight of 1239 (404.9) grams. Median (range) Apgar scores at 5 minutes was 9 (8, 9) and postnatal age was 7 (4, 10) days. Twenty five (41.7%) subjects were small for gestational age and the remainder were appropriate for gestational age and 25 (41.7%) were delivered vaginally. The mean (SD) noise level inside the incubator during the control and intervention periods was 57.6 (3.9) and 57.3 (3.5) dBA, respectively (P=0.27).

The number of spikes as a proportion of all individual observations was significantly higher in the control period compared to the intervention period for all three parameters (P<0.01) (**Table I**). There were statistically significant reductions in the median number of spikes of tachycardia, tachypnea and hypoxia in the intervention period compared to the control period (P values of <0.01, 0.01 and <0.01, respectively) (**Table II**).

We compared the median CoV of each parameter between the two periods (**Web Table I**). There was a significantly higher variability of HR (P=0.03) and SpO_2 in the control vs intervention periods (<0.01). There were significantly higher median AUC for HR (P=0.01) and RR, whereas, for SpO_2, there was almost no difference (P=0.97).

Table I Spikes of Physiological Parameters Among Individual Observations in Preterm Neonates With and Without Earmuffs (*N*=60)

Physiological parameters (number of spikes)	*Without earmuffs (n= 7200 observations)*	*With earmuffs (n= 7200 observations)*
Heart rate ≥160 bpm	1769 (24.5)	1037 (14.4)
Heart ratee ≥180 bpm[a]	168 (2.3)	70 (0.97)
Respiratory rate ≥60 per min	1491 (20.7)	1162 (16.1)
Oxygen saturation <90%	117 (1.6)	41 (0.5)

Values in no. (%). Bpm-beats per minute. All P<0.01; [a]P<0.001.

Table II Spikes of Physiological Parameters per Subject in Preterm Neonates With and Without Earmuffs (*N*=60)

Physiological parameters (no. of spikes per subject)	*Without earmuffs (n=60)*	*With earmuffs (n= 60)*
Tachycardia (rate ≥160 bpm)[a]	20.5 (2.25, 37.75)	2.5 (2.5, 18)
Tachycardia (rate ≥180 bpm)[b]	0 (0, 4)	0 (0,0)
Tachypnea[c]	18 (2, 40)	11.5 (11.5, 25)
Hypoxemia[a]	0 (0, 1.75)	0 (0, 0)

Values in median (IQR). [a]P<0.01; [b]P<0.001; [c]P=0.01.

WHAT THIS STUDY ADDS?

- This study shows that application of earmuffs among stable preterm neonates nursed in incubators results in significantly less spikes and less variability of physiological parameters.

DISCUSSION

We evaluated earmuffs for their effect on three critical physiological parameters. One of the study's challenges was that the data was collected at 1-minute intervals for two hours during each period. Hence, we examined the data from various perspectives – observations above a pre-defined threshold, the variability of the observations per subject, and an integral of all the observations for each subject. The application of earmuffs resulted in lower HR and RR and higher SpO_2; less abnormal spikes, and less variability of these parameters. Although SpO_2 showed higher fluctuation in the control compared to the intervention period, its AUC was similar in both periods because the dips from baseline were compensated for by the peaks, thus maintaining AUC constant.

Our results are concordant with some previous studies. In a non-RCT, Abujarir, et al. [10] applied earmuffs, identical to ours, to neonates admitted in one area of the NICU and did not apply in another area. HR, systolic blood pressure (BP), RR, SpO_2 significantly improved among neonates wearing earmuffs, but mean BP, diastolic BP, and temperature did not. In the RCT by Abdeyazdan, et al. [2], environmental sound levels were higher than in our unit, and there was a significant difference in mean SpO_2, RR and HR between the groups with and without earmuff. Other authors also report that infants with earmuffs have greater mean SpO_2 values, less fluctuation in SpO_2, and sleep more [11].

A few research groups did not find a benefit of earmuffs [3,4]. Duran, et al. [4] evaluated earmuffs, identical to those in our study, in a prospective cross-over study on 20 clinically stable preterm VLBW neonates older than 7 days and nursed in incubators [4]. They reported no significant differences in body temperature, HR, RR, SpO_2, and BP. Bott, et al. [3] found no effect of earmuffs on intermittent hypoxia [3].

There are studies that looked at outcomes other than immediate physiological outcomes. Li, et al. [12] reported 100 preterm ventilated neonates randomly allocated to earmuffs and no earmuffs groups. The group wearing earmuffs had significantly lower incidence of hearing loss, periventricular hemorrhage and leukomalacia, and better developmental indices on follow-up. The only study included in the Cochrane meta-analysis reported better weight gain and neurodevelopmental outcomes, but no effect on physiological parameters [5,6].

A limitation of our study was that the sequence of cross-over was not randomly allocated. We did not perform a formal sample size calculation. Also, we did not maintain a record of the handlings and procedures done on preterm neonates during data collection, as we had chosen a period of the day expected to have minimal interventions. We did not measure non-invasive BP, because frequent non-invasive BP (NIBP) recording was not clinically indicated in our stable population and would have itself been stressful. Intermittent NIBP recording serves a limited purpose as it is unable to capture the BP record continuously.

We conclude that applying earmuffs protects premature infants from noise-induced adverse changes in physiological parameters. The application of earmuffs decreases the number of spikes of tachycardia, tachypnea and hypoxemia; and decreases the variability of HR and SpO_2. Routine use of earmuffs may be considered to improve the physiological stability of preterm infants nursed in incubators in the NICU.

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

Ethics clearance: PGIMER Institute Ethics Committee; No. 41520/14/910, dated March 24, 2014.

Contributors: AK: substantial contributions to the design of the work, acquisition and analysis of data, and drafted the work; SK: substantial contributions to the conception of the work, interpretation of the data for the work, and revised the manuscript critically for important intellectual content; SM: substantial contributions to the design of the work, and revised it critically for important intellectual content; SD: substantial contributions to the concept and design of the work, analysis and interpretation of the data, and drafted and revised the work for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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NOTES AND NEWS

Web Table I Coefficients of Variation and the Area Under Curve of Physiological Parameters Per Subject Among Preterm Neonates With and Without Earmuffs (*N*=60)

Physiological parameters	*Without earmuffs*	*With earmuffs*
Heart rate (beats/min)[a]	0.059 (0.041,0.077)	0.050 (0.041,0.061)
Coefficient of variation		
Respiratory rate (per min)	0.221 (0.175,0.284)	0.208 (0.158,0.263)
Oxygen saturation[b]	0.014 (0.010,0.022)	0.0117 (0.008,0.015)
Area under curve		
Heart rate (beat-min)[c]	17604 (16735.7, 18764.6)	17318.75 (16319.2, 18190.2)
Respiratory rate (breath-min)[b]	5507.5 (4927, 6454.2)	5467.25 (4681.4, 6089.9)
Oxygen saturation (% -min)	11565.2 (11406.9, 11662.9)	11566.5 (11390.2, 11679)

Values are median (IQR). [a]P=0.03, [b]P<0.01, [c]P=0.01.

RESEARCH PAPER

Brain Injury Patterns in Neonates With Hypernatremic Dehydration: Single Center Experience

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Objective: To find out the incidence, spectrum, and topographical distribution of brain lesions in neonatal hypernatremic dehydration. **Method**s: We prospectively enrolled 100 consecutive neonates admitted with hypernatremic dehydration. 93 neonates underwent magnetic resonance imaging brain to identify the nature and site of neurological injury. **Results**: Neuroradiological lesions were found in 42 (45.2%) babies. Edema was the most common finding in 37 (39.8%), followed by hemorrhage in 13 (13.9%) and thrombosis in 6 (6.4%).Edema predominantly affected juxtacortical/subcortical white matter followed by periventricular white matter and centrum semiovale, posterior part of internal capsule, and basal ganglia/thalamus. Occipital horns of lateral ventricle were the main sites of hemorrhage. Thrombotic lesions predominantly involved sagittal, straight and transverse sinuses. Brain lesions were observed only in severe hypernatremia group. **Conclusion**: In neonatal hypernatremic dehydration, edema was the most common neurological lesion, followed by hemorrhage and thrombosis. Subcortical/juxtacortical white matter was the most commonly affected site.

Keywords: *Edema, Hemorrhage, Neuroimaging, Thrombosis.*

Neonatal hypernatremic dehydration (NHD) is a serious and potentially devastating condition, with cases being increasingly reported from all over the world [1]. Neurological involvement in NHD is considered dangerous, as it may not only produce acute neurological dysfunction, but also permanent brain damage [2]. In a recent study, one fourth of NHD cases had abnormal development at 6 months follow up [3].

Neuro-radiological changes developing in NHD still remain an under-researched area. Previous small studies have reported cerebral edema, brain hemorrhage, and cerebral venous sinus thrombosis in these neonates [4]. The exact incidence of brain lesions and patterns of injury are largely not known. This study was conducted to study magnetic resonance imaging (MRI) identified brain lesions, in the neonates admitted with hypernatremic dehydration.

METHODS

This study was conducted in 30-bedded dedicated extramural neonatal intensive care unit (NICU) of a teaching hospital among 93 neonates consecutively seen between August, 2018 and July, 2019. Ethical approval was taken from the institutional ethics committee, and written informed consent was obtained from the caregivers of enrolled neonates.

Our study population was outborn term neonates admitted with hypernatremic dehydration. Presence of any one of excessive weight loss (≥10%), oliguria or delayed skin turgor was considered as a clinical feature of dehydration. Serum sodium levels of these neonates were estimated along with other routine investigations. All neonates with serum sodium levels >150 mmol/L were enrolled. Those neonates who had any congenital malformation, history of delayed cry or Apgar score <8 at 1 minute after birth, hypoglycemia, sepsis, suspected inborn errors of metabolism, coagulopathy, history of abortion or unexplained sibling death, history of stroke, deep venous thrombosis, early age myocardial infarction or thromboembolic phenomena in family were excluded.

Fully automated analyzer (EM360, ERBA Diagnostics Manheim GmBH) was used to measure serum sodium levels. For MRI brain, 1.5 Tesla MRI machine (Achieva 1.5 T, Philips) was used. T1, T2, fluid attenuated inversion recovery, diffusion weighted imaging, apparent diffusion coefficient map, and gradient echo sequences were taken in all the cases. MRI reporting was done for all neonates by a single senior radiologist. Standard treatment protocols were universally followed in all babies (**Web Box I**).

The study by Unal, et al. [5] has reported the incidence of neuroradiological changes among hypernatremic dehydrated infants to be around 10% (with some newborns having more than one change). Assuming an incidence of 10%, with 5% absolute precision and 95% confidence interval, the calculated sample size was 94 neonates. Assuming an attrition of 5% due to in-hospital deaths, the final sample size was calculated to be 100.

Statistical analysis: Data were collected in Microsoft Excel sheet and were analyzed using SPSS 20.0 software.

RESULTS

A total of 100 hypernatremic neonates were enrolled; out of which seven died during hospital stay due to decompensated shock and associated respiratory failure, and remaining 93 were analyzed. Decreased urine output was the most common presentation (*n*=90, 96.8%), followed by poor acceptance of feed (*n*=76, 81.7%), fever (*n*=74, 79.6%), seizures (*n*=39, 41.9%), and jaundice (*n*=21, 22.6%). On examination, 54 (58%) babies were lethargic and 15 (16.1%) were irritable; and neonatal reflexes (Moro's, grasp, rooting and sucking reflexes) were depressed in 76 (81.7%) babies. Mean gestational age, birth weight and age at MRI scan were 39.61 (1.43) weeks, 2889 (0.48) grams and 11.81(1.03) days, respectively. Mean serum sodium, blood urea nitrogen and serum creatinine levels were 177.12 (11.90) mmol/L, 33.58 (19.7) mmol/L, and 309.47 (207.79) μmol/L, respectively. Most of the babies (*n*=46, 49.5%) had serum sodium levels exceeding 180 mmol/L, followed by 42 (45.2%) in 161-180 mmol/L category, and only 5 (5.4%) had mild hypernatremia.

Table I Magnetic Resonance Imaging Patterns of Cytotoxic Edema in Neonates With Hypernatremic Dehydration (N=37)

Site of lesion	*No. (%)*
Juxtaventricular white matter/ deep white matter (n=26)	
Periventericular white matter	14 (37.8)
Centrum semiovale	14 (37.8)
Internal capsule	13 (35.1)
Corona radiate	10 (27)
Capsuloganglionic region	9 (24.3)
Corpus callosum	9 (24.3)
Subinsular	1 (2.7)
Juxtacortical/subcortical white matter (n=21)	
Frontal	21 (56.7)
Parietal	21 (56.7)
Occipital	17 (45.9)
Temporal	14 (37.8)
Subinsular	1 (2.7)
Basal ganglia/thalamus	11 (29.7)
Cerebral cortex (n=6)	
Frontal	6 (16.2)
Parietal	6 (16.2)
Occipital	6 (16.2)
Temporal	3 (8.1)
Insular	1 (2.7)

Brain lesions were noted in 42 (45.2%) hypernatremic neonates with edema being the most common (*n*=37, 39.8%), followed by hemorrhage in 13 (13.9%), and thrombosis in 6 (6.4%) babies. Among the isolated lesions, cytoxic edema alone was noted in 24 (25.8%), and hemorrhage alone in 4 (4.3%) babies. None of the neonates developed isolated thrombosis, or both hemorrhage and thrombosis. Among combination of lesions, edema was associated with thrombosis in 4 (4.3%) babies, with hemorrhage in 7 (7.5%) babies, and with both thrombosis and hemorrhage in 2 (2.15%) babies. Cytotoxic edema predominantly affected juxtacortical/ subcortical white matter (*n*=21, 56.7%), followed by periventricular white matter and centrum semiovale (*n*=14, 37.8% each). Isolated white matter edema dominated the picture, it was observed in 21 (56.7%) brain edema patients (**Table I**). Fifteen hemorrhagic lesions were observed in 13 patients. Intraventricular hemorrhage (IVH) was the most common. Eight thrombotic lesions were observed in six patients. Superior saggital, transverse and straight sinuses were the most commonly affected site (**Table II**). Edema, hemorrhage and thrombosis were noted only when serum sodium levels exceeded 160, 170 and 180 mmol/L, respectively.

DISCUSSION

In the present hospital-based study conducted among 93 hypernatremic neonates; we observed brain lesions in 45.2% babies. The incidence of edema, hemorrhage, and thrombosis was 39.8%, 14%, and 6.4%, respectively. Cytotoxic edema affected both gray and white matter, but isolated involvement of white matter was more common. Brain edema, hemorrhage and thrombosis were noted only when serum sodium levels exceeded 160, 170 and 180 mmol/L, respectively.

The major limitations of our study are lack of a comparison group, and non-uniform timing of MRI brain scan. In our study MRI scan was carried out only after ensuring stability of the baby in the MRI suit. Lesions observed in our study cannot be purely ascribed to hypernatremic dehydration, as some of the complications might have evolved during rehydration therapy. However, for clinical purpose, outcome lesions (ultimate lesions at discharge) are more important than the initial insult.

As compared to previously available retrospective data [5], the incidence of brain edema, hemorrhage and thrombosis are approximately 5-10 times higher in the present study. Lack of neuroimaging in all cases,

WHAT THIS STUDY ADDS?

- Subcortical/juxta cortical white matter edema is the most common lesion in neonatal hypernatremic dehydration.

Table II Magnetic Resonance Imaging Patterns of Hemorrhagic and Thrombotic Brain Lesions in Neonates With Hypernatremic Dehydration (N=19)

Type	*No (%)*
Hemorrhagic lesions	13 (13.9)
Intraventricular hemorrhage (IVH)	
Bilateral occipital horns+ choroid plexus	3 (23)
Bilateral occipital horns	2 (15.3)
Left occipital horns+ choroid plexus	1 (7.7)
Subacute subdural hemorrhage (SDH)	
Overlies right temporal and right parietal lobe	1 (7.7)
Overlies left paramedian cerebellar convexity	1 (7.7)
Overlies posterior interhemispheric falx, tentorium, and posterior occipito parietal convexity	1 (7.7)
Late subacute subarachnoid hemorrhage (SAH)	1 (7.7)
Parenchymal hemorrhage	
Right frontoparietal, right centrum semiovale, left superior frontal	1 (7.7)
Left cerebellar hemisphere	1 (7.7)
Micro/punctiform hemorrhage	
Right parietal and left temporal lobe	1 (7.7)
Right occipital and right temporal lobe	1 (7.7)
Bilateral cerebellar hemisphere	1 (7.7)
Thrombotic lesions	6 (6.4)
Dural venous sinus thrombosis/ Subacute occlusive thrombosis of veins	
Straight sinus, trocula and bilateral transverse sinuses	2 (33.3)
Superior sagittal sinus	1 (16.7)
Anterior half of superior sagittal sinus, superior frontal cortical vein	1 (16.7)
Left transverse and sigmoid sinus, trocula, posterior one third of superior sagittal sinus, straight sinus, vein of galen, right internal cerebral vein, right basal vein of rosenthal	1 (16.7)
Vein of galen and bilateral internal cerebral veins	1 (16.7)

predominant use of ultrasonography and computerized tomography (CT) scan for brain imaging, and less severe hypernatremia might explain the lower incidence of brain lesions in the previous study. The most common type of lesion and/or combination of lesions has not been defined in previous studies [2,4,6,7], as these were based on few case reports/small case series or retrospective analyses. The most common site of lesions also remained inconclusive in the past except for thromboses, which in most case reports showed predominant involvement of sagittal, straight and transverse sinuses [8-11], similar to our findings. These findings are in contrast to adults with hypernatremia, in whom osmotic demyelination syndrome has been noticed as the most common neuroradiological lesion; extra pontine myelinolysis (EPM) being more common than central pontine myelinolysis (CPM) [12,13].

In our population besides hypernatremia, associated presence of uremia and metabolic acidosis might also have contributed to the neurological insults. Uremia predominantly affects the basal ganglia followed by cortical/subcortical regions and white matter. This pattern of injury has an important bearing on neurodevelopment, as reversibility is less and outcome is poor [12, 14]. Most of our babies had isolated white matter edema which usually carries a good prognosis. Associated involvement of basal ganglia and cortical/subcortical white matter might have been contributed by uremia and acidosis.

Our center caters to a wide spread of population of the Thar desert. Some of the settlements are located more than 300 km away from our center. Long travel probably further aggravates the dehydration in the neonates coming from far-flung areas. As almost half (49.5%) of our babies had serum sodium levels higher than 180 mmol/L, the present findings may not be generalizable to the predominantly mild hypernatremia group.

MRI brain should be advocated in all neonates admitted with hypernatremic dehydration, especially in severe hypernatremia (serum sodium levels exceeding 160 mmol/L). Further multi-centric research is required to focus on neuroradiological and neurodevelopmental outcomes of this high risk population. As brain edema, which was the most common lesion in our study, usually evolves during rehydration therapy, choice of rehydrating fluid and its rate of infusion also needs exploration.

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

Ethics clearance: Institutional Ethics Committee, Dr SN Medical College, Jodhpur. No. SNMC/IEC/2019/55 dated March 16, 2019.

Contributors: AM: data acquisition, and initial manuscript; AS: conception, design and manuscript revision; VKG: conception, design and intellectual content; NG: data analysis and manuscript revision; VP: conception, data interpretation, initial manuscript; KC: data interpretation, initial manuscript. All authors approved the final manuscript.

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NOTES AND NEWS

Web Box I Management Protocol of Hypernatremia Followed in the Study

Clinical status and intervention
Fluid resuscitation in shock Intravenous bolus of isotonic saline, 10 mL per kg, repeated as required
Initial rehydration and correction of hypernatremia Free water deficit (36-48 ml per kg per 24 hour) plus usual maintenance fluid, targeting reduction in serum sodium at a rate of 0.5mmol/l per hour
Subsequent rehydration and correction of hypernatremia Serum sodium levels were checked every 6 hour. Subsequent composition of fluid and its rate of infusion was guided by drop in serum sodium levels and urine output
Parameters monitored
Clinical and non-invasive monitoring Heart rate, respiratory rate, SpO_2, and temperature were continuously monitored. Blood pressure, capillary refill time and Urine output were checked at every one hour.
Blood/serum parameters Serum electrolytes (sodium, potassium, and calcium), blood sugar and blood gas - every 6 hourly initially. Renal function tests (serum urea, creatinine), and liver function tests (serum bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase) – daily initially. Complete hemogram was done on admission, and was repeated, if abnormal hematocrit or platelet deficiency was observed or required correction.

RESEARCH PAPER

Comparison of Clinical Features and Outcome of Dengue Fever and Multisystem Inflammatory Syndrome in Children Associated With COVID-19 (MIS-C)

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Objective: To identify clinical and laboratory features that differentiate dengue fever patients from MIS-C patients and determine their outcomes. **Methods:** This comparative cross-sectional study was done at a tertiary care teaching institute. We enrolled all hospitalized children aged 1 month - 18 years and diagnosed with either MIS-C and/or dengue fever according to WHO criteria between June and December, 2020. Clinical and laboratory features and outcomes were recorded on a structured proforma. **Results:** During the study period 34 cases of MIS-C and 83 cases of Dengue fever were enrolled. Mean age of MIS-C cases (male, 86.3%) was 7.89 (4.61) years. MIS-C with shock was seen in 15 cases (44%), MIS-C without shock in 17 cases (50%) and Kawasaki disease-like presentation in 2 cases (6%). Patients of MIS-C were younger as compared to dengue fever (P=0.002). Abdominal pain and erythematous rash were more common in dengue fever. Of the inflammatory markers, mean C reactive protein was higher in MIS-C patients [100.2 (85.1) vs 16.9 (29.3) mg/dL] (P<0.001). In contrast, serum ferritin levels were higher in dengue fever patients (P=0.03). Mean hospital stay (patient days) was longer in MIS- C compared to dengue fever (8.6 vs 6.5 days; P=0.014). **Conclusions:** Clinical and laboratory features can give important clues to differentiate dengue fever and MIS-C and help initiate specific treatment.

Keywords: *Diagnosis, Evaluation, Inflammatory markers, Management*.

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Multisystem inflammatory syndrome in children (MIS-C), an inflammatory condition following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has manifestations similar to toxic shock syndrome or Kawasaki disease [1,2]. Dengue fever can have clinical presentations similar to MIS-C with presence of fever, erythematous rash, vomiting, abdominal pain and development of shock in severe cases. Correct diagnosis and appropriate management are critical to reduce mortality in both the conditions.

We conducted this study to identify clinical and laboratory features that differentiate dengue fever from MIS-C patients admitted in a tertiary care center and determine their outcomes.

METHODS

In this cross-sectional study, we evaluated all hospitalized children aged 1 month to 18 years diagnosed with MIS-C and/or dengue fever admitted in the department of pediatrics, at our center from June to December, 2020. All patient data were entered in a structured proforma. Patients were followed up till discharge. Written informed consent was taken from all participants and the study was approved by the institutional ethics committee.

All patients with fever for more than three days and fulfilling the World Health Organization (WHO) criteria for MIS-C [1] were included. SARS-CoV-2 infection was diagnosed by nasopharyngeal swab, real time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection using TRUPCR SARS-CoV-2 (3B BLACK BIO, Kilpest India Ltd) and/or rapid antibody test for SARS-CoV-2 (n=50) using Elevate Anti-SARS-CoV-2 (IgG and IgM) (Roche Diagnostics GmbH). Additionally, history of contact with a COVID-19 (coronavirus disease 2019) positive patient was also considered positive as per the WHO criteria.

Only confirmed case of dengue fever based on serological evidence by IgM ELISA or by NS1 antigen positivity were included. Patients with dengue infection were classified into two groups viz., dengue with warning signs and severe dengue, according to WHO classi-

fication [5]. Dengue antibody test for IgM detection was done using an IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) (PanBio, Standard Diagnostics Inc). Dengue NS1 antigen was detected with the ELISA technique (J Mitra & Co Pvt Ltd).

Patients were serially monitored clinically and by laboratory parameters and managed as per standard guidelines. We collected demographic data; past medical history, co-morbidities, clinical signs and symptoms, results of imaging, cardiac, and laboratory testing for signs of inflammation (elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin) and organ involvement, at presentation and throughout the hospital stay. The information with respect to need for respiratory and inotropic support, medications like steroids and intravenous immune globulin (IVIG), duration of hospital stay and survival was also collected. Clinical patterns of MIS-C patients including those with or without shock and coronary involvement were also noted. Left ventricle dysfunction was graded on 2D-echo as: normal function (EF >55%), mild dysfunction (EF 41-55%), moderate dysfunction (EF 31-40%), and severe dysfunction (EF ≤30%) [6]. The American Heart Association criteria for Kawasaki disease were used [7].

To achieve a power of 80% and a level of significance of 5% (two sided), for detecting a true difference of 4 days (7.9-3.8 days) in mean duration of hospital stay between MIS-C and dengue fever cases from previous studies [3,4] assuming a pooled standard deviation of 5 days, minimum sample size of 24 for each group was calculated.

Statistical analysis: Comparison of quantitative variables was done using Student *t*-test and Mann–Whitney *U* test for independent samples for parametric and non-parametric data, respectively. For comparing categorical data, chi-square test was used. Kaplan–Meier analysis was used to estimate the duration of hospital stay in the three groups, with the end point as time of discharge. Statistical analyses were performed using SPSS version 24.0. $P<0.05$ was considered statistically significant.

RESULTS

Of the 34 MIS-C cases, MIS-C with shock was seen in 15 (44%) children, MIS-C without shock in 17 (50%) children and Kawasaki like presentation in two children (6%). Of the 83 cases of dengue fever, 51(61%) cases had severe dengue by WHO classification. Mean (SD) age of children with dengue fever was 10.07 (4.43) years compared to MIS-C, 7.18 (4.81) years ($P=0.002$). MIS-C patients had more frequent symptoms of fever, conjunctival injection, swelling of hand and feet, diarrhea and altered sensorium. Whereas, abdominal pain and erythematous rash were more commonly noted in dengue fever patients **(Table I).** Clinical bleeding was seen only in dengue fever patients (7%). Mean (SD) hematocrit was significantly higher in dengue fever compared to MIS-C patients [38.6% (8.1%) vs. 29.1% (6.9%); $P<0.001$]. Mean platelet count and total leukocyte count was significantly lower in dengue fever compared to MIS-C patients.

Of the inflammatory markers, mean CRP was higher in MIS-C patients than dengue fever patients. Mean IL-6

Table I Clinical Profile, Management and Outcome of Children With MIS-C and Dengue Fever

Group	*MIS- C (n=34)*	*Dengue (n=83)*
Age [a]		
0-5 y	12(35)	12 (14)
6-10 y	16 (47)	35 (42)
11-18 y	6 (18)	36 (43)
Male gender	28 (82)	62 (75)
Signs/ symptoms		
Fever at admission[b]	34 (100)	60 (72)
Diarrhea[a]	4 (12)	0
Abdominal pain[c]	12 (35)	47 (57)
Vomiting	17 (50)	57 (69)
Erythematous rash[b]	9 (26)	55 (66)
Swelling of hand and feet[b]	10 (29)	0
Respiratory distress	14 (41)	38 (46)
Altered sensorium[c]	8 (24)	6 (7)
Conjunctival injection[b]	7 (21)	0
Myalgia[b]	6 (18)	68 (83)
Signs of capillary leak	13 (38)	36 (43)
Hypotension at admission	15 (44)	33 (39)
Imaging		
USG-moderate ascitis	10 (59)	15 (71)
X-ray pleural effusion	10 (29)	28 (34)
LV dysfunction[b]	7 (21)	0
Management		
Non-invasive ventilation	6 (18)	18 (22)
Mechanical ventilation[a]	6 (18)	2 (2)
Inotropes	13 (38)	22 (27)
Platelet transfusion[c]	0	10 (12)
Patient outcome		
PICU admission	11 (32)	21 (25)
Discharged	31 (98)	81 (98)

All values in no. (%). MIS-C: multi-system inflammatory syndrome in children associated with COVID-19; *USG: ultrasonography, IVIG: intravenous Immunoglobulin, LMWH -* low *molecular weight heparin, PICU: pediatric intensive care unit. Steroids, intravenous immunoglobulin, low molecular weight heparin and aspirin were used in 22, 11, 8 and 8 children with MIS-C and none with dengue fever.* [a]$P<0.01$; [b]$P=0.001$; [c]$P<0.05$.

levels, D-dimer and fibrinogen levels were also higher in MIS-C patients. In contrast, mean serum ferritin levels were higher in dengue fever patients. Left ventricular dysfunction was present only in MIS-C patients **(Table II** and **Web Fig 1)**. Need for mechanical ventilation was more in MIS-C cases as compared to dengue fever cases. Intravenous immunoglobulin (IVIG) infusion, steroids, low molecular weight heparin and aspirin were used only in MIS-C cases **(Table I).**

Kaplan-Meier survival curve with discharge as end point showed significantly longer duration of hospital stay in MIS-C patients [8.58 days (95% CI 7.13 - 10.03)] compared to dengue fever patients [6.54 days (95% CI: 5.78 - 7.21)] (*P*=0.014) **(Fig. 1**).

Repeat 2D-echocardiography was done before discharge in all patients with LV dysfunction/ Kawasaki disease like presentation. Only two children (5.9%) showed cardiac dysfunction, one case each with mild and moderate dysfunction. Both the cases showed resolution during follow-up.

DISCUSSION

The study compares the clinical and laboratory differences and outcomes of children hospitalized with MIS-C and dengue fever. Patients with dengue fever were significantly older as compared to MIS-C. Inflammatory marker levels of CRP, IL-6, D dimer and fibrinogen were significantly higher in MIS-C as compared to dengue fever patients.

Table II Laboratory Profile and Outcomes of Children With MIS-C and Dengue Fever

Laboratory parameters	*MIS- C (n=34)*	*Dengue (n=83)*
Serum values		
CRP (mg/L)[a]	100 (85)	17 (29)
Ferritin (ng/mL)[b]	2878 (5876)	6136 (6600)
D-Dimer (ng/mL)[b]	1619 (1313)	733(291)
Interleukin-6 (pg/mL)	677 (1505)	11 (15)
Fibrinogen (mg/dL)[c]	547 (98)	238 (121)
Hemoglobin (g/dL)[a]	9.7 (2.3)	12.9 (2.7)
Leukocyte count ($\times10^9$/L)[a]	16.6 (12)	7 (5.7)
Platelets ($\times10^9$/L)[a]	173.4 (134.7)	48.1 (42)
AST (U/L)	524 (1633)	641 (1359)
ALT (U/L)	236 (569)	277 (531)
Albumin (g/dL)[b]	3 (1.1)	3.5 (0.8)
LV ejection fraction (%)	52 (13)	60 (0)
PRISM II score	9 (8)	8 (6)
Hospital stay (d)	8.1 (4.1)	6.5 (3.3)

Data prepented as mean (SD). *MIS-C: Multi-system inflammatory syndrome in children* associated with *COVID-19; CRP-C-reactive protein; AST-aspartate transaminase; ALT-alanine transaminase; LV: Left ventricular;PRISM score II-Pediatric risk of mortality score.* [a]*P<0.001;*[b]*P<0.05;*[c]*P<0.01.*

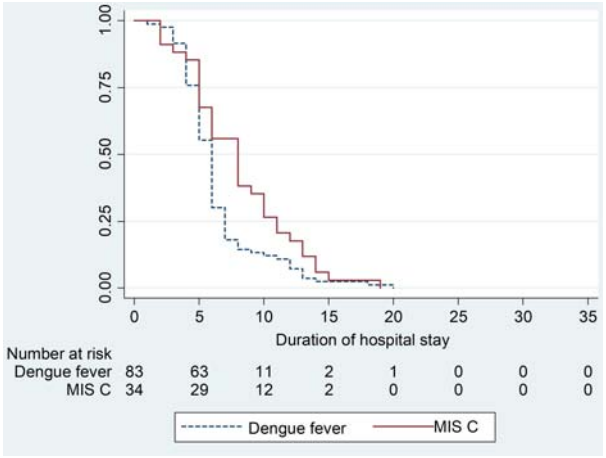

Fig. 1 Kaplan-Mayer graph showing mean duration of hospital stay in children with dengue fever and multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C).

All studies on MIS-C have reported hyper-inflammatory state as a primary hallmark [8,9]. The massive release of inflammatory mediators seen with exaggerated activation of the immune system is similar to cytokine storm syndrome [10]. It has been hypothesized that severe dengue is also caused by a cytokine storm inducing systemic inflammatory effects [11].

Although post-COVID MIS-C can present with lower platelet counts but the severe thrombocytopenia (<50 $x10^9$/L) as seen in dengue fever, is not common [8]. Also, hemoconcentration is uncommon in MIS-C patients, making it an important differentiating feature of dengue fever from MIS-C. Leukopenia followed by thrombo-cytopenia, capillary leak and hemoconcentration is very classic and pathognomonic of dengue fever.

Cornelia, et al. [12] showed presence of hyper-ferritinemia could discriminate between dengue and other febrile diseases. Other dengue studies also found an association between increased ferritin levels and severity of disease [12,13]. We also found serum ferritin levels to be higher in dengue fever patients than MIS-C patients.

In the present study, most patients requiring invasive ventilation were in MIS-C group (18%) as compared to dengue patients (2%). Other studies have also shown similar results. [9,14].

The differentiation between dengue fever and MIS-C is important in contemporary times because of entirely different management strategy for the two conditions. Dengue fever patients being managed with aggressive

WHAT THIS STUDY ADDS?

- We provide clinical and laboratory indicators that can give clues to differentiate dengue fever from MIS-C patients.

fluid management of crystalloids and colloids with inotropic support and platelet transfusions wherever needed. On the other, such aggressive fluid management in MIS-C patients would be detrimental in patients with cardiac dysfunction that is often present in MIS-C patients with shock. Moreover, vital role of intravenous immunoglobulin and steroids in management of MIS-C patients can never be overemphasized.

The study has few limitations. Firstly, the study is an experience from a single center. The diagnosis of dengue fever was based on serology in one third of cases. Studies have shown that COVID-19 cases may be misdiagnosed as dengue fever when relying on DENV IgM, which can remain positive months after COVID-19 infection [15].

To conclude, the presence of conjunctival injection, swelling of hand and feet, diarrhea, and altered sensorium in a febrile child with laboratory evidence of hyperinflammation (highly raised CRP, leukocytosis, raised D-dimers are pointers more in favor of MIS-C. Whereas, vomiting, myalgia and erythematous rash along with hyperferritinemia, hemoconcentration, leukopenia and severe thrombocytopenia are more common in dengue fever patients.

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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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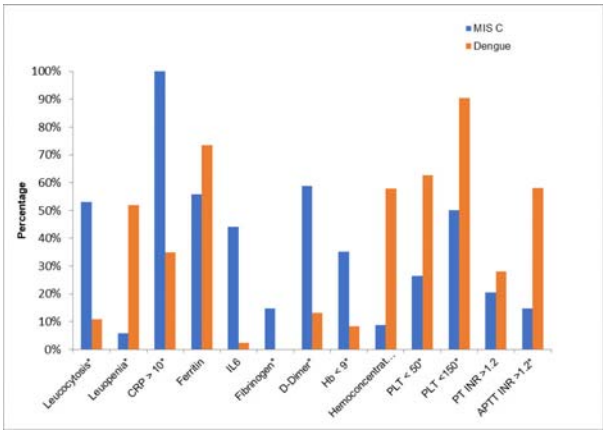

Web Fig. 1 Proportion with abnormal inflammatory markers among children with multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) and dengue fever.

RESEARCH PAPER

Clinical Spectrum of Children With Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 Infection

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Objectives: To compare the clinical profile, treatment, and outcomes of PCR-positive and PCR-negative antibody-positive critically ill children with multisystem inflammatory syndrome (MIS-C). **Methods**: This retrospective observational study was done at a tertiary care coronavirus disease 19 (COVID-19) pediatric intensive care unit in India. The baseline characteristics, clinical profile, treatment, and outcomes in seventeen critically ill children diagnosed with MIS-C were analyzed from 1 July to 31 October, 2020. **Results:** Sixteen out of 17 children presented with hypotensive shock and respiratory distress. Mean (SD) age of PCR-negative antibody-positive and PCR-positive children was 11 (4.4) and 5 (3.7) years, respectively (*P*=0.007). The former group had significantly higher mean (SD) D-dimer levels [16,651 (14859) ng/mL vs 3082 (2591) ng/mL; *P*=0.02]. All received intensive care management and steroid therapy; 7 children received intravenous immunoglobulin. 14 children survived and 3 died. **Conclusions:** The outcome of children with MIS-C was good if recognized early and received intensive care.

Keywords: *COVID-19, Hypotensive shock, Respiratory distress, Steroids*.

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Coronavirus disease (COVID-19) is a contagious pathogen affecting children less commonly than adults with incidence of 1-6.4% and a varied presentation in children [1,2]. In early April, UK clinicians noticed increasing numbers of children presenting with multisystem involvement and symptoms similar to Kawa-saki disease and termed it as hyper inflammatory synd-rome from COVID-19 [3]. Most of these children were healthy prior to the presentation.

This study was done to describe the clinical and laboratory features and outcomes in children with multisystem inflammatory syndrome in children (MIS-C) [4], admitted to an intensive care unit, and to compare these features between polymerase chain reaction (PCR)-positive and PCR-negative antibody-positive children.

METHODS

This was a retrospective observational study. The medical records of the patients admitted to the pediatric intensive care unit (PICU) from July to October 2020 were retrieved from the hospitals electronic database and inpatient records after obtaining necessary approval from the institutional review board. The records were analyzed for clinical and laboratory characteristics, treatment modalities and outcomes in PCR-positive and PCR-negative antibody-positive children.

The diagnosis of MIS-C was based on the WHO case definition, as any child with fever for three or more days and any two of the following, *i*) rash, conjunctivitis and/or mucocutaneous inflammation, *ii*) hypotension (SBP <5th centile), *iii*) features of myocardial dysfunction, *iv*) evidence of coagulopathy, *v*) acute gastrointestinal problems; and elevated markers of inflammation, with no obvious microbial cause on testing (including negative blood cultures, dengue and scrub typhus serology), and a positive COVID-19 test or contact with a COVID-19 patient [4]. The laboratory parameters that were assessed included ferritin, D-dimer, pro-brain natriuretic peptide BNP, troponin-T, procalcitonin, C-reactive protein (CRP), serum albumin and platelets. Diagnosis of SARS-CoV-2 infection was made by real-time reverse transcription-polymerase chain reaction (RT-PCR) assays done from nasopharyngeal swabs of children at admission. The COVID antibody test was done by rapid antibody tests to SARS-CoV-2 by chemil-uminescent immunoassay (CLIA) by 2 different kits, Siemens S1-RBD rapid antibody test (total or IgG by Siemens Healthineers) with measuring interval/index value 0.05-10 AU/mL and Roche and Abbott-Nucleocapsid (antibody) with cut off index <1 being non-reactive .

All children who were SARS-CoV-2 PCR positive or antibody positive fulfilling the MIS-C criteria were managed as per standard WHO treatment guidelines for critical disease including shock and ARDS (based on PaO2/FiO2 ratio and chest *X*-ray) [5], and the American College of Rheumatology (ACR) guidance on treatment of MIS-C [6], which included dexamethasone at 0.15 mg/kg/dose once daily and anticoagulant therapy with low molecular weight heparin (LMWH) at a dose of 0.5 mg/kg/dose twice daily in all children with D-dimer >500 ng/mL. Critically ill children on mechanical ventilation received unfractionated heparin at 5-10 units/kg/hour as an intravenous infusion for 24-48 hours till they were stable, which was then changed to LMWH. Intravenous immune globulin (IVIG) at a dose of 2 g/kg over 2 days was given to children with catecholamine-resistant shock and severe left ventricular dysfunction.

Statistical analysis: Statistical analysis was done using SPSS 23.0 (SPSS Inc.). Percentages and mean (standard deviations) were calculated for categorical and continuous variables, respectively. Independent sample *t*-test was used for comparing the means and two proportions test to compare the proportions between groups.

RESULTS

Over the study period, 415 children were admitted and screened for COVID-19 of whom 215 were admitted to COVID PICU (age range 1 month to 15 years). Thirty-six children (16%) were SARS-CoV-2 PCR positive, of whom 7 (19%) had moderate illness, 5 (14%) had severe and 24 (66%) had critical disease. Of the 24 children with critical disease, 10 (41%) had MIS-C. An additional 7 children with MIS-C were RT-PCR negative but COVID antibody-positive. Three PCR-positive infants aged one month, six months and 11 months had prematurity as a premorbid risk factor, and the 6 month old had also undergone Kasai procedure at 2 months of age for biliary atresia.

Clinical presentations were similar with fever in all and fluid-refractory hypotensive shock in 16 (75% of children being in cold shock) and respiratory distress in 16 children. The comparative clinical features between PCR-positive and PCR-negative antibody positive children are shown in **Table I.** Additional atypical manifestations seen in 2 children included refractory thrombocytopenia in a one-month-old infant and CNS stroke in a 6-year-old who had received steroids prior to admission and did not have respiratory distress or hypotensive shock at admission.

The antibody titre in 7 children who were PCR-negative by Siemens antibody test was >10 AU/mL in all. Roche analyses showed 5 out of 7 being positive with mean (SD) titres of 72.06 (38.3) while 2 of the children did not have the test done as there was inadequate sample for the second test. The comparative clinical and laboratory features between PCR-positive and PCR-negative antibody positive children are shown in **Table I**.

Blood cultures were sterile, dengue serology was negative, and scrub IgM ELISA was negative in all 17 children, ruling out other microbial causes. Twelve children had moderate-severe LV dysfunction, of whom seven were PCR-positive. Mild pericardial effusion was seen in two of the PCR-negative antibody positive children. Bedside echocardiographic screening showed no evidence of coronary artery ectasia or aneurysm.

Respiratory support was provided through HHFNC in 9 children (including 7 PCR-positive children), non-invasive ventilation in two PCR-positive children and invasive ventilation in five of whom four were PCR-

Table I Characteristics and Laboratory Parameters of Children With Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 Infection

Parameter	*SARS-CoV-2 PCR positive (n=10)*	*SARS-CoV-2 PCR negative (n=7)*
Age, y[a]	5 (3.71)	11 (4.4)
Sex ratio (female:male)	1.5: 1	0.4:1
Symptomatic prior to ICU admission, d	4.5 (1.9)	4.1 (1.34)
Clinical features, n		
Fever	10	7
Gastrointestinal symptoms	5	6
Respiratory symptoms	5	4
Rash	7	3
Hypotensive shock	10	6
Respiratory distress	10	6
Laboratory parameters[b]		
Ferritin (ng/mL)	1118 (838)	2095 (2696)
D-dimer (ng/mL)	3082 (2591)	16651 (14859)
NT ProBNP (pg/mL)[c]	14,139 (18107)	19,158 (22405)
Troponin- T (pcg/mL)	58 (78)	152 (257)
Procalcitonin (ng/mL)	16.5 (15.2)	39.1 (14.8)
C-reactive protein (mg/dL)	105.6 (41.5)	241.0 (159.2)
Albumin (g/dL)	2.75 (0.64)	3.14 (0.49)
Platelets ($X10^9$/L)	198 (1.24)	157 (0.76)

[b]*Values in mean (SD). All PCR negative children were SARS-CoV-2 antibody positive. SARS-COV-2 - severe acute coronavirus 2; PCR-polymrerase chain reaction; ICU-intensive care unit; NT ProBNP: N-terminal Pro Brain Natrieuretic Peptide.*[a]*P=0.02;* [c]*P=0.007. Among children with and without PCR-positivity, ferritin was abnormal in 10 and 6, D-dimer in 9 and 7, NT-ProBNP in 3 and 2, Troponin-T in 5 and 4, Procalcitonin in 3 and 6, and C-reactive protein in 5 each, respectively.*

WHAT THIS STUDY ADD?

- Multi-system inflammatory syndrome in children (MIS-C) can present as critical illness needing ICU care, and responds well with steroid therapy in the resource-limited setting in the absence of IVIG.

negative antibody positive children. There was evidence of acute respiratory distress syndrome (ARDS) in 8 children, with 4 each of PCR-positive and PCR-negative antibody positive children. Of these 8 children, two improved with non-invasive mechanical ventilation and one improved with heated humidified high flow nasal cannula therapy (HHHFNC), with the total duration of supplemental oxygen ranging from 3 to 5 days. The remaining five required invasive mechanical ventilation. Oxygenation Index ratio in three of these five children was >16, suggestive of severe ARDS. Inotropic support was needed for 14 children, with two inotropes (adrenaline and noradrenaline) needed in five of seven PCR-negative antibody positive children and six of ten PCR-positive children. Two children were treated with peripheral veno-arterial extra-corporeal membrane oxygenation (ECMO) for a period of 7 days for severe cardiac dysfunction with refractory shock. One child received continuous renal replacement therapy (CRRT) for acute kidney injury. All 17 received dexamethasone and 16 had anticoagulant therapy (except the one-month-old with refractory thrombocytopenia), and seven of the seventeen with catecholamine-resistant shock and severe LV dysfunction received intravenous immune globulin. None of the children received tocilizumab or investigational antiviral agents.

The mean duration of ICU stay was 7.3 (range 4 to 19) days. Fourteen (82%) children were discharged. Three children died duing the study. One was a 1-month-old infant with refractory thrombocytopenia and multiorgan involvement treated with IVIG and a single dose of methylprednisolone at 30 mg/kg and cyclosporine for probable MAS (macrophage activation syndrome). Two others were adolescents with severe cardiac dysfunction, refractory shock and multiorgan failure, one of whom was on ECMO.

DISCUSSION

This series of seventeen children adds to the growing body of literature from India on manifestations, management and outcomes among critically ill COVID positive children with MIS-C associated with COVID-19 [7,8]. Majority of the children were PCR-positive for SARS-CoV-2 infection while only seven were COVID antibody positive, unlike most reports from Western countries where PCR-positivity in children with MIS-C is seen in about a-third [9,10]. The majority of children in this study had no major comorbidities comparable to studies from Italy and the US showing that children were mostly well prior to SARS-CoV-2 infection [10-12].

All the children were critically ill needing intensive care admission and inotropic support corresponding to earlier studies [11-13]. Although, they needed respiratory support, less than half of them required mechanical ventilation, similar to other studies that show that children with MIS-C have mild to moderate lung involvement, and that outcomes are good with appropriate respiratory support [11-13].

Within this cohort, children with only COVID-19 antibody positivity were older, and predominantly male. They presented with more gastrointestinal symptoms and had more severe lung involvement needing invasive mechanical ventilation, as well as special supportive therapy including ECMO in two children and CRRT in one child. Levels of inflammatory markers and cardiac enzymes were also higher in this group of children with higher mortality compared to those with PCR-positivity, suggesting that hyperinflammation and cytokine storm are more evident in those presenting later in SARS-CoV-2 infection, probably due to the presence of higher titres of IgG SARS-CoV-2 receptor binding domains that are associated with increased disease severity [14].

The mainstay of treatment in these children remains prompt identification and treatment with anti-inflammatory and immunosuppressive agents. Dexamethasone was given to all children as per the ACR guidance on treatment of MIS-C [6] and the lower mortality in patients on oxygen supplementation or ventilation as demonstrated in the RECOVERY trial [15]. IVIG has been suggested as the primary modality of therapy for MIS-C [6,10,11,13]. However, steroids are a promising option in the resource-limited setting which have shown to be equally effective in children with critical illness with good ICU care [8,11,13]. Larger studies would be beneficial to compare the effect of steroids alone or in combination with IVIG in the treatment of MIS-C.

As COVID-19 antibody testing was not available at our institution during the initial study period, it is possible that some PCR-negative cases of MIS-C may have been

missed. However, as none of the other children with critical illness during that period fulfilled the clinical diagnostic criteria for MIS-C, we feel it was probably minimal. Larger studies would be beneficial to compare the effect of steroids alone or in combination with IVIG in the treatment of MIS-C.

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Indian Academy of Pediatrics Revised Guidelines on School Reopening: First Revision, September 2021

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Justification: The COVID-19 pandemic has affected schooling for more than 24 crores students, since March 2020. Students need a respite from the long standing social isolation so that they regain their chance to develop holistically, but after the devastating effects of the second wave, the administrators as well as parents are skeptical about the decision of school reopening. **Process:** The Indian Academy of Pediatrics constituted a task force comprising of national and international experts in the field who deliberated on the issue. **Objectives:** To bring out scientifically supported guidelines on the prerequisites of opening and attending the schools, in the current context of the COVID-19 pandemic. **Recommendations:**The task force recommends *i*) Decentralization of the school reopening decision; *ii*)Three epidemiological parameters, case positivity rate (<5 or steadily declining number of cases for past two weeks), number of new cases(<20 per lakh population per day for past two weeks) and vaccination coverage (>60% of the vaccine-eligible population) to be met at the local level, before the schools reopen; and *iii*) Criteria regarding health and vaccination to be met by the schoolattendees.

Keywords: COVID-19, Education, Formal education, Pandemic.

During the COVID-19 pandemic, crores of children and adolescents are negatively affected across various domains of their health and development [1]. With prolonged school closures, the educational void is increasing day by day and education is probably suffering the most [2]. An Indian survey study on more than 16000 students across five states has shown that, about 92% and 82% children have declined in (at least one) mathematical and linguistic abilities, respectively [3]. Another survey study conducted across 15 States revealed the gross failure of online learning methodology to reach out to all the students. Only 24% students from urban area and 8% from rural area are reported to study online regularly; 37% rural children are completely out of the education stream [4]. Children are homebound for more than 17 months now. Consequently, they are displaying significant physical and psychosocial health issues [1]. Reopening of the schools and bringing back normalcy in their lives is eagerly awaited.

It has been amply proved that more than half of the children infected with COVID -19 are either asymptomatic or develop mild form of the disease [5]. There are studies to prove that schools do not act as major sources of viral transmission [6]. Outbreaks have been reported where the mitigation measures were not strictly adhered to [7].

The latest body of research on COVID-19, particularly in children, and the advent and the availability of the vaccines, are scientifically favorable factors for relaxing the social restrictions imposed on children. But the horrific experiences during the second wave are unforgettable and act as a big barrier when there is any attempt to bring the children back to schools. The Government authorities, the school administrators, as well as the parents appear to be in a state of dilemma and confusion. The decision for school reopening therefore, needs to be taken meti-culously and with scientific evidences.

To address the issues of schooling during the pandemic, the Indian Academy of Pediatrics (IAP) had framed recommendations on 'School Reopening, Remote Learning and Curriculum during and after COVID-19 Pandemic', in October, 2020 [8]. We, herein, provide an update to these guidelines.

OBJECTIVES

To frame guidelines to readdress the epidemiological parameters for school reopening, and to formulate recommendations for individuals (staff, students and visitors) while attending the school.

METHODOLOGY

The Indian Academy of Pediatrics constituted an expert panel, the 'Task Force on School Reopening 2021' in August, 2021. The panel members exchanged their ideas and thoughts through Zoom meetings, group mails and other social networks. They studied relevant latest research papers and articles, other currently released guidelines and took into consideration, the experiences of school reopening at various places across the globe. After deliberating on the matter, the guidelines were drafted and circulated to all the members for their suggestions and approval. The Task Force thereafter finalized the following revised recommendations on 'when' to open the schools:

RECOMMENDATIONS

General Recommendations

- Decision-making regarding the school reopening should be decentralized. It should be taken at the level of districts (or taluka/city/village/school) according to the local situations, rather than at the national or state level.
- Strict compliance to the COVID appropriate behaviour (social distancing/masking/sanitization/respiratory hygiene etc.) by each and everyone in the community should be encouraged and ensured.
- Isolation, testing and contact tracing of symptomatic school attendees should be carried out as per local health guidelines.
- Healthcare system should be adequately geared up to handle any potential outbreaks through meticulous microplanning.
- Local COVID-19 statistics should be vigilantly followed. The decision regarding keeping the schools open should be reviewed every 15 days.
- COVID vaccination drives should be undertaken to cover vaccine eligible population as early as possible.

Criteria for School Reopening

These criteria need to be met at the local level.

1. The case positivity rate for COVID-19 (i.e., the number of RT-PCR positive per hundred tests) should be less than 5% for the preceding two weeks OR if the case positivity rate is greater than 5%, the total number of new cases should have been steadily declining over the preceding two weeks [8].
2. Number of new cases per 1 lakh population per day should be less than 20 for preceding two weeks [8].
3. Vaccination coverage (as measured by at least one dose of any of the COVID vaccines) of the adult (or the vaccine-eligible) population should be 60% or more [9,10].

When all these three criteria are met, the local authorities may consider opening of the schools.

Criteria for Attending the School

- All the adult members working at and closely associated with schools, including the teachers, non-teaching staff, support staff, commute drivers, attendants, and school visitors, should have received at least one dose of any COVID-19 vaccine.
- Students above the age of 18 years should have received at least one dose of COVID-19 vaccine.
- Both parents and all other household adults of the student should have received at least one dose of COVID-19 vaccine.
- Parents should be willing and should give consent for sending the ward to the school.
- High risk staff members (like those suffering from diabetes, high blood pressure, obesity, lung diseases etc.) should have completed two doses of COVID -19 vaccination 15 days prior to joining the schools.
- High-risk children (like those suffering from chronic diseases like asthma, kidney diseases, children with special needs, children on steroids etc.) should consult their pediatricians before joining the schools.
- Anyone who is not feeling well should refrain from attending the school and consult a medical professional before returning to the school.

The current evidence suggests that the seroprevalence is a highly volatile indicator with high false positivity and it is not a robust criterion for policy decisions on social restrictions. The results of seroprevalence surveys are influenced by several factors like restricted populations, non-representative samples, uncertainty around test accuracy, and limited knowledge about presence of antibodies in the long term. Further, these are required to be interpreted in the context of other external information, such as confirmed cases, deaths, and infectious disease models, to understand the disease better[11,12].

IAP will update the advisory as and when new scientific data emerges.

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POSITION PAPER

Indian Academy of Pediatrics Position Paper on Nurturing Care for Early Childhood Development

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Early childhood development (ECD) refers to the physical, motor, socio-emotional, cognitive, and linguistic development of a young child. The 'Countdown to 2030' global distribution of 'children at risk of poor development' indicates the need for urgent action and investment in ECD. Nurturing care enhances ECD, even in the presence of adversities. Strategic actions should exist at multiple levels: the family, community, health care providers and government. Previously, child health related policies and programs of the Government of India functioned in isolation, but have recently started demonstrating multi-sectoral collaboration. Nonetheless, the status of ECD in India is far from optimal. There is strong evidence that parenting programs improve outcomes related to ECD. This is dependent on key programmatic areas (timing, duration, frequency, intensity, modality, content, etc.), in addition to political will, funding, partnership, and plans for scaling up. Each country must implement its unique ECD program that is need-based and customized to their stakeholder community. Barriers like inadequate sensitization of the community and low competency of health care providers need to be overcome. IAP firmly believes that responsive parenting interventions revolving around nurturing care should be incorporated in office practice. This paper outlines IAP's position on ECD, and its recommendations for pediatricians and policy makers. It also presents the roadmap in partnership with other stakeholders in maternal, neonatal, and child health; Federation of Obstetric and Gynaecological Societies of India (FOGSI), National Neonatology Forum (NNF), World Health Organization (WHO), and United Nation Children Fund (UNICEF)

Keywords: *IAP-Nurture, Office practice, Parenting intervention program, Responsive parenting*.

Early childhood development (ECD) is an integrated concept that refers to the physical, motor, socio-emotional, cognitive, and linguistic development of children [1], as well as the multiple sectors required for their attainment, i.e., health, nutrition, education, social protection, and global finances. The foundation of future health, well-being, and productivity are laid down in the first three years of life. This period is considered especially critical in terms of development. Anatomically, the velocity of brain growth continues to be rapid (albeit slower than the fetal period), while psychologically, experiential learning occurs. Understandably, ECD can get affected by multiple factors; genetic, environmental, biological, social and demographic [2]. An estimated 250 million (43%) children under 5 years, from low- and middle-income countries (LMICs) are not expected to reach their expected developmental potential [3] due to risk factors outnumbering protective influences. Adverse childhood experiences like poverty, stunting and severe psycho-social deprivation have long-term physiological and epigenetic effects on brain development and cognition [4]. These may result from development of anatomical abnormalities (i.e., smaller hippocampal grey matter, and decreased frontal and temporal lobe volumes) [5]; and reduced activation of the areas of the brain involved in memory, language, and cognition. They can

also lead to a constant state of increased stress hormones due to dysregulation of the hypothalamic-pituitary-adreno-cortical axis [6].

The Nurturing care for ECD (NC-ECD) framework is a holistic approach developed by multiple global stakeholders to serve as a roadmap for action [7]. This includes measures that help young children to survive (reduce mortality), thrive (be healthy), transform (be exposed to an enabling environment), and attain one's expected human potential. The five components of NC known to enhance ECD are good health, optimal nutrition, opportunities for early learning, responsive parenting, and safety and security. It has been reported that provision of nurturing care can also reduce the negative impact of existing adversities [8]. This can be delivered by the family, community and/or the government. Strategic actions that promote NC-ECD at the country level include: lead and invest, focus on families and communities, strengthen services, monitor progress, and use data and innovation.

The Indian Academy of Pediatrics (IAP) launched a three-year (2021-2023) Presidential action plan on NC-ECD, IAP-Nurture [9]. Key evidence-based actions that have been proposed to ensure that the NC–ECD components are incorporated in pediatric practice are: changing knowledge, perception, attitudes and practices of pediatricians; changing knowledge and perception of parents, medical students and allied professionals; and documentation. The 'Mumbai 2021 Call for Action' pledge taken by the members of IAP, National Neonatology Forum (NNF), and Federation of Obstetric and Gynaecological Societies of India (FOGSI), with support from WHO, and United Nations Children's Fund (UNICEF) at the Central IAP National Conference (PEDICON) 2021 displayed a strong commitment to provide an optimal healthy, safe, nurturing and enabling environment to all children from conception to three years of life [10].

We, herein, present the position of IAP on providing NC-ECD for all children aged 0-3 years in India.

Current Status

The 2011 Indian census [11] revealed that there were 164.5 million children aged 0-6 years, with a proportion of them marginalized, unreachable and unaccounted for, in terms of benefitting from all the services that promote ECD. The status and trend of indicators related to health and nutritional status of Indian children under the age of 5 years can be compared with other countries using statistics obtained from the National surveys including National Family Health Surveys and Comprehensive National Nutrition Survey (CNNS). As in other LMICs, the challenge arises when it comes to assessing the status of the remaining components of NCECD, as data on safety and security, responsive parenting and oppor-tunities for early learning are not easily available.

To address these lacunae, the 'Countdown to 2030' initiative has outlined several indicators that can be used by a country for global comparison, provided local data is available [12]. **Table I** depicts the developmental profile of ECD related indicators for 2020. The Sustainable Developmental Goal indicator 4.2.1 (proportion of children aged 24-59 months who are developmentally on track in health, learning and psychosocial well-being, by sex) [13] does not reflect the status of the first three years. Population-based global indicators like the Caregiver-Reported Early Development Index (CREDI) [14] and Early Child Development Index [15] are in the process of being developed and validated for children in this age group, but are currently difficult to ascertain in most LMICS. Till then, the most common indicator that is used to assess children at risk of poor development in young children is the 'Composite Index' (CI), which is based on the prevalence of stunting and poverty, as per the World Bank poverty rates [16,17]. Countries are color coded based on the CI–pink, ≤33%; orange, 34-66%, and red, ≥67%, with a higher index indicating lower performance [18]; Though the CI of India has decreased progressively over the years (from 72 in 2005 to 45 in 2015), it is still evident from **Table I** that urgent escalating action and investment is needed to promote, support and sustain ECD in India by all stakeholders, and that too on a war-footing.

Policy and Program Environment

ECD services should be universal, inclusive, accessible and equitable [1]. Context-specific customization is required when formulating policies and programs related to ECD as threats to ECD, available workforce, health care providers' capacities, and implementation mechanisms vary across countries. **Web Table I** depicts key policies [19-27] of the Government of India (GoI) that have been framed in the last decade, and which demonstrate multi-sectoral and multi-dimensional perspectives in relation to child health and ECD. Adjunct policies that cover maternal health and provide enabling environments for working women, encourage more women to work without the fear of compro- mising infant/child care. Worthwhile mentions are the Building and Other Construction Workers (Regulation of Employment and Conditions of Service) Act, 1996 [28] and the National Policy on Empowerment of Women 2001 [29].

The oldest and largest national program launched by the Government of India (GoI) in 1976 to promote child health is the Integrated Child Development Services (ICDS) [30]. Other national health programs that have been

Table I Countdown to 2030 Country Profile of India (2020)

Indicators	*2020*
Demography	
Children under 5 years	8% total population
Under five years mortality	34/1000
Composite index	-
Inequity of risk	
Gender: Girls/boys	45%/ 45%
Rural/ Urban	50%/32%
Threats to ECD	
Low birth weight	-
Preterm	13%
Child living in poverty	14%
Inadequate supervision	
Violent discipline	
Under five years stunting	35%
Developmentally on track	-
Functional difficulty	-
Services: Health	
Antenatal care	51%
Postnatal care	65%
Seeking care for pneumonia	78%
Services: Nutrition	
Exclusive breastfeeding	58%
Minimum acceptable diet (6-23 mo)	6%
Early learning	
Books at home	
Playthings at home	
Early stimulation	
Early childhood education	38%
Responsive caregiving	-
Safety & security	
Birth registration	83%
Positive discipline	
Basic sanitation	60%
Basic drinking water	93%
Facilitating environment	
Paid maternity leave	26 wk
Paid paternity leave	None
Minimum wage	Present
Child protection services	Yes (ICPS)
Code marketing of breast milk substitutes	Substantial
International conventions on	
Right of the child	Enforced
Rights of persons with disability	Enforced
Protection of children	Enforced
Sale of children, pornography, prostitution etc.	Enforced

introduced in the last decade with focus on infants and children in the first three years and cover some components of nurturing care are given in **Web Table II** [31-38]. However, despite the implementation of all these policies and programs, the status of ECD in India, as evident from the Composite Index, is far from optimal.

There have been several ECD-directed programs in other LMICs [39-52] and the Global WHO/UNICEF Care for Child Development (CCD) -3 [53], that have demonstrated a positive impact on the development of young children. All of these are parenting programs that aim at improving parent-child interactions, behaviors, knowledge, beliefs, attitudes, and practice [54]. They include high quality promotive and preventive health services, caregiver capacity building, and providing support by enabling policies. A review of these programs led to the identification of key program areas (**Box I**) with strong evidence for improved child outcomes (physical health, cognition, social and emotional well-being) and parent outcomes (better parental behavior/ parenting practices).

There has been a paradigm shift in health policy in the last two decades from survival to healthy survival and

Box 1 Key Program Areas with Strong Evidence for Improved Child and Parent Outcomes for Early Child Development

Political and legal will: Strong legal frameworks and policies for inter-sectoral coordination. Creation of apex bodies at top levels of government for efficient coordination among stakeholders, and to assure accountability and alignment across financing streams.

Partnership: Involvement of international and national agencies, non-government organizations, professional organizations, policy makers, and funding partners.

Content: Programs based on NC-ECD modules, Care for Child Development modules, Road to Health cards that include all components of NC-ECD, or responsive caregiving, supported parent behavior management skills, and positive discipline.

Duration, frequency and intensity: The minimum duration should be 12 months. Best outcomes are seen with at least 2 years. The frequency should be high enough to ensure that practices change according to the developmental needs of the child (>9). Good quality intensity should allow direct interaction between the child and the parent. Didactic doctor-parent sessions are considered low quality with no or minimal impact.

Program modality: Multiple modalities are most effective. These include: individual sessions with active parent-child engagement; group sessions; home visits; illustrated posters/ cards depicting opportunities for play and responsive parenting; guidance on parenting practices, and problem-based strategies.

Use of other platforms: Digital media/portals, mobile apps and/ or text messages can be used to disseminate information, and serve as reminders of scheduled visits.

Optimal service provider: Authority figures (doctors, nurses and educators) are most effective for office practice. Community health workers with higher education and training are associated with higher program quality in the field.

Administrative: All care providers should receive proper incentive and remuneration.

Scaling up: Starting small, learning, adapting and increasing coverage.

transformation. To give effect to this policy change, a three-pronged approach would be required. First, overcoming existing governance challenges in ECD-directed national programs [55]. All stakeholders need to be made aware of the advantages and cost-effectiveness of multi-sectoral action for ECD directed programs, especially when there are competing interests, and ineffective inter-sectoral collaboration between government agencies and public initiatives. Second, capacity of healthcare providers has to be built in order to deliver frequent, intensive and interactive parental counselling on NC-ECD. The missing NC-ECD components i.e., early learning opportunity, responsive caregiving and safety and security need to be added to existing public health programs and office practice. Barriers that will need to be overcome include low sensitization of health care providers regarding the importance of NC-ECD [56,57], poor competency levels due to lack of training in ECD, and time constraints of the clinician that precludes including parental education during a health visit. A critical barrier is the lack of felt need of parents resulting in low demand generation for such services by the families. The concept of well-child visits needs to be popularized, along with creating awareness in the community about the advantages of adopting child-care practices that influence their children's develop-mental outcomes [58].

IAP POSITION ON EARLY CHILDHOOD DEVELOPMENT

IAP has been actively involved in several ECD-directed presidential action programs/activities during the last decade including the National training program on parent skills for children and adolescents. Poor scholastic performance program (2012), Child Rights and Protec-tion program (2012), Mission uday (2013), Cradle to crayons program (2016), Management of school emergencies: Child safety module (2019), and IAP Palak Project (2019).

IAP recognizes the strong felt need for, and positive implications of incorporating ECD directed child and parent comprehensive services into routine office practice and this has resulted in the launch of the 2021-2023 Presidential Action Plan for NC-ECD [9, 10], and the release of the 2021 IAP guidelines for parents [59]. IAP's 30000 members can become a collective workforce capable of making a significant impact in the lives of young children and their families.

Based on the aforementioned lessons learnt, and in continuity with the 2019 IAP consensus statement and guideline on ECD [60], we propose the following universal recommendations intended for all children between the age of 0-3 years, irrespective of their needs or circumstances. IAP Recommendations for targeted (at high risk) and indicated groups (children with developmental disorders/ disabilities) including some of the individual components of NC-ECD [61-68], which are available in the public domain are not addressed in the current position paper.

1. For Expanding Well-Child Visits

1.1 Initiation of at least 11 well-child visits in the first 3 years of life of a child will include ECD-directed elicitation of history, evaluation (monitoring of growth), delivery of specific health care services, counselling and anticipatory guidance related to the components of NC-ECD.

1.2 The schedule will be as follows: within a week of birth, 1.5, 2.5, 3.5, 6, 9, 12, 18, 24, 30 and 36 months.

1.3 The focus and content will vary according to the age of the child.

1.4 This should be a collaborative effort by multiple service providers (pediatrician, clinic staff) using multiple modalities (administering a checklist, one-on-one counselling, group sessions, demonstration, audio-visual programs, hand-outs and displays in waiting area, etc.) and providing resources to the parent for self-learning.

1.5 An appointment system can be utilized so that the well-child visits can be staggered according to the convenience of the practitioner to avoid interference with service delivery for sick patients.

2. Addition to Missing Links and Developing Competencies in the Pediatrician/Office Staff

2.1 Health-related issues currently not covered in routine well-child visits should be added i.e., referrals for screening hearing or vision, educating parents about oral, sleep and personal hygiene, screen time, sanitation, and safe drinking water.

2.2 Select components of the revised GoI Mother-Child Protection (MCP) card [69] should be used at each visit for growth and developmental monitoring and parents advised to refer to the information related to developmental stimulation and other health related messages.

2.3 Counseling regarding age-appropriate minimal acceptable diet (frequency, dietary diversity, healthy foods).

2.4 Parents should be provided information on parental education on safety at home, during play, and on the road.

2.5 Pediatricians should learn to recognize signs of possible child neglect and abuse, and manage cases of child abuse according to the established protocols.

3. Developing Parental Competencies

3.1 Issues related to responsive feeding, responsive

caregiving, positive parenting and positive discipline should be discussed.

3.2 Early stimulation and play-based non-formal education should be taught by demonstration and interactive sessions to help parents provide opportunities for early learning at home.

3.3 Special emphasis to be given to involve fathers in the delivery of interventions actively.

3.4 Other caregivers from within the family like siblings older than 12 years, uncles, aunts and grandparents should be involved.

3.5 Provision of standardized resource material and IAP guidelines to parents.

3.6 Display of salient health messages in office displays.

THE ROAD AHEAD

High quality peri-conceptional, antenatal, intrapartum and postnatal care during pregnancy and the first three years of life increases the likelihood of physically and developmentally healthy children, and by extension, the future of India. We include the visions of various stakeholders in maternal, neonatal, and child health with respect to what their respective organizations have planned for the future.

Indian Academy of Pediatrics

Multiple strategies are going to be employed for increasing awareness of parents, the community, pre-service and in-service health care providers, allied professional bodies and the government about NC-ECD. The aforementioned IAP-Nurture will span three years (2021-2023), and aims at enhancing NC-ECD for all children under 3 years. The IAP platform will be used with involvement of social media and print to sensitize and disseminate information to the community regarding the importance of NC-ECD for the physical, cognitive and psychological well-being of a child. An ongoing nationwide mixed-method study will generate quantitative and qualitative data related to the awareness, perceptions and challenges of pediatricians in incorporating nurturing care in office practice. A stakeholder meeting sensitizing all partners and allied agencies has been held for implementing a universal ECD program in the country, and one of the outcomes is this position paper. A taskforce formulated recommendations for including ECD in the medical undergraduate and pediatric post graduate curriculum [70]. A WHO sponsored supplementary issue of *Indian Pediatrics* on ECD will be published this year and disseminated among members. Training workshops will be conducted across the country for capacity building of pediatricians to impart knowledge and skills to caregivers in office practice by multiple modalities. The concept of holistic well child visits throughout the first three years will be popularized. The impact of these workshops on pediatricians, parents and children will be evaluated. Training videos will be uploaded on the IAP website.

Federation of Obstetric and Gynecological Societies of India

The aim is to improve practices related to NC- ECD by preparing training modules, sensitizing, and conducting capacity building workshops for obstetricians (in collaboration with IAP, WHO and other partners), and imparting knowledge and skills to parents regarding ECD-directed child rearing practices. Other initiatives include a nationwide survey of the knowledge, attitude and practices of its members pertaining to pre-conceptual care and counselling (PCC), antenatal care, and ECD, as well as a certificate course on ECD. A community connect e-conclave will be held on social media for mass education and awareness. Fact sheets, an advocacy statement, training videos, resource material from the training work-shops, and other educational material will be uploaded on the society's website. FOGSI will continue its advocacy with policy makers to implement a universal ECD program with all allied professional bodies, so that no child is left behind.

National Neonatology Forum

The society recognizes that the neonatal period and early infancy form critical periods in the continuum of ECD. It has been involved in standardization of care in neonatal intensive care units (NICU) across India, providing technical inputs to the India Newborn Action Plan (2014), Facility Based Newborn Care (FNBC) training and mentoring visits, Kangaroo mother care (KMC) work-shops, and establishment of sick newborn care units (SCNU). NNF will continue to support and train health care providers for early initiation of breast feeding and the provision of exclusive breast feeding for all infants. It will continue its advocacy with policy makers for the establish-ment of more human milk banks. FBNC training and mentoring activities will continue for hospitalized low birth weight and preterm infants. This involves the training and monitoring of health care providers in evidence-based practices. The family is supported in the providing KMC and family participatory care, which enable them to become responsive care givers. Other aspects of nurturing care will be taken care of during follow-up visits. NNF will also support implementing the national initiative for providing postnatal home-based visits by community health workers to impart ECD-directed parental interventions that cover health, nutrition, hygiene, sanitation, age-appropriate early stimulation, and responsive care.

WHO India

As is apparent from mapping the landscape of laws, policies and programs in India, several initiatives and

opportunities support NC-ECD. WHO strongly advocates harmonizing these into a comprehensive, rights-based, child-centric, equitable and inclusive approach delivered through diverse service delivery channels, and coordinated across multiple sectors. WHO suggestions to strengthen services and achieve the national vision to build human potential are outlined below:

- Establish an empowered inter-sectoral council at national, sub-national and local administrative levels to govern the programs for NC for ECD.
- Ensure sustained and predictable financing for child related expenditure in the age group 0-3 and 4-8 years; track per child expenditure, particularly in the states with poor maternal and child health indices.
- Improve services delivered by all sectors (mainly health) by integrating responsive caregiving and perinatal maternal mental health and setting standards to ensure quality of services.
- Invest in sustained capacity building of pre- and in-service workforce.
- Implement a comprehensive communication strategy to create demand for services and strengthen NC practices at the family level; harmonise key messages across sectors
- Include ECD monitoring indicators into the SDG India Index and national information systems, and commission joint multisectoral reviews of the implementation, including coverage and quality.
- Design and implement scalable innovations, capitalize on digital platforms and solutions, document experiences, create learning networks and identify research priorities.

UNICEF India

All children from conception to the first three years of life, especially the most disadvantaged, should achieve their full developmental potential. UNICEF focuses on two outcomes to accomplish this: *i*) Strengthening service delivery systems to ensure that all young children have equitable access to essential quality health, nutrition, protection, and early learning services that address their survival, growth, and developmental needs; and *ii*) Supporting parents, caregivers, and families and encouraging them to provide their children with nurturing care and responsive parenting. UNICEF India is working with the union and state governments to support the delivery of health, nutrition, water, sanitation and hygiene (WASH) strategy, early learning, early screening/intervention, special needs, and parental/family support to promote holistic ECD. The focus areas of intervention include:

- Supporting multi-sectoral programs/interventions for ECD, including India's newborn action plan, The Prime Minister's Overarching Scheme for Holistic Nutrition (POSHAN) Abhiyaan, Rashtriya Bal Swasthya Karyakram (RBSK), Home Based Care for Young Child (HBYC) , early learning, Swachh Bharat Mission, and interventions that promote maternal health, nutrition, infant and young child feeding, and prevention and treatment of childhood illnesses.
- Strengthening systems to support the delivery of essential services prioritized capacity building, strengthening monitoring systems, and evidence generation.
- Supporting family and community engagement and empowerment to stimulate demand for inclusive, quality services and ensure nurturing care for children at home.
- Strengthening and expanding partnerships with ECD networks and allied agencies to increase demand for services.
- Supporting responsive parenting in health, nutrition, early stimulation, positive discipline, protection from stress, fathers' engagement, and gender equity.
- Using advocacy and communications to support programmatic goals.

CONCLUSIONS

It is imperative that we promote and support ECD, if we want to attain the vision of developing and transforming human potential from 'todays survivor' to 'tomorrow's future.' Investing in ECD has a positive impact on child health and a nation's gross domestic product [71]. All the stakeholders involved in the well-being of the mother and child need to work in tandem. This can be achieved by synergy among different sectors and their corresponding ministries (health, nutrition, education, women and child welfare, and child protection services); different levels (family, community, health care provider and the government); and different organizations (public, private, and NGOs).

By virtue of their profession, pediatricians have a unique role in sensitizing and influencing parents, the public, and policy makers. IAP takes the position to be a part of the process to galvanize all the aforementioned strategic actions and facilitate collaboration among all partners and stakeholders. By including preventive and promotive health services to existing well-child visits in office practice, not only do we decrease childhood mortality and morbidity, but we also can act as a bridge between the parent and the child that results in enhancement of ECD. Nurturing care by the family, village, supported by the society, the healthcare workers and the government will ultimately ensure optimal ECD.

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SBM reviewed literature of all the sections of the paper and drafted the manuscript, with the help of DM and SHD. DS, AN and ST reviewed and provided literature on the magnitude of burden. DA, AT and ML reviewed and provided literature on existing policies and programs. NC, JU, KB, JT and RKP reviewed and provided literature on existing recommendations. DS, SR, AG, RM, VVS, AdW, LdA wrote the roadmap for their respective organizations. PG, SR, GVB and RR did the critical appraisal of the paper. All authors have approved the final manuscript.

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Web Table I Policies of the Government of India directed at Early Childhood Development

Policy	*Domain*	*Specific details*
The National Vaccine Policy 2011 [19]	Good Health	Creation of a database of babies at birth who will be tracked and complete vaccine coverage ensured by linkages with a geographic information system.
The National Early Childhood Care and Education Policy, 2013 [20]	Early opportunities for learning Responsive caregiving	Integrated services for 0 – 6-year-old children that enables caregivers to learn developmentally appropriate practices, provide play-based, non-formal education, make toys and helps in the transition to primary school.
The National Policy for children 2013 (NPC) [21]	Good Health Adequate nutrition Maternal health Safety and Security	Covers preventive, promotive, curative and rehabilitative dimensions of universal health care. It safeguards from hunger, deprivation and malnutrition. Policies on Child protection
The National Plan of Action for Children 2016 [22]	Good Health Adequate nutrition Maternal health	This provides the roadmap for NPC 2013. It focuses on the 'first 1000 days', and reaching the last and least-served children.
The National Health Policy 2017 [23]	Good Health Adequate nutrition	Covers comprehensive primary health care services and undernutrition.
The National Food Security Act (NFSA), 2013 [24]	Adequate nutrition	For 6 months to 6-year-old children. It promotes exclusive breastfeeding, gives free meals, identifies malnutrition, and carries out deworming.
Protection of Children from Sexual Offences Act, 2012 [25]	Safety and Security	A comprehensive law that protects children from sexual assault, sexual harassment, and pornography by safeguarding the interests of the child at every stage of the judicial process
Criminal Law (Amendment) Act, 2013 [26]	Safety and Security	Two new sections were added that amended the protection of children from criminal offences Act, by the addition of alternate punishment.
Juvenile Justice (care & protection of children) Act, 2015 [27]	Safety and Security	The law relating to children alleged and found to be in conflict with the law and children in need of care and protection by adopting a child friendly approach.

Web Table II Indian National Health Initiatives Directed Towards Early Childhood Development

Program/ Timeframe	*Population*	*NC-ECD Domains*	*Description*
Umbrella Integrated Child Development Scheme (ICDS) [31]	Pregnant/ lactating women, 0-6 y old children	• Good health • Adequate nutrition • Safety and security	Integration of the following services Anganwadi Services Scheme Pradhan Mantri Matru Vandana Yojna National Creche Scheme POSHAN Abhiyaan Scheme for adolescent girls Child Protection Scheme
Rashtriya Baal Suraksha Karyakram (RBSK) [32]	0 – 18 y	• Good health • Adequate nutrition • Early Opportunities for learning	Early identification of 4 D's: Defects at birth, Disorders, Deficiencies, Developmental delays and Disabilities Management and Referral
Home Based Care of the Newborn and Young Child [33]	Birth to 1 y of life Post-partum Mothers	• Good health • Adequate nutrition • Responsive feeding	Home visits by the ASHA according to a specified schedule till 42 days of life, followed by quarterly visits till 1 year
Family Participatory Care (FPC) [34]	Sick and preterm babies admitted in Newborn care facilities	• Good Health • Responsive caregiving	Involving families as partners in caregiving and decision making in the care of vulnerable newborns during hospital stay.
Mothers Absolute Affection (MAA) Program [35]	Lactating mothers	• Adequate nutrition	Promotion, protection and support of exclusive breast feeding with the involvement of the family and community
Beti Bachao, Beti Padhao scheme [36]	Families with girls < 10 ys and a *Sukanya Samriddhi* bank account	• Safety and security	Focuses on areas with skewed sex ratio Campaigns against antenatal sex determination and termination of pregnancy Celebration of birth of girl child Schooling of girls
National Health Mission Journey of First 1000 days [37] 2018 onwards "Ayushman Bhava" [38]	Pregnancy Children 0 – 2 y	• Good Health • Adequate nutrition • Responsive caregiving • Early opportunities for learning	Illustrative, culturally contextual book for delivering simple, practical messages that helps families get sensitized to preconception care, conception, practices during pregnancy that support foetal growth (reducing stress, proper nutrition with local foods, interaction with the foetus), delivery (do and don'ts) and child rearing practices An android mobile App designed to display the above educational information

ANM Auxillary Nurse Midwife; CBO Community based organization; CCD Care for Child Development; CHW Community health worker; GIS Geographical information system; GMCD Guide for Monitoring development; GOI Government of India, NC-ECD Nurturing Care for Early Childhood Development; y year

SPECIAL ARTICLE

COVID-19 Eradication for Vaccine Equity in Low Income Countries

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The coronavirus disease 2019 (COVID-19) pandemic will transition into endemic phase with perpetual risk of severe disease and high mortality in vulnerable people – the elderly and those with co-morbidities, unless eradicated. Although several vaccines are already available to rich countries, low-income countries face gross vaccine inequity. We propose COVID-19 eradication to address both problems. An eradication program will ensure vaccine equity and international cooperation to establish public health surveillance and high quality laboratory diagnostic services in all countries. Eradication is biologically and technically feasible. We hope the World Health Organization will accept the proposition and design the necessary strategy without delay.

Keywords: *Herd effect, Herd immunity, SARS-CoV-2.*

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Severe Acute Respiratory Syndrome (SARS) caused by SARS Coronavirus type 1 (SARS-CoV-1) began spreading within China in November, 2002, became pandemic in March 2003, and affected 29 countries, with 8096 cases and 774 deaths [1]. By July, 2003, SARS was eradicated under the leadership of the World Health Organization (WHO), using non-pharmacological interventions to curtail virus transmission [1,2].

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 began spreading in China in late 2019, and became pandemic affecting all countries of the world in 2020. By mid-May, 2021, the reported number of global cases exceeded 160 million, with over 3 million deaths [3]. Unfortunately many countries resorted to political rather than public health approaches to contain in-country epidemics; international cooperation was conspicuously absent and WHO leadership did not become effective for a global coordinated effort, in contrast to the global response to SARS.

COVID-19 eradication will be a daunting task for global public health agencies and experts. It will entail high vaccination coverage of a broad age range, in all geographic communities, thus achieving vaccine equity, the major spinoff benefit of an eradication program. The pandemic and responsive interventions have affected existing disease control programs. However, eradication efforts must be carefully designed and implemented so as not to disturb any existing disease intervention.

WHY AN ERADICATION GOAL NOW?

Vaccines against COVID-19 were developed by many companies in several countries, including India, and some became available for Phase III trial or emergency use authorization in 2020 itself. Presently, quite a few vaccines are in use in many countries. While this speed was phenomenal, vaccine inequity is embarrassingly stark. The WHO-led COVAX project was for vaccine equity but its success was less than expected [4,5]. Many high income countries have secured vaccine doses to cover 200% of their population while most low income countries have no access to any COVID-19 vaccine [5].

To make sufficient amounts of vaccines available to low income countries, there has to be a realistic program that binds all nations together. We propose that an eradication goal set by the World Health Assembly (WHA) and managed through the six WHO Regional Offices network will have the double benefit of vaccine equity and also, through it, the targeting of COVID-19 eradication. It will also provide a much needed platform for inter-government cooperation, accountability, and exchange of surveillance information for united action. Unless eradicated, COVID-19 will become pan-endemic with occasional surges [6]. The risk to life among the elderly and those with cancers, chemotherapy, immunosuppression for transplants, and the well-known co-morbidities, will remain and perpetual control measures will be required.

IS ERADICATION BIOLOGICALLY FEASIBLE?

Eradication is the extreme form of disease control, defined as zero incidence of disease globally [7]. To sustain eradication status, transmission of the agent has to be interrupted in all countries [7]. Since a majority of SARS-CoV-2 infections are subclinical, similar to polio, eradication trajectory has to be monitored through protocol-based detection of transmission chains. The goal of eradication is feasible since vaccines for primary prevention and diagnostic tools for confirming infection for clinical diagnosis, and for detecting silent transmission, are available. As control seems to be possible, eradication also is assumed to be possible by enhancing all interventions in all countries.

Smallpox eradication was successful as there was no extra-human reservoir and as the two essential biomedical intervention tools, namely vaccine for primary prevention and diagnostic tests for surveillance were available [7]. These criteria are fulfilled for COVID-19 as of now, although they may change in the future as we will describe herein. Eradication must be achieved before extra-human reservoir develops or vaccines lose protective efficacy due to emergence of vaccine-escape mutants.

The problems of mutant variants with potential for higher transmission efficiency and lower immunity protection will occur even without setting an eradication goal. But under eradication mode, these will be detected fast in all countries and addressed in real-time. New generation vaccines and/or modified diagnostic tests may become essential but the eradication program will be ready for such challenges.

If man-on-moon mission was asked if it would be successful, proof could emerge only after the experiment. Similarly, COVID-19 eradication mission has to prove itself by its success.

WILL VACCINATION LEAD TO INTERRUPTION OF TRANSMISSION?

All currently available vaccines protect against disease, but not against infection. As vaccination coverage increases and vaccine-induced herd immunity level rises, herd protective effect (i.e. probability of reduced human-to-human transmission) can be expected in the unvaccinated segment of population [8-10]. Immune individuals tend to have only sub-clinical infections or with mild to moderate symptoms of COVID-19. They tend to shed less viruses as their virus loads are low, and they shed viruses for shorter durations, than non-immune infected, leading to herd protective effect [8,9]. Recent experience in Israel illustrates rapid decline in COVID-19 cases following high vaccine coverage, confirming herd effect [11]. We may legitimately anticipate interruption of transmission by high herd immunity and consequent herd effect.

CAN WE MONITOR THE DECLINE AND DISAPPEARANCE OF INFECTION?

Clinical, virological and genomic surveillances are crucial to monitoring control trajectory, reach national and regional elimination goals, and finally reach and certify global eradication. Already laboratory diagnostic methods have proved themselves to be of eradication standard and are available in all rich nations. Its global expansion is eminently possible.

Public health surveillance, generally neglected in developing countries except for polio eradication, can be built for COVID-19 eradication on the existing polio platform, using 'influenza-like illness' in all ages as the clinical counterpart of 'acute flaccid paralysis' in under-15 children. To monitor silent community transmission of SARS-CoV-2, existing sewage surveillance to monitor circulating vaccine-derived polioviruses can be adapted and expanded, after the transmission status transits from the pandemic phase.

Genomic surveillance will be needed to detect mutant variants that have potential to escape immunity from natural infection or vaccination, and possibly also from diagnostic tests. Countries should sequence at least 5% of all viruses to detect such emerging variants [12]. Circulation of mutant variants like Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and recently detected variants Delta (B.1.617.2) and Kappa (B.1.617.1) attest to the need of a standardized protocol and rapid dissemination of information.

Such a global program needs to be designed, covering all low- and middle-income countries.

WHY SHOULD ERADICATION AGENDA BE PROPOSED NOW?

We believe that the basic biological criterion of eradicability, namely absence of extra-human reservoir, may not remain valid for long [13]. SARS-CoV-2 started as a zoonosis (vertebrate-to-human transmitted) but the source remains unknown. Now the pandemic is exclusively human-to-human transmitted anthroponosis. However, several species of *Canidae*, *Felidae*, *Mustelidae* and *Cervidae* have been infected by humans by reverse zoonosis. Some species of *Mustelidae* and *Cervidae* had to be drastically culled when horizontal enzootic transmission was detected. Such animals have the potential of becoming new extra-human reservoirs [14]. Eradication must succeed to pre-empt such eventuality.

The world is at about the peak of herd immunity due to the pandemic itself. If an eradication agenda is initiated now, the vaccination coverage needed to top it up to eradication level herd immunity threshold will be relatively easy. Such an opportunity will not stay valid much longer. Eradication effort must begin before herd immunity level is diluted by new birth cohorts without immunity and by the waning of immunity in the infected.

Since control and eradication are hierarchical goals, the best time to set the eradication goal is when the control goal is in place. The world in general and every country in particular, wants the epidemic controlled. However, low income countries are handicapped with lack of proper public education for behavioral modification and without access to vaccines and to technology of quality diagnosis. The fastest way to building COVID-appropriate behaviors and equity of vaccines and diagnostics, is to set an eradication goal now and work progressively towards bringing all countries under control mode and then graduate to eradication mode.

Setting goal and preparing plans of action are intellectual ideas translated to documents. This exercise will not interfere with ongoing pandemic response activities. Vaccine requirements by timeline and surveillance methodologies for eradication need to be articulated. When the eradication program is implemented, we may expect several hurdles, but we are confident that every problem can be resolved. As public awareness and anxiety are high, raising sufficient funds will hopefully be possible. If we do not attempt eradication, we will be failing to rise to the occasion.

CONCLUSION

We have argued that COVID-19 eradication may be an expedient way to achieve vaccine equity in all low income countries. Under an eradication program low income countries will have to be supplied with vaccines under the program budget – a major step towards building vaccine equity. COVID-19 can be eradicated if a program is designed for both universal vaccine delivery and for monitoring the eradication trajectory.

COVID-19 should be eradicated for the welfare and well-being of humanity – allowing endemic COVID-19 will put the elderly and vulnerable (due to co-morbidities) at perpetual fear of risk to life. An eradication program will ensure cooperation between nations and also give WHO the opportunity to play its legitimate leadership role.

As for India, we have the opportunity to take this agenda forward through the WHO and World Health Assembly, as the WHO Executive Committee Chairman is our own Health Minister and the WHO Chief Scientist is the past Director-General of the Indian Council of Medical Research.

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SYSTEMATIC REVIEW

Gastric Lavage for Prevention of Feeding Intolerance in Neonates Delivered Through Meconium-Stained Amniotic Fluid: *A Systematic Review and Meta-Analysis*

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Background: The role of gastric lavage in neonates delivered through meconium-stained amniotic fluid remains unclear.

Objective: This study evaluated the effects of gastric lavage, compared to no gastric lavage, on the incidences of feeding intolerance, respiratory distress, meconium aspiration syndrome, time to establish breastfeeding, hospitalization and procedure-related complications in late-preterm and term neonates delivered through meconium-stained amniotic fluid.

Design: Systematic review and meta-analysis.

Data sources and selection criteria: MEDLINE, EMBASE, CENTRAL, and other databases were searched for randomized controlled trials and quasi-randomized controlled trials using search terms: neonate OR newborn infant, meconium OR meconium-stained amniotic fluid, and lavage OR gastric lavage from inception to May 2020. Data were pooled in RevMan and analyzed in GRADE.

Results: Pooled effects (9 randomized controlled trials, number=3668), showed a significant reduction in the incidence of feeding intolerance (relative risk 0.70; 95% confidence interval 0.58,0.85, I^2=0) after gastric lavage. No difference was observed for the incidence of meconium aspiration syndrome (4 studies) or procedure-related complications (7 studies). Only one study, reporting the proportion of neonates with low oxygenation (SpO2<85%), did not find any significant difference. No study evaluated the effects of gastric lavage on respiratory distress, breastfeeding, and hospitalization.

Conclusions: Low-quality evidence supported the role of gastric lavage for the prevention of feeding intolerance in late-preterm and term neonates born through meconium-stained amniotic fluid. Applicability of results was limited by the high risk of bias. Well-conducted randomized controlled trials with impor-tant patient outcomes are needed before recommending the practice of gastric lavage.

Keywords: *Feeding intolerance, Gastric lavage, Meconium-stained amniotic fluid, Neonate*

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Meconium-stained amniotic fluid, complicating 9-12% of all deliveries [1,2], may be associated with recurrent vomiting and feeding intolerance, due to meconium-induced chemical gastritis [3], which may delay the establishment of oral feeding resulting in a risk of hypoglycemia, need for parenteral fluid therapy [4] and a possibility of secondary meconium aspiration [5]. Though a quasi-randomized study showed the benefit of gastric lavage performed in the delivery room in reducing feeding intolerance [6], later randomized controlled trials (RCTs) failed to document benefit [5,7-14]. Though oro/nasogastric feeding tube placement and gastric lavage are apparently simple procedures, complications such as feeding tube placement errors, oxygen desaturation, bradycardia, gastric, and esophageal perforation, are often reported [15-19]. A previous meta-analysis in 2015 [4] included 6 studies and found limited evidence to favor gastric lavage to reduce the incidence of feeding intolerance in infants delivered through meconium-stained amniotic fluid. This systematic review and meta-analysis intended to identify, appraise, and synthesize available evidence regarding the efficacy and safety of gastric lavage after initial delivery room stabilization, to prevent feeding intolerance, among neonates delivered through meconium-stained liquor.

METHODS

The protocol for this systematic review was registered in the International Prospective Register of systematic Reviews (PROSPERO) database. This systematic review was conduc-ted and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

Search eligibility and search strategy: The review included RCTs and quasi-RCTs comparing the effect of prophylactic gastric lavage with normal saline versus no

lavage after initial stabilization at delivery room, before initiation of feeding, in late-preterm and term neonates delivered through meconium-stained amniotic fluid on the prevention of feeding intolerance. Feeding intolerance was defined as gastric residue ≥30% of the previous feed, and/or regurgitation, abdominal distension, emesis/retching [21]. The primary outcome was the incidence of feeding intolerance, secondary outcomes being incidences of respiratory distress and meconium aspiration syndrome, need and duration of respiratory support, time to establish breastfeeding, exclusive breastfeeding rate at discharge, duration of hospital stay, and the adverse effects of gastric lavage Crossover trials, non-English publications, and conference abstracts were excluded.

All authors independently searched the databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, Scopus, and Web of Science, from inception to May, 2020. Details of search words and search results are given in **Web Table I**. The references of full text articles were checked for possible inclusion as additional articles.

Data extraction and quality assessment: After removing duplicates, individual study details were extracted in a pre-designed format by two authors (PS, MS) independently, including author, year of publication, geographic location, study period, research design, sample size (calculated and analysed total and in each group), inclusion and exclusion criteria, procedure details, characteristics of participants, including mean gestation, birth weight, gender, thick/thin meconium, definitions and incidences of outcomes. Any disagree-ment related to collated data was resolved by the third author (SB).

Quality of studies was assessed independently by all authors using Cochrane Collaborations Risk of Bias tool [22] based on the domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; other bias. Any disagreement was resolved by mutual discussion.

Statistical analysis: Statistical analysis was performed using Review Manager Version 5.3 [23]. Relative risk (RR) with 95% confidence interval (CI) was calculated for all primary and secondary outcomes. Risk difference (RD) and number needed to benefit/harm were also calcu-lated. Heterogeneity was assessed using I^2 statistics. A fixed or random-effects model was used based on heterogeneity. Random-effects model was used where heterogeneity was more than 50%. Sub-group analysis was done in possible areas of heterogeneity such as consistency of meconium, vigorous/non-vigorous, need of positive pressure ventilation (PPV), and the postnatal age of performing gastric lavage. Grading of Recommen-dations Assessment, Development, and Evaluation (GRADE) approach [24] was applied to assess the quality of evidence for the predefined outcomes.

RESULTS

Out of the initial database search of 374 articles and 3 additional articles through manual search, 12 articles were retrieved, after screening titles, abstracts and removing duplicates. Of these, 9 studies, including 3668 neonates [5-13], met our inclusion criteria and were subjected to meta-analysis (**Fig.1**). The characteristics of the studies included in this review are summarized in **Web Table I**. Seven trials were conducted in India [5,7-10,12,13], and two were conducted in Saudi Arabia [6] and Nepal [11]. Two studies were quasi-randomized [6,10], while the rest were RCTs. The study population was homogenous across the studies. All studies included vigorous late-preterm and term neonates born through MSAF, who did not develop respiratory distress at birth.

The definition of feeding intolerance varied across the studies. While five studies [5,7,10-12] defined feeding intolerance as vomiting, abdominal distension, and increased gastric residuals, two studies [6,9] considered vomiting and retching and one study took vomiting and abdominal distension as a signs of feeding intolerance [13]. Singh, et al. did not mention the criteria of feeding intolerance in their trial [8]. Very slow feeding/poor suck was considered a component of feeding intolerance in the study of Narchi, et al. [6]. Period of observation for feeding intolerance ranged from 48-72 hours [5,7-12] or till discharge [7,9] whereas it was not specified by Narchi, et al. [6] and Yadav, et al. [13].

The procedure of gastric lavage varied across the studies, using feeding tubes of variable sizes, 6 Fr [10-12], 8 Fr [7,9,10,13] or 10 Fr [5] through oral [5,9] or nasal route [7,10-13] and lavage being conducted using 10 mL/kg [5,7,10-13] or 20 mL [9] of normal saline [5,7,9-13] in the aliquots of 5 mL [10] or 10 mL [7,11,12]. Feeding intolerance was the primary outcome in seven studies [6,7,9-13], while proportion of infants developing meconium aspiration syndrome within 72 hours of age [5] and the need for subsequent gastric lavage [8], respectively, were the primary outcomes in the other two studies. Only one study monitored the procedure of gastric lavage using a pulse oximeter [5]. **Web Fig. 1A** and **Web Fig. 1B** summarize the quality of the studies**.** There was no publication bias as per the Funnel plot (**Web Fig.2**).

Gastric lavage resulted in a significant reduction of feeding intolerance (pooled RR 0.70; 95% CI 0.58 to

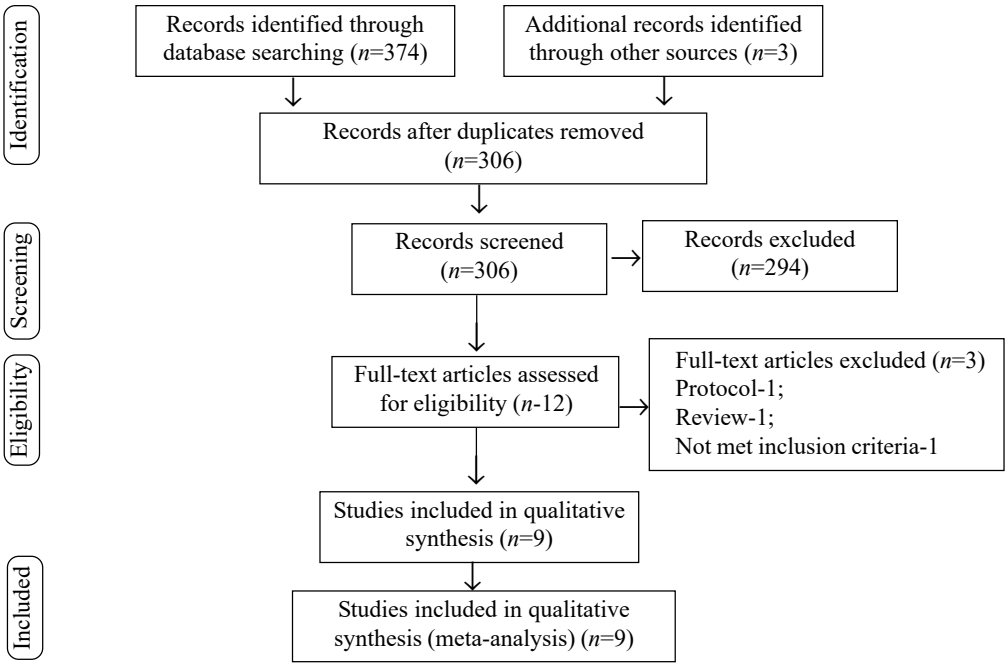

Fig. 1 PRISMA flow diagram.

0.85, I^2 0%), with a risk difference of -3.39% (95% CI -5.34 to -1.44), and number needed to benefit being 29.5 (95% CI 18.69 to 69.83) (**Fig. 2**). Subgroup analysis of two trials [6,7] in neonates delivered through thick meconium-stained amniotic fluid did not find any significant difference, though pooling of data could not be done due to incomplete reporting. Sensitivity analysis performed after the inclusion of only RCTs [5,7-9,11-13] and those with a uniform definition of feeding intolerance [5,7,10-12] also showed significant beneficial effects of gastric lavage (**Web Table II**).

While none of the neonates in any group developed meconium aspiration syndrome in three studies [8,9,13], one study [5] reported insignificant difference in the incidence of meconium aspiration syndrome between gastric lavage and no-gastric lavage group. No difference was observed across the studies in the incidences of bradycardia [5,7,9-13], desaturation/cyanosis [5,7,11,12] or local trauma [5-7,9-13], between neonates with and without gastric lavage. One study [5] reported no significant difference in the proportion of neonates with low oxygenation (SpO_2<85% at 15 minutes of life)

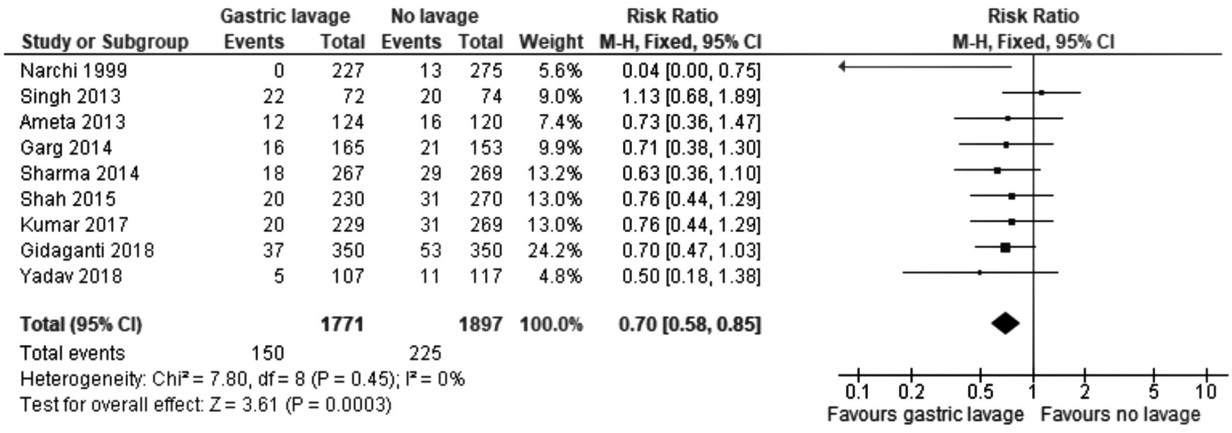

Fig. 2 Forest plot analyzing the incidence of feeding intolerance in neonates with and without gastric lavage.

between the groups. None of the studies reported complications like secondary vomiting, aspiration, respiratory distress [6,7,9,10] or apnea [5-7, 9-13].

The time of establishment of breastfeeding, exclusive breastfeeding rate at discharge, need and duration of respiratory support, as well as complications like feeding tube placement errors and gastric/esophageal perforation were not reported by any of the studies.

The quality of evidence assessed using the GRADE (**Web Table III**), shows that except for the incidence of feeding intolerance, the effect size of other outcomes was non-estimable due to the small number of occurrences.

DISCUSSION

In the present systematic review, low-quality evidence from nine RCTs showed that gastric lavage performed immediately after delivery room stabilization before initiation of feeding resulted in a significant reduction in the incidence of feeding intolerance in vigorous late preterm and term neonates born through meconium-stained amniotic fluid. None of the studies reported any adverse events related to gastric lavage and none of the studies looked for feeding tube placement errors and gastric/esophageal perforation.

The studies included in this review had high rates of bias, mainly attributable to lack of allocation concealment, quasi-randomized design [6,10] and absence of blinding of the outcome assessors [5-13]. Seven studies evaluated the adverse effects of gastric lavage in the form of apnea, bradycardia, local trauma or cyanosis and no difference was found between the groups [5,7,9-13]. Narchi, et al. [6] assessed for apnea and local trauma, which was not documented in any study neonate. Though all the studies reported gastric lavage to be a safe procedure, desaturations were not evaluated with pulse oximeters, except in one study [5]. The route of feeding tube placement being non-uniform across studies, it could affect the incidence of adverse effects [25]. Gastric aspiration with feeding tube placement has been shown to increase the mean arterial blood pressure, retching, disruption of pre-feeding behavior [26], with the development of functional gastrointestinal disorders later in life [27].

None of the studies have mentioned the time of occurrence of vomiting/retching in relation to the procedure or the initiations of feeds. The definition of feeding intolerance was not uniform across the studies. Slow/poor sucking, taken as feeding intolerance, by a study is more suggestive of neurological problems or immaturity. None of the studies have evaluated the effect of the intervention on clinically more relevant outcomes such as time to establish breastfeeding, exclusive breastfeeding rate at discharge, or initiation of immediate skin-to-skin contact in the delivery room.

Gastric lavage can potentially affect the incidence of meconium aspiration syndrome. While on one hand, gastric lavage may prevent meconium aspiration syndrome by clearing meconium from the stomach, thereby preventing subsequent vomiting and aspiration [3]; on the other hand, it may predispose to meconium aspiration syndrome by inducing retching, vomiting and aspiration of gastric content while inserting the feeding tube [28]. The incidence of meconium aspiration syndrome, reported by four studies, was low [5,8,9,13], which could be attributed to the inclusion of only vigorous neonates with neonates at risk for meconium aspiration syndrome, like those with low Apgar scores, respiratory depression requiring resuscitation were excluded.

The limitation of the review was that data for outcomes like meconium aspiration syndrome and adverse events could not be pooled as the reported incidences were nil in most of the studies. Proposed subgroup analyses could not be done due to the lack of data in the included trials. Non-vigorous neonates requiring delivery room resuscitation were excluded by all.

To conclude, low-quality evidence supported the role of gastric lavage for the prevention of feeding intolerance in vigorous late preterm and term neonates born through meconium-stained amniotic fluid. Though the procedure seems to be apparently safe, one should be cautious to recommend this practice as the adverse events related to gastric lavage were not evaluated critically and the effects of this procedure on the routine newborn care practices such as skin-to-skin contact, and breastfeeding rates were lacking. Evidence in non-vigorous neonates, who are more prone for the development of respiratory distress and feeding intolerance, were lacking. Well-designed RCTs with defined outcome variables under strict monitoring for procedure-related complications are needed.

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

Contributors: PS: conceptualized the review, literature search, data analysis and manuscript writing; MK: literature search, data analysis and manuscript writing; SB: conceptualized the review, literature search, data analysis and manuscript writing.

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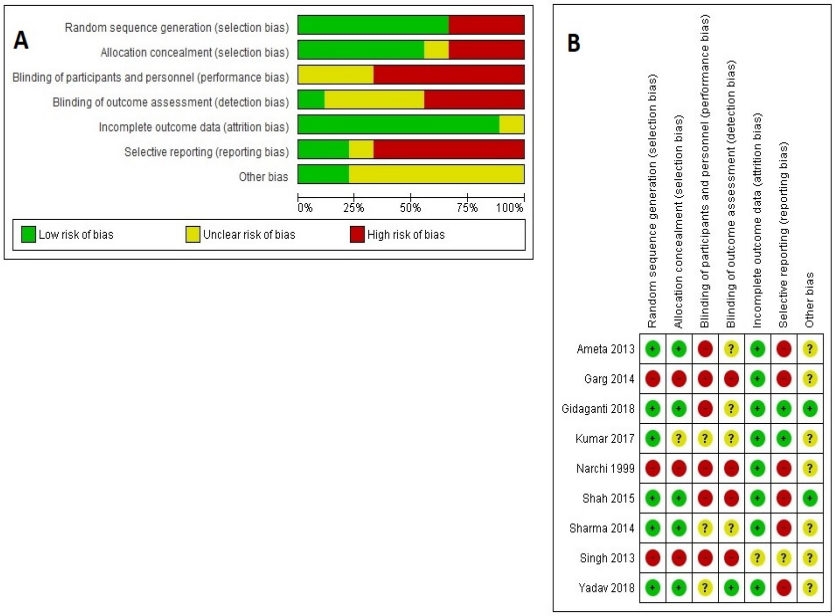
Web Table I Details of Database and Search Results

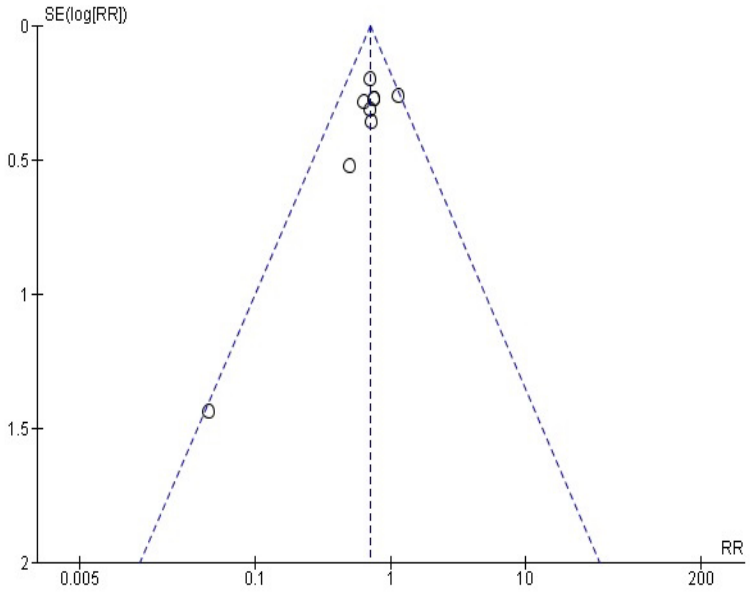
Database	*Date*	*Search Strategy*	*Number of articles obtained*
PubMed	28.05.2020	((“meconium stained liquor” [Title/Abstract] OR “Meconium stained amniotic fluid” [Title/Abstract]) OR “meconium” [MeSH Terms]) AND ((“gastric lavage” [MeSH Terms] OR “gastric lavage” [Title/Abstract]) OR “lavage”[Title/Abstract])	57
Embase	28.05.2020	(‘meconium’/exp OR ‘meconium’ OR ‘meconium stained amniotic fluid’ OR ‘meconium stained liqour’) AND (‘stomach lavage’ OR ‘lavage’)	300
Cochrane central register of controlled trials (CENTRAL)	28.05.2020	“meconium” OR “meconium stained liquor” OR “meconium stained amniotic fluid” AND “gastric lavage” in Title Abstract Keyword	17
Cumulative index to nursing and allied health literature (CINAHL)	28.05.2020	“meconium” OR “meconium stained liquor” OR “meconium stained amniotic fluid” AND “gastric lavage” in Title Abstract Keyword	0
Google Scholar	28.05.2020	“meconium” OR “meconium stained liquor” OR “meconium stained amniotic fluid” AND “gastric lavage” in Title Abstract Keyword	0
Scopus	28.05.2020	“meconium” OR “meconium stained liquor” OR “meconium stained amniotic fluid” AND “gastric lavage” in Title Abstract Keyword	0
Web of Science	28.05.2020	“meconium” OR “meconium stained liquor” OR “meconium stained amniotic fluid” AND “gastric lavage” in Title Abstract Keyword	0

Web Table II Sensitivity Analysis

Analysis	*Studies included in sensitivity analysis*	*Reason for inclusion*	*Number (n)*	*Risk Ratio (95% confidence interval)*	I^2
1.	Ameta 2013 [7] Singh 2013 [8] Sharma 2014 [9] Shah 2015 [11] Kumar 2017 [12] Gidaganti 2018 [5] Yadav 2018 [13]	Randomized controlled trial design	2848	0.74 (0.60, 0.91)	0%
2.	Ameta 2013 [7] Garg 2014 [10] Shah 2015 [11] Kumar 2017 [12] Gidaganti 2018 [5]	Uniform definition of feeding intolerance	2260	0.73 (0.57, 0.92)	0%



Web Fig. 1 A. *Risk of bias graph summarizing each risk of bias item as a percentage across all studies*; **B**: *Risk of bias graph summarizing risk of bias items for each included study*.



Web Fig. 2 *Funnel plot for publication bias.*

Randomized Controlled Trial Evaluating Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries

***Source Citation*:** Thayyil S, Pant S, Montaldo P, et al. Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh. Lancet Glob Health. 2021;9:e1273-285.

SUMMARY

In this open-label, randomized controlled trial in seven tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh, infants born at or after 36 weeks of gestation with moderate or severe neonatal encephalo-pathy and a need for continued 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), were recruited. In a web-based randomization system, infants were allocated into a group receiving whole body hypothermia (33·5°C) for 72 h using a servo-controlled cooling device, or to usual care (control group), within 6 h of birth. All recruiting sites had facilities for invasive ventilation, cardiovascular support, and access to 3 Tesla MRI scanners and spectroscopy. 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. Analysis was by intention to treat. After exclusions, 202 eligible infants were assigned to the hypothermia group and 206 to the control group. Primary outcome data were available for 195 (97%) of the 202 infants in the hypothermia group and 199 (97%) of the 206 control group infants. 98 (50%) infants in the hypothermia group and 94 (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). 84 infants (42%) in the hypothermia group and 63 (31%; *P*=0·022) infants in the control group died, of whom 72 (36%) and 49 (24%; *P*=0·0087) died during neonatal hospitalisation. Five serious adverse events were reported: three in the hypothermia group (one hospital readmission relating to pneumonia, one septic arthritis, and one suspected venous thrombosis), and two in the control group (one related to desaturations during MRI and other because of endotracheal tube displacement during transport for MRI). 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, but significantly increased death alone. The authors conclude that 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.

COMMENTARIES

Evidence-based Medicine Viewpoint

Introduction: Therapeutic hypothermia (TH) is widely practiced in new-born infants with hypoxemic ischemic encephalopathy (HIE). It has been included as a standard of care in many guidelines published in developed as well as developing countries. Its use has become so widespread that the International Liaison Committee on Resuscitation (ILCOR) statement in 2020 cautioned that TH should only be used in neonatal care units with facilities for multidisciplinary care, respiratory support, oxygenation monitoring, etc. [1]. TH appears to be supported by robust evidence. A network meta-analysis of randomized controlled trials (RCT) examining multiple interventions for HIE [2], identified whole-body cooling as the top-ranking intervention that reduced mortality at 18 months of age, closely followed by selective head cooling. Both interventions were also associated with better neuro-developmental outcomes at that age. Even cerebral palsy in later life was found to be decreased with TH [3].

Despite the overall benefit reported with TH, it is not always successful, particularly in severe HIE. Perhaps this is why there is intense search for alternate interventions for neuroprotection and/or improvement of neuro-developmental outcomes following neonatal encephalopathy. Several interventions have been explored with and without TH, including erythropoietin [4,5], melatonin [6,7], and xenon [8]. There are also several pre-clinical studies as well as registered human RCTs exploring stem cell therapy [9,10]. These diverse data suggest that there is room for further evidence despite the reported benefits of TH. Recently, a multi-centric RCT in three developing countries, evaluated TH in moderate-to-severe HIE [11]. **Table I** summarizes the trial details.

Critical appraisal: Overall, the trial [11] had low risk of bias. The random sequence was generated using an online program that controlled for the stage of encephalopathy as well as study site. Random permuted blocks of variable sizes were used, although the range of block sizes was not specified. Allocation was concealed from the on-site investigators, who had to enter participant details after informed consent was obtained, to identify the arm to which the neonate was allocated. Adherence to the assigned arm, was cross-verified by a team based in London. Although the treating physicians/teams were not blinded, the assessors recording the primary outcome, long-term outcomes, and the MRI data were blinded to the allocation of each neonate. A wide range of clinically important outcomes were recorded, without omitting any from reporting. There was very low attrition in this trial, as 97% of the enrolled infants could be followed-up. This RCT [11] was not only registered, but its protocol was also published [12], and there are no significant deviations from either. Even after randomization, there were hardly any protocol deviations.

The trial [11] included several refinements in addition to meticulous planning, execution and analysis. This enabled the investigators to overcome many biases that crept into previous similar trials. For example, neonates who underwent passive cooling prior to randomization were not included. Variability in assessments that could creep into clinical examinations, neuro-developmental evaluation, etc. were diminished, because these were performed by well-experienced physicians, and stringent definitions were used for every subjective evaluation. Even the MRI scanning procedure, protocols, and acquisition time, were standardized across the sites. Raw data from MR scanning were centrally evaluated for quality before processing. Two experienced neonatal neurologists used a prior-validated scoring system to read the images, while blinded to all clinical information.

In addition to the clinical outcomes, the investigators included a large number of MRI-related parameters. The choice of these is supported by a systematic review [13] which confirmed that ratios of NAA/creatine and NAA/choline in the basal ganglia/thalamus, as well as myo-inositol/choline in the cerebral cortex on Proton magnetic resonance spectroscopy, correlated well with adverse effects in neonates undergoing TH. Similarly, MRI findings of injury to the internal capsule posterior limb (on diffusion weighted imaging), and increased lactate/N-acetylaspartate peak on MR spectroscopy, had high predictive value for adverse neurodevelopmental outcomes [14]. All these were analyzed in this trial [11].

The extremely low attrition in this RCT [11] was achieved by research nurses maintaining contact with the families of enrolled infants between discharge and follow-up. Special search teams were constituted to track families who failed to follow-up as scheduled. These teams were able to make home visits not only to local families, but even to those who had migrated.

Very few limitations could be identified in this trial [11], none of them serious. For example, although the analysis was described as intention-to-treat, the calculations were based on the number whose primary outcome was available, rather than the number randomized. As in many multi-centric trials, only aggregated data across study sites was presented, making it difficult for readers to judge whether data are driven by experiences in a limited number of sites with larger proportion of enrolments. This is important because in this trial [11], two sites accounted for 55% of the enrolled neonates, whereas 3 sites, each enrolled less than 10% of the sample size. One site enrolled only 12 neonates.

Since many of the enrolled neonates had clinical seizures, it can be argued that EEG data would be important. A systematic review showed that abnormal amplitude integrated electroencephalogram (aEEG) at 72 hours had high reliability to predict death or moderate/severe disability [15]. Another systematic review of 37 publications also confirmed that aEEG at 24 and 72h, had high predictive value for adverse neurodevelopmental outcomes [14]. However, this RCT [11] did not perform EEG.

The robust methodology and multiple refinements in this trial [11] generate high level of confidence in the results. There was no difference between the RCT arms for the primary outcome. Among the long-term outcomes, all-cause mortality at 18 months was increased with no benefit in the other two outcomes. Among the 17 short-term outcomes, 7 were worse in TH group, with no benefit in the other 10. Among 13 additional clinical outcomes, only one viz. disabling cerebral palsy showed a statistically significant reduction with TH, whereas there was no difference in the other 12. The multiple MRI findings were all comparable between the groups. In addition to the outcomes presented above, the supplementary files [11], have a plethora of additional data including hematological parameters, biochemical values, and clinical support requirements, recorded at 24h, 48h, 72h, and 96h. A wealth of MRI data (too extensive to present here) is also included. Overall, none of these showed any benefit of TH.

The authors also undertook multiple subgroup analyses of one secondary outcome "mortality at discharge." Three comparisons stood out. First, the increased mortality at discharge was driven by outborn neonates. Surprisingly, there was increased mortality in

Table I: Critical Appraisal of the Study

Clinical question	The research question in the PICOT format is: "In full-term newborns having moderate or severe encephalopathy (*P=Population*), what is the effect of therapeutic hypothermia (*I=Intervention*), compared to no hypothermia (*C=Comparison*), on mortality or disability (*O=Outcome*) at 18-22 months of age (*T=timeframe*)?
Study design	Randomized controlled trial with allocation of individual neonates to the trial arms.
Study setting	Tertiary level neonatal care units based in three developing countries viz. India, Sri Lanka, and Bangladesh. All the participating neonatal units fulfilled the ILCOR criteria for safe administration of TH. In addition, all had adequately trained manpower to look after sick neonates.
Study duration	Recruitment of neonates was done from August 2015 to February 2019. Follow-up was conducted till 18-22 months of age.
Inclusion criteria	Newborns (gestation ≥36wk, birth weight ≥1800g), with neonatal encephalopathy defined by the presence of two criteria viz. *i*) Evidence of perinatal asphyxia (defined as need for ongoing resuscitation at 5min of life, or a 5-minute Apgar score <6, or absence of crying by 5min of age for home-delivered neonates; and *ii*) Evidence of moderate or severe encephalopathy between 1-6h of life (determined by clinical examination and modified Sarnat staging).
Exclusion criteria	Neonates without heartbeat at 10min of life inspite of appropriate resuscitation, and those having major life-threatening congenital malformation, were not included. Neonates whose parents declared inability to attend scheduled follow-up assessment visits, were also excluded.
Recruitment procedure	Not described in detail.
Intervention and Comparison groups	Neonates in the TH arm underwent controlled reduction of core (rectal) temperature to 33·5°C, starting within 1-6h of birth, for a total of 72 h. Thereafter, automated re-warming at the rate of 0·5°C every hour was initiated, until normothermia was achieved. Neonates experiencing shivering or unexplained tachycardia were sedated. TH was ceased if there was refractory hypotension, or a life-threatening/massive haemorrhage.Those in the Comparison arm did not receive hypothermia. Both groups received the usual care as per the clinical condition, including respiratory support, cardio-vascular support, avoidance of iatrogenic hyperthermia, careful clinical and lab monitoring, and correction of abnormalities detected.
Outcomes	The primary outcome in this RCT was death or (moderate/severe) disability. There were three long-term secondary outcomes viz. all-cause mortality at 18mo of age, severe disability among survivors, and microcephaly at 18-22mo of age. There were 17 short-term secondary outcomes evaluated before discharge viz. mortality, length of hospital stay, abnormal neurological examination at discharge, culture-proven early-onset neonatal sepsis, pneumonia, necrotizing enterocolitis, renal failure, cardiac arrhythmia, major intracranial hemorrhage, pulmonary hemorrhage, gastric bleeding, persistent hypotension, prolonged coagulation necessitating treatment, severe thrombocytopenia, persistent metabolic acidosis, and subcutaneous fat necrosis.Additional clinical outcomes included survival without disability, moderate disability, disabling cerebral palsy, Bayley-III cognitive, motor, and language composite scores, persistent seizures, gross motor function classification system level, visual deficit, and auditory deficit. Anthropometric measurements included microcephaly, wasting, and stunting. Infants underwent MRI at 7-14d of age, to identify markers of neuronal damage including brain injury scores on conventional MRI, thalamic N-acetyl aspartate (NAA) concentrations; lactate:NAA ratio, NAA:creatine ratio, and NAA:choline peak area ratio; and whole brain white matter fractional anisotropy.
Follow-up protocol	Enrolled neonates were followed-up at 18-22mo of age. Detailed neurological examination was done by a neuro-developmental pediatrician, who administered Bayley Scales in local languages. In infants who could not be examined either at the site, or at home, families were contacted over telephone, and information on mortality ascertained.
Sample size	The investigators assumed an effect size of 30% reduction in the primary outcome (from 50% to 35%) with TH. Calculating for 5% alpha error, 20% beta error, and 10% attrition, the required sample size was 408 infants. The trial achieved this sample size.
Data analysis	Intention-to-treat analysis was planned. Appropriate statistical methods and tests were used to examine the data.
Comparison of groups at baseline	Maternal age, gravidity, parity, and pregnancy complications were evenly distributed between the groups. Delivery characteristics including mode, place, and red-flag events were also comparable. There were no differences in the trial arms for various neonatal characteristics including gender, gestational age, birth weight, anthropometric parameters, features of birth asphyxia, stage of encephalopathy, seizures, and core temperature.
Summary of results (TH vs control arm)	Primary outcome: • Death or (moderate/severe) disability: RR1·06 (95% CI 0·87,1·30)

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Secondary outcomes:

- All-cause mortality at 18mo of age: RR 1·35 (95% CI 1·04,1·76)*
- Severe disability among survivors: RR 0·61 (95% CI 0·34,1·11)
- Microcephaly at 18-22mo of age: RR 1·09 (95% CI 0·74,1·62)
- Mortality before discharge: RR 1·50 (95% CI 1·10,2·04)*
- Length of hospital stay: Median difference 2.20 (95% CI 0.70, 3.80)*
- Abnormal neurological examination at discharge: RR 0·93 (95% CI 0·70,1·24)
- Culture-proven early-onset neonatal sepsis: RR 1·22 (95% CI 0·54,2·77)
- Pneumonia: RR 1·06 (95% CI 0·63,1·77)
- Necrotizing enterocolitis: RR 5·10 (95% CI 0·60,43·2)
- Renal failure: RR 1·40 (95% CI 0·76,2·59)
- Cardiac arrhythmia: 5/202 vs 0/206; RR not calculable
- Major intracranial hemorrhage: RR 0·51 (95% CI 0·09,2·75)
- Pulmonary hemorrhage: RR 1·53 (95% CI 0·99,2·37)
- Gastric bleeding: RR 1·86 (95% CI 1·28,2·69)*
- Persistent hypotension: RR 1·84 (95% CI 1·17,2·88)*
- Prolonged coagulation: RR 1·55 (95% CI 1·16,2·07)*
- Severe thrombocytopenia: RR 2.24 (95% CI 1.26, 4.00)*
- Persistent metabolic acidosis: RR 1·95 (95% CI 1·24,3·08)*
- Subcutaneous fat necrosis: 1/202 vs 0/206; RR not calculable
- Survival without disability: RR 1·23 (95% CI 0·89,1·68)
- Moderate disability: 0/111 vs 3/135; RR not calculable
- Disabling cerebral palsy: RR 0.53 (95% CI 0.28, 0.98)*
- Bayley-III score <70 and 70-84, compared against ≥85: RR 0·61 (95% CI 0·32,1·18) and 1·28 (95% CI 0·77,2·11), respectively
- Motor score: RR 0.52 (95% CI 0.27, 1.00) and 0·95 (95% CI 0·33,2·72), respectively
- Language score: RR 0·73 (95% CI 0·43,1·21) and 0·73 (95% CI 0·50,1·05), respectively
- Persistent seizures: RR 0·40 (95% CI 0·11,1·44)
- Gross motor function classification system level: Median difference 0
- Visual deficit (blindness): RR 0·61 (95% CI 0·21,1·72)
- Auditory deficit: RR 0·60 (95% CI 0·16,2·37)
- Microcephaly: RR 1.01 (95% CI 0.58, 1.76)
- Wasting: RR 1.04 (95% CI 0.75, 1.45)
- Stunting: RR 1.11 (95% CI 0.87, 1.41)

MRI findings:

- Basal ganglia or thalamic injury: RR 0.84 (95% CI 0.54, 1.30)
- White matter injury: RR 1.06 (95% CI 0.94, 1.20)
- Cortical injury: RR 0.80 (95% CI 0.54, 1.18)
- Subdural bleeds: RR 1.19 (95% CI 0.75, 1.87)
- Mean (SD) thalamic N-acetyl aspartate (NAA) concentration: 8·06 (1·8) vs 8·04 (1·6)
- Median (IQR) Lactate:NAA ratio: 0·14 (IQR 0·106,0·200) vs 0·14 (IQR 0·099,0·175)
- Mean (SD) NAA:creatine ratio: 1·51 (SD 0·29) vs 1·51 (SD 0·26)
- Mean (SD) NAA:choline peak area ratio: 0·83 (SD 0·18) vs 0·85 (SD 0·16)
- Whole brain white matter fractional anisotropy: No significant difference
- Mean (SD)fractional anisotropy values over posterior limbs of the internal capsule: 0·32 (0·05) vs 0·32 (0·06)

Serious adverse events: RR 1.53 (95% CI 0.26, 9.06)

**Statistically significant.*

the TH group, among infants without sepsis, and those having no perinatal sentinel events. It is unclear why the primary outcome was not similarly analyzed.

Given that this methodologically robust RCT [11] showed contrary results to several other studies, (thereby challenging the hitherto accepted practice of TH in HIE), several questions emerge.

First, how do the results of this trial [11] compare with other data? A Cochrane review published in 2013 (11 RCT, 1505 participants) demonstrated statistically and clinically important reduction in mortality or major neuro-developmental disability at 18 months of age [16]. However, this review is outdated and merits no further consideration. A very recent systematic review with literature search updated to April 2020 [17], identified 28 RCTs among nearly 3600 neonates with moderate to severe HIE. Meta-analysis showed that the pooled relative risk of mortality was (statistically and clinically) significantly reduced with TH. However, in addition to some methodological flaws, the authors did not specify the time-frame at which mortality was determined [17]. This makes it difficult to interpret the data from the review [17]. On the plus side, the authors did not identify significant publication bias (i.e. lower probability of publication of trials showing no beneficial effects of TH).

Since the publication of the systematic review [17], additional trials have emerged. A recent RCT conducted in Chennai [18] examining the same outcomes as this trial [11] in over 160 neonates, reported a statistically significant difference in mortality or abnormal neurological outcome, at 18mo, although there was no significant difference within 28d. Another RCT [19] in a single Indian institution among 50 neonates with moderate or severe HIE, examining MRI changes in the posterior limb of the internal capsule, reported a statistically significant beneficial effect with TH, although this could be analyzed in less than half the recruited infants. Conventional MRI findings also suggested that TH was beneficial. Yet another RCT among 120 neonates with HIE at JIPMER Puducherry, reported lower mortality with TH [20], and also less frequency and severity of acute renal injury. Markers of myocardial injury (cardiac enzyme levels at 72h) and ECG as well as echocardiography findings were more favorable in those receiving TH [21]. An RCT in 40 Chinese infants [22], also reported lower incidence of severe disability, better psychomotor development scores, and higher neuro-development scores at 15 months of age in those receiving TH. These infants also had better neonatal neuro-behavioural score at 28 days of age. However, there was no difference in mortality and no difference in the levels of neuronal biomarkers after 72 hours of treatment. Overall, none of these RCTs had the methodological rigour associated with this trial [11].

Despite the overall benefit reported in systematic reviews of TH [16,17], not all trials showed the same effect. Even trials showing benefit differed in its magnitude. A group of authors tried to analyze the reason for statistically significant differences in the efficacy of TH in two fairly large trials [23]. Despite similar inclusion criteria, there were differences in the sickness level of included neonates, severity of HIE, use of anti-convulsant medication, sedation, and many in one of the trials had received cooling before randomization itself.

To be fair, this is not the first robust piece of evidence that failed to find a beneficial effect of TH. A systematic review focusing on studies conducted only in low-and middle-income countries, identified 7 trials [24]. These trials included 567 infants, of whom 15% had only mild encephalopathy. Various formal and non-formal cooling systems were used. However, there was no statistically significant decrease in neonatal mortality with TH. The authors attributed this to heterogeneity, poor methodological quality, inappropriate cooling devices, or inadequate intensive care facilities. However, they also considered population-based differences (compared to high-income countries) such as perinatal infection, obstructed labor, intrauterine growth retardation, etc.

There are other indirect pieces of evidence suggesting limitations to the effects of TH. A community-based study in the UK followed up 145 survivor children, 6-7 years after being randomized to TH or otherwise, to determine their health-related quality of life (HRQL) [25]. However, no statistically significant differences were observed. A similar analysis on healthcare resource utilization and costs among 130 survivors aged 6-7 years (from the same cohort), showed lower resource utilization in the TH arm, though the differences were not statistically significant [26]. Another indirect evidence is that hypothermia for longer than 72 hours, cooling to temperature lower than 33.5°C, or both together, did not add further benefit in terms of mortality or severe disability at 18 months of age [27,28].

The second important question is, what could be the explanation for the results of this trial being remarkably different? One possible explanation is that previous trials often included neonates with mild HIE also, whereas this trial [11] included only those with moderate or severe HIE. In this context, a systematic review [29] identified 13 studies wherein almost one in six included neonates had mild HIE. On meta-analysis, about 22% of the infants who underwent TH had only mild HIE. Another systematic review also identified 117 babies with mild HIE who had been inadvertently included in 5 TH trials [30].

Another potential explanation is that, the mechanism (and consequences) of perinatal asphyxia in low-resource settings may be different from developed country settings. In this context, the trial authors [11] themselves suggested that the included babies underwent subacute, or partial prolonged hypoxia (based on MRI findings). Further, the occurrence of seizures in many infants in this trial [11] suggested intra-partum hypoxia before birth, which could reduce the neuro-protective effects of TH. There is also data that, among neonates with birth asphyxia, the presence of hyperoxemia at admission increases the risk of HIE [17]. This is referred to as the oxygen paradox, wherein excess oxygen supplementation following hypoxia worsens the outcome. In this trial [11], over 70% enrolled neonates were born at other institutions, wherein less-skilled physicians may have used excess oxygen to manage the hypoxia. One wonders whether this could be a contributing factor.

Conclusion: This very well-designed and well-executed landmark RCT confirmed that therapeutic hypothermia (for 72h) in full-term neonates having moderate or severe encephalopathy did not reduce the composite outcome of mortality or disability at the age of 18-22 mo. On the contrary, short-term, as well as long-term mortality were increased. Several other clinically important outcomes were also worse in those receiving TH, making it a harmful intervention. An urgent review of the clinical practice of offering TH is warranted at the institutional, as well as national levels.

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Neonatologist's Viewpoint

Therapeutic hypothermia (TH) is the only intervention well-proven to improve intact survival in neonates with moderate-severe hypoxic ischemic encephalopathy [1]. It is the standard of care in high income countries (HICs) and is recommended by the International Liaison Committee on Resuscitation (ILCOR) 2020 in low- and middle-income countries (LMICs), though it is a weak recommendation with low evidence [2]. A recent meta-analysis of 675 infants from 7 RCTs from LMICs showed a 50% reduction in mortality in LMICs and found higher effect size in LMICs as compared to HICs [3]. The results of the HELIX trial with 408 infants are in contradiction to this and the conclusion and the commentaries by the authors have cast a cloud on the practice of TH in LMICs [4].

The HELIX trial, an apparently well-conducted trial with excellent follow-up rates, did not find a difference in the primary outcome of disability-free survival at 18 months and has recommended to stop TH in LMICs [4]. However, there are several issues in the trial that need further clarification. The first is the case-mix. Unlike most other hypothermia trials from India, two-third of the infants were outborn who reached the cooling center at a median time of >3 hours. The screening for enrolment is unlikely to have been optimal considering that only 2296 infants were screened in 3.5 years in seven very high-volume public health facilities, where the annual NICU admission is often double this number. Further, the lack of an objective risk assessment score raises concerns that the babies in the study, particularly in the hypothermia arm, were sicker, indicating a selection bias. The complications in pregnancy and emergency cesarean section were higher in the hypothermia arm. This is especially a cause for perturbation in this study, where the authors state that "*professionals showed a strong bias towards cooling therapy*" coupled with "*parental decisions that were heavily influenced by a trust in doctors to make the right decision on their behalf*" [5].

The second issue is the fidelity to the intervention. Early initiation of cooling and the 'time to target temperature' is critical to improved outcomes. Cooling beyond 6 hours has been found to be of no benefit [6]. In fact, a recent study suggests cooling to be done before 3 hours. In the HELIX trial, the inclusion criteria states that baby should be "randomized" within 6 hours of birth and the mean randomization time is mentioned; the time to target temperature is not mentioned. Review of **Fig. 1** shows that the mean time of achieving 33.5º is 6 hours post-randomization. The mean age at admission to the cooling unit in outborn babies who constitute 2/3rd of the subjects being 3 hours suggests that most infants in the intervention arm achieved the target temperature at approximately 9 hours. This could be one major difference from other studies that have shown benefit, where the time to target temperature has been less than two hours [7,8]. The rate of rewarming was also 0.5 per hour as against the currently recommended 0.25 per hour [9].

A higher proportion of babies in the hypothermia arm were treated with inotropes, sedatives/analgesics and antibiotics [4]. Assessment of shock is a challenge during therapeutic hypothermia [10], and it is plausible that medications are confounders in this study.

The next issue is the high mortality in both arms. Of the seven centers, five centers that contributed >90% of the subjects had high regional neonatal mortality. High regional neonatal mortality, which is a reflection of the quality of care coupled with the learning curve of a new intervention, may not permit the true benefits of an intervention to surface.

This is in contrast to Indian RCTs that have reported low mortality (1.7-28%) during TH [3]. Characteristics of the HELIX hospitals with quality-of-care measures such as survival rates, shared use of thermal control device and infection control rates in the supple-mentary appendix would have helped understand the generalizability of the study. The wide variation in survival in centers across India that has been highlighted in other collaborative studies [11] and the results of the HELIX trial cannot be extrapolated to centers with low mortality rates.

It is worth noting note that the primary composite outcome of death or disability in hypothermia arm was similar to the control arm despite higher mortality, suggesting that there is indeed some benefit of hypothermia in preventing brain damage [4]. Severe disability among survivors were halved and disabling cerebral palsy was reduced by 47% [11% vs 21%; RR (95% CI) 0.53 (0.28-0.98)].

Considering the above issues, the sweeping recommendation of the authors not to offer TH in all tertiary care intensive care facilities is unfounded on evidence. However, what the HELIX trial has shown that it is not the time for all NICUs to embrace TH without setting the infrastructure, resources and quality care for safe implementation of TH. With the high burden of asphyxia-related mortality and morbidity, we need to explore and study how to make TH safe in LMICs. Collaborative efforts by hospitals that have low mortality with cooling therapy, constant vigil, a national database, benchmarking and efforts to get outborn babies early to cooling hospitals that have shown good outcomes are some of the steps way forward. I feel that it is certainly not the time to write the epitaph on cooling in LMICs.

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Pediatric Neurologist's Viewpoint

Protection of the developing brain had been the holy grail of neonatal practice over the years. The important goals of early and accurate identification of the insults to the fetal and neonatal brain, understanding the complex neurobiology of these insults and developing appropriate mitigation strategies still remain elusive. The utility of classical clinical approach is often very minimal in the newborn in view of the limited repertoire of neurological signs and symptoms [1].

Early identification and stratification of the insults to the immature brain, based on the potential for future neurodevelopmental disabilities, will help the clinicians predict the clinical and developmental outcomes much more accurately. Families too can take better learned decisions regarding the continuation of life support in the NICU. It will also help the research community to develop better targeted acute interventions for the really vulnerable babies improving the benefit: risk ratio. However, the current understanding of neonatal neurology is far from satisfactory to make such accurate assumptions. Some

general categorizations are possible based on the clinical data and investigations.

Neonatal encephalopathy at term with documented evidence for intrapartum sentinel hypoxic/ischemic events is possibly such a group. This cohort is usually much more homogenous in developed countries, where there are robust protocols for antenatal care and intrapartum monitoring. In populations with poor maternal health status, antenatal care and intrapartum monitoring, the clinical syndrome of neonatal encephalopathy might be the composite end result of multiple on going and one-time insults to the developing brain occurring throughout the antenatal and perinatal periods. Without reliable biomarkers, either imaging or biochemical, it will be difficult to stratify this cohort into much more homogenous groups.

The story of neuroprotective interventions for majority of the acquired brain insults has not been very encouraging till now. Most of the proposed ones fell by the wayside while moving from bench to the bedside, mainly due to the undesirable side effects or lack of the predicted clinical benefits [2]. However, TH for moderate/severe hypoxic ischemic encephalopathy in term newborn babies has shown to be consistently effective in reducing long term disabilities in several well-conducted trials and is currently considered the standard of care in most of the developed world [3,4]. TH has also shown to be effective in reducing the burden of neonatal seizures in this group [5].

The recently published HELIX trial [6] – a randomized controlled trial conducted in a few large public hospitals in South Asia, has raised major safety concerns for therapeutic hypothermia in LMICs. The HELIX trial data suggested that therapeutic hypothermia alongside optimal tertiary neonatal intensive care significantly increased the incidence of death relative to a control group without any reduction in brain injury on MRI or improvement in the combined outcomes of death or disability after neonatal encephalopathy [6]. There are two very important aspects here – lack of efficacy and potential for harm. The latter has much more serious implications, in view of the potentially higher risk of occurrence in routine clinical practice compared to the controlled settings of a randomized trial.

Why did the HELIX trial show a potential for serious harm? Such a serious safety signal was not apparent in any of the previous studies conducted in the developed world. The reasons might be neurobiological as the authors are trying to argue. The clinical syndrome of neonatal encephalopathy in LMICs might represent a totally different cohort compared to the developed world for the reasons described above. Moreover, there might be some inherent genetic variations affecting the suscepti-bility to hypoxic ischemic injury as well as response to cooling in this population. The pragmatic design and processes used in this trial, developed probably to suit the already existing practices in the study centers [6], might also have contributed to this outcome. However, one factor clearly emerging out of this well-conducted study is that safety margins are very narrow for the current practice of therapeutic hypothermia for neonatal encephalopathy. The tendency to offer this intervention across all settings might result in considerable harm, especially in the LMICs.

What's the way forward? We can look at the HELIX data more closely to identify any potential subgroups with higher or lower safety margins compared to the total cohort. Such an analysis might possibly give us more insights into the complex neurobiology of neonatal encephalopathy/ therapeutic hypothermia and might also help us modify the current clinical care protocols. It might also lead to further studies to identify new biomarkers and to explore better preventive and interventional strategies for neonatal encephalopathy. There is an urgent need to set up large prospective multicentric neonatal brain consortiums in the country with standardized protocols for clinical care, data capture and outcome analysis. Such an approach might possibly help us stratify neonatal encephalopathy into more homogenous groups for better targeted interventions.

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Basics of Statistical Comparisons

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All study designs in medical research, barring descriptive studies, involve comparative analysis to achieve its objective/s. Comparisons between groups based on outcomes, or risk factors, or interventions, are the basis of hypotheses in evidence-based medicine. Statistical tests support in making criterion-based decisions about the validity of the hypothesis. A basic knowledge of statistical comparisons helps medical researchers to apply valid statistical tests. Novice medical researchers struggle to decide when, and which statistical test must be applied. There is a need to further reduce the mathematical jargon in statistics related publications for medical researchers. In this article, we aim to provide the readers with practical pointers about the applied aspects of basic statistical comparisons in medical research.

Keywords: *Analysis of Variance, Biostatistics, Chi-square distribution, Nonparametric tests, t-test, Hypothesis testing.*

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Most evidence to guide clinical decision making comes from observational and experimental studies [1]. These involve statistical comparisons between groups based on outcomes or exposures.

The choice of a particular statistical test for analysis depends on the objectives of the study. As the objectives are decided in the protocol, the statistical tests are also chosen at this time itself. One needs to determine whether a statistical test is needed for a research objective, and if yes, then which statistical test is best suited. Inexperienced researchers are often confused while choosing the appropriate statistical test to examine the hypothesis. Most published articles are directed towards describing the various statistical tests, rather than explaining how to choose the appropriate statistical test [2,3]. Those which deal with application of statistical tests are often focused on related issues (including the mathematical equations) such that there is a reduced focus on the basic theoretical concepts which would have helped to understand the principles of selection of the respective test [4,5].

This article aims to provide practical tips to novice researchers to approach the application of basic statistical tests for comparing groups in medical research.

Hypothesis Testing

Statistical tests are used to test hypotheses. Hypothesis is a prediction about a new phenomenon. It makes a statement about the existence of a relationship or effect of a factor on a phenomenon [6]. The objectives which are descriptive in nature, rather than comparative, have no hypothesis to test, and do not need of any statistical test. The researcher just wants to see what is there rather than to compare [7]. In case of more than one objective, statistical tests may be applicable on certain objectives but not on others.

Let us consider the following objectives: *i*) To estimate the proportion of children who are completely vaccinated in a given community; and *ii*) To determine the effect of an educational intervention on child immunization coverage in a given geographical area. The first objective does not intend to predict anything or does not state any possible relationship or effect of a factor on a phenomenon and therefore, is not a hypothesis statement. Hence, no statistical test will be needed for this objective. The second objective tries to find the impact of factor X (educational intervention) on phenomenon B (child immunization coverage). This being a hypothesis statement, will require a statistical test.

For hypothesis testing, the statistical tests attempt to reject the null hypothesis. Null hypothesis makes the assumption that there is no difference between the two groups or there is no relationship between the two variables. We apply statistical tests to find whether the null hypothesis is true or false. The *P* value obtained from a statistical test is the probability that both the groups come from the same population rather than two different populations. In simple terms, it is the probability that the difference observed between the two groups is a chance finding. The lower the *P* value, the lesser the probability that the observed difference is by chance [8]. Statistical tests either reject or accept the null hypothesis, depending on whether the *P* value is less than 0.05 or more than or equal to 0.05, respectively [9].

Comparison Between Two Groups

An algorithm to choose an appropriate statistical test for comparison is given in **Fig 1**. Parametric tests require estimation of variables that define the underlying distribution of data, like mean and standard deviation for normally distributed data [10]. Simply put, when means are compared, the tests used are known as parametric, whereas for comparison of medians or categorical variables, the tests used are referred to as nonparametric.

When variable X is compared between two (or more) groups, we decide about the type of data and whether data are paired or not.

Types of Data

Categorical or Continuous Data

The first step is to ascertain the type of data being compared. For most practical purposes, data can be considered as categorical or continuous [11]. A variable such as sex (male/female) or intensity of pain (mild, moderate, severe) where responses will be grouped in one or more categories are categorical variables. They are called nominal when there is no order or grade, and ordinal when they are graded or ordered. Continuous data are those where each observation gets a score. It can be an interval data wherein there is no absolute zero like intelligence quotient scores or temperature in Celsius or ratio data or when an absolute zero exists like heart rate, number of episodes of diarrhea and age.

Continuous data can be transformed to categorical data by applying cut-offs e.g., hemoglobin level is continuous data, but can be converted into categorical data i.e., anemic and non-anemic by applying cut-offs for classifying anemia. However, such conversions must be avoided because it leads to a loss of data, and also reduces the power. Dichotomization leads to loss of variability and dichotomizing at the median value leads to loss of power by one-third. The values near either side of the cut-off, go far away in two categories in this conversion [10]. Care should also be taken to choose appropriate cut-off points. It is preferable to use already recognized cut-offs or they should be justified and decided *a priori*, before the beginning of the study.

Quantitative data should be decided and mentioned *a priori*, whether they will be considered as continuous or categorical data for the purpose of statistical analysis.

Paired or Unpaired Data

The second step to decide about the statistical test is to find out whether the data is paired or unpaired. Data is considered to be paired if: *i*) Two measurements are taken from the same individual either at two different time points e.g., before and after an intervention or exposure; or at the same time but for two different tests to be compared e.g., when comparing two or more diagnostic tests; *ii*) Measurements are taken from pairs of subjects which have been matched at the time of inclusion; and *iii*) Data from siblings and twins are also considered as paired [13].

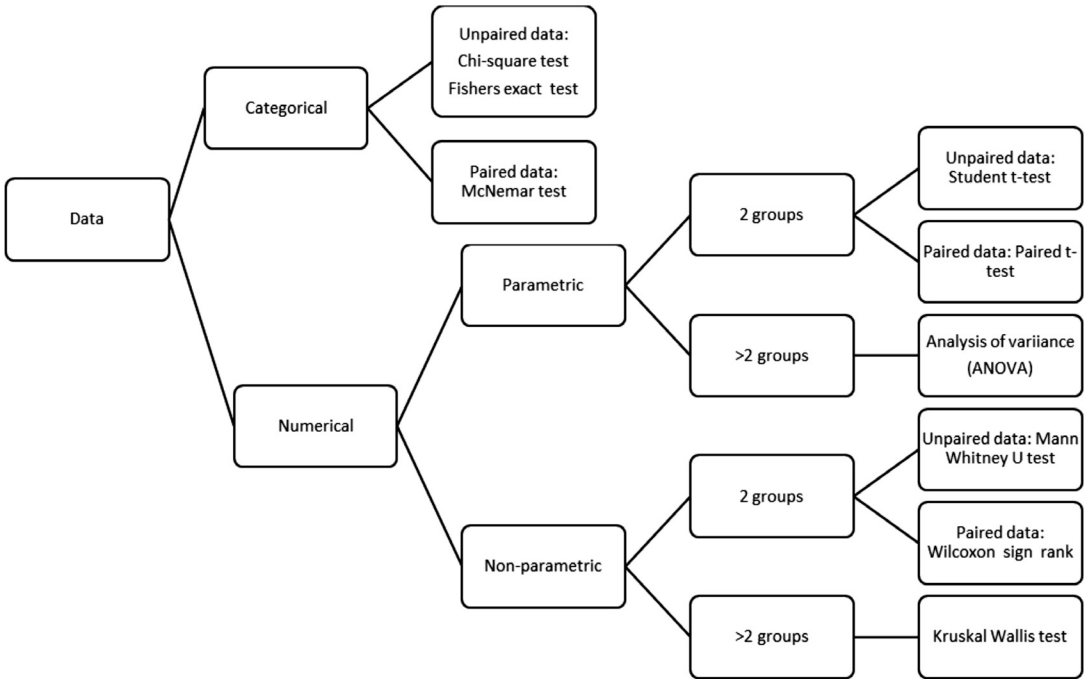

Fig. 1 Algorithm to decide the appropriate statistical test in medical research.

Comparing Categorical Variables

Data such as sex (male or female); disease status (diseased or healthy) and risk factor (present or absent) is categorical in nature. The frequency distribution of two or more categorical variables is presented in a matrix format called as contingency tables or crosstabs.

Pearson chi-square or just chi-square test is applied to compare this kind of data. Being a non-parametric test, it is robust with respect to the distribution of data. Even though there is no limit on the number of rows and columns, to meet the assumptions of chi-square test and for ease of interpretation, too many cells must be avoided [14]. For each cell in a contingency table, expected cell count can be calculated by the product of row total and column total, divided by the grand total. The assumptions for chi-square test are given in **Box I**.

Mc Nemar test should be used, while comparing paired categorical data [15]. Chi-square test is also not helpful when the numbers in the table are small. In such instances, Yate correction or Fisher exact test is applied. A general rule of thumb to apply Yate correction is when the sum of all the values in the cells is less than 100 or the value in any one cell is less than 10 [16]. In contingency tables, if more than one-fifth of the cells the expected values are less than 5, chi-square test is inappropriate and Fisher exact test may be more appropriate [16]. When reporting results of a chi-square test the style of individual journal should be checked – at *Indian Pediatrics,* we only ask that the *P* value must be reported.

Comparing Quantitative Variables

Quantitative variables may be of various types such as discrete or continuous, as described previously, and ratio or interval (not described here). Usually these are summarized as mean or median, for normally and non-normally distributed data, respectively. The distribution of data can be checked either by generating a histogram and examining it visually or by using a statistical test such as Shapiro-Wilk test. A quick (but less accurate) way to assess the normality of data is to compare the mean and standard deviation (SD). If mean is nearly similar to median and the mean is more than 2-3 times of SD, then it can be considered 'normally distributed'. However, this should only be used when sample size is more than 50 [17,18].

Even for ordinal data or non-normal distribution, with a reasonably large sample size, parametric tests can be used. A rule of thumb states that while comparing 2-9 groups if each group has more than 15 observations then the sample is sufficiently large [19].

Variances

While choosing tests, another parameter to consider is the equality of variances in the two groups. This can be checked by Levene test. Parametric tests are best when the variances in the two groups to be considered are equal. Even when one variance is up to 2-3 times the other, parametric tests can be used. However, if the difference in variances is greater, a parametric test is no longer valid.

For comparing quantitative data between two groups, the parametric tests used are Student *t*-test (for unpaired data) and paired *t*-test (paired data). For more than two groups, Analysis of Variance (ANOVA) is the appropriate test to use. While applying the Student *t*-test or ANOVA some assumptions must be met as given in **Box II**.

Parametric tests are preferred because of higher statistical power as they have a greater chance to detect a statistically significant difference, if a difference actually exists [20]. In cases where data are not normally distributed, an attempt can be made to transform it (to normal distribution), so that a parametric test may become applicable. Taking natural logarithms (log transformation) or squares of values are some methods that can be used to transform data. For larger studies (sample size >200), parametric tests can and should be used even for skewed data [21]. While reporting a result of a *t*-test, its important to mention the number of observations in each group, the mean and SD of each group, and the *P* values associated with it.

The non-parametric equivalent (to compare medians) are Mann-Whitney *U*-test (unpaired data) and Wilcoxon

Box I Assumptions for Chi-square Test

- Only two variables can be taken into consideration, both of which must be categorical.
- The cell values must be in counts or frequencies. Percentages or means or any other transformation of data.
- The two samples or groups are independent of each other. They data should not be paired. The expected count in all cells must be at least 1, and in more than four-fifths of the cells must be more than 5.

Box II Assumptions for Student *t* test or One-way ANOVA

- Data must be quantitative (represented by mean)
- The sample must have been randomly drawn from the population
- The data should be normally distributed
- Similar variances in the two groups
- Reasonably large (>15 in each group) sample size
- Independent or unpaired data
- Robust to violations of normality distribution assumption

sign rank test (paired data). When comparing between more than two groups, Kruskal Wallis test is the non-parametric equivalent of the parametric analysis of variance (ANOVA).

This article focuses on bivariate analysis. Multivariate analysis which adjusts for the confounding effects of the independent variables or the predictors is beyond the scope of this article. Bivariate analysis often helps to identify variables for developing multivariable regression models. The statistical tests used to compare sensitivity and specificity etc. in diagnostic studies are also based on the principles described in the article.

CONCLUSION

Comparisons of data points using statistical tests form an important aspect of hypothesis testing in evidence-based research. The type and distribution of data, and pairing status, are helpful to decide the appropriate statistical test (**Box III**). The algorithm presented in the paper will be helpful in decision making. Chi-square, Student *t*-test, Mann Whitney *U* test, and ANOVA are some of the statistical tests used commonly in medical research. The assumptions for the tests must be met when applying a particular statistical test.

Box III Illustration of Use of Algorithm to Decide an Appropriate Test

We want to compare hemoglobin levels after a randomized control trial using oral iron supplements between the treatment and placebo groups.

Step 1. What is the type of variable? Haemoglobin (Hb) is a quantitative variable and is continuous. This will help us determine whether we need to apply tests for categorical data or quantitative data.

Step 2. What is the distribution (normal or not normal) of Hb levels? This can be done by a visual inspection of a histogram or by applying the statistical test (Shapiro Wilk) to test for normality. This will help us determine whether we should use parametric or non-parametric test.

Step 3. Are the groups paired or matched? If paired, you will use paired tests (paired *t*-test) else a Student's *t*-test would suffice.

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Chylous Ascites and Cervical Lymphadenopathy: Variable Presentations of Perinatal Tuberculosis in Extreme Preterm Twins

Abdominal tuberculosis has been widely reported as a cause for chylous ascites in adults and children [1]; though, not in neonates and young infants. We report an extreme preterm infant, who presented at 2.5 month of age with chylous ascites caused by perinatal tuberculosis.

A 2.5-month-old girl presented with fever, excessive crying and grunting. The infant was first of twins born at 27 weeks with birthweight of 870 g. Both twins had received surfactant therapy, and ventilation of 48 hours followed by continuous positive airway pressure (CPAP) for five weeks. The second twin girl had birthweight of 1090 g. She had enterobacter sepsis in the third week of nursery stay from which she recovered after receiving intravenous antibiotics. She had also received packed cell transfusion for anemia. The first twin did not require any transfusion. Both infants were fed initially with pasteurized donor milk (PDHM) followed by mother's own milk. They gained weight along the 10th centile for preterm Fenton growth chart. At the time of discharge, the first and second twin weighed 1.58 kg and 1.6 kg, respectively. Both twins received iron, calcium and vitamin D supplements at discharge at corrected gestational age of 35 weeks. Their mother received antibiotics for fever and cesarian section wound dehiscence in the second post-partum week.

At the time of re-admission, the infant was febrile and her systemic examination was normal. The investigations showed leukocytosis (28.9×10^9/L) with raised C-reactive protein (CRP, 97.5 mg/L). The infant was started on intravenous fluids and antibiotics. The fever spikes reduced and CRP showed declining trend over the next week. Blood and urine cultures were reported sterile. In the second week of admission, the infant started developing abdominal distention. Her abdominal ultrasound showed moderate ascites with multiple necrotic abdominal lymph nodes. An abdominal paracentesis showed milky ascitic fluid. Ascitic fluid microscopy showed high leukocytes count (3.6×10^9/L) with lymphocyte predominance (95%). Triglycerides in ascitic fluid were high (836 mg/dL), suggestive of chylous ascites. The infant was started on octreotide infusion and medium chain triglyceride (MCT)- based formula feeds. The ascitic fluid was negative for acid fast bacilli, bacterial culture and polymerase chain reaction (PCR) for cytomegalovirus and Epstein Barr virus. GeneXpert for tuberculosis was reported as positive. A tuberculin skin test was negative after 72 hours. A computerized tomography (CT) scan of abdomen and chest revealed multiple necrotic lymph nodes in gastro-hepatic, celiac, periportal and retroperitoneal areas with necrotic lesions in spleen, and moderate ascites. A repeat ascitic fluid and gastric lavage sample for GeneXpert was also reported positive.

The infant was started on anti-tuberculosis therapy (isoniazid, rifampicin, pyrazinamide and ethambutol). Repeat abdominal paracentesis days later showed reduced triglycerides content (230 mg/dL). Octreotide infusion was stopped after seven days. Over the next four weeks, the abdominal circumference returned back to normal on MCT-based formula feeds. Family screening for tuberculosis was advised but got delayed due to coronavirus disease (COVID-19) related lockdown, and non-availability of non-emergency laboratory services.

At five months of age, the second twin was noted to have cervical lymphadenopathy. An excisional biopsy of lymph node showed caseating granuloma with *Mycobacterium tuberculosis* grown on Bactec MGIT system. The mother's sputum tested positive for tuberculosis on GeneXpert. The second twin and the mother were also started on four drug anti-tuberculosis treatment. The twin girl with chylous ascites was gradually shifted from MCT-based formula to term formula after 12 weeks. The infant had no ascites and was gaining weight at four months of follow up.

In addition to the known etiological factors such as congenital lymphatic malformations or surgical injury to the lymphatic system and infections, in a large number of cases the cause for chylous ascites remains unidentified [2]. The presence of necrotic lymph nodes in the ultrasound (and later in the CT scan) prompted us to investigate for tuberculosis as the cause of chylous ascites. We used GeneXpert for the diagnosis of tuberculosis in this child as gene-based tests have been shown to increase the diagnostic yield in infantile and childhood tuberculosis [3].

In spite of widely reported criteria for differentiation between congenital and postnatal onset of tuberculosis and its subsequent modification, tuberculosis infection in utero can be indistinguishable from perinatal or early post-partum infection [4,5]. Therefore, we have used the term 'perinatal tuberculosis' for both the twins. As such, the differentiation is only of epidemiological importance and their mode of presentation, treatment, and immediate prognosis do not differ [6]. In our case, the mother had fever during post-partum period, the cause for which was attributed to the wound dehiscence. However, it is likely that the mother could have contracted tuberculosis infection during this period. Women in early postpartum period are twice as likely to develop tuberculosis as nonpregnant women. In our case, both twins did not have any evidence of tuberculosis at birth as well as during their prolonged nursery stay. The identification of tuberculosis bacilli in mother itself indicates her being the source of TB leading to affection of both infants.

We wish to sensitize the readers about the need to also consider tuberculosis as a cause of chylous ascites in infants,

especially in high disease burden countries.

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An Unusual Case of Auto-Immune Hemolytic Anemia

Autoimmune hemolytic anemia in association with insect bites is a rare presentation, but delay in diagnosis can cause significant morbidity and mortality. Here, we report a case of Coombs positive hemolytic anemia after a wasp bite.

A 12-year-old male without significant past medical history was transferred to our hospital by his primary care physician with persistent fatigue, bilateral lower extremity pain, and history of undocumented fever. His laboratory work-up was remarkable for hemolytic anemia with hemoglobin of 4.5 g/dL, reticulocyte count of 6.4%, elevated indirect bilirubin of 9.2 mg/dL, and lactate dehydrogenase (LDH) of 1702 U/L. His serum creatinine kinase was also elevated at 1927 U/L.

Upon arrival to our hospital, he was febrile (102.9ºF) and had tachycardia. On physical exam, he was icteric and noted to have 1×2 cm and 1×3 cm eschars with surrounding induration on left side of his abdomen. Direct anti-globulin test (DAT) was positive with anti-IgG reagent (3+). He was admitted to the pediatric intensive care unit (PICU) with a cinical diagnosis of auto-immune hemolytic anemia (AIHA) due to insect bite. Mother gave a history of seeing wasps in the house on the day of bite and per the toxicologists, the rash was consistent with a *hymenoptera* bite.

Upon admission, he was given blood transfusion and started on methylprednisolone. He was also started on empiric vancomycin and cephalosporin, which were discontinued 48 hours later after negative blood cultures. During his course in the ICU, he continued to require blood transfusion with ongoing drop in hemoglobin. After three days of steroids, hemolysis stopped and his hemoglobin stabilized at 8.9 g/dL. Creatinine kinase, LDH, and reticulocyte count also decreased. He was discharged home after two days on a steroid taper with recommendations for outpatient follow up. Infection was ruled out on the basis of negative cultures. No other known exposure to a new medicine was elicited. The rash being localized, specific history to a topical agent was asked but was negative. Moreover, DAT positive for IgG reagent in the presence of history of exposure to wasp in the house was suggestive of warm auto-immune hemolytic anemia (AIHA).

AIHA is defined as the destruction of circulating red blood cells (RBCs) in the setting of anti-RBC autoantibodies that optimally react at 37°C [1]. About 50% of the warm AIHA cases are called primary because no specific etiology can be found, whereas the rest are recognized as secondary to lympho-proliferative syndromes, malignant diseases, rheumatologic diseases, especially systemic lupus erythematosus, infections (mostly viral), drugs, or a previous transfusion or trans-plantation. Laboratory work-up of the patient was not suggestive of any of these secondary causes.

This presentation caused by insect bite is a rare clinical entity. The exact mechanism of this type of hemolytic anemia is unclear. However, it has been proposed that the toxin from the insect bite alters the red blood cell membrane structure making it more vulnerable to complement-mediated lysis [1]. Medical management primarily consists of supportive treatment. General consensus for first line pharmacologic treatment is glucocorticoids. It is believed that steroids not only decrease antibody production, but also suppress the effect of tissue macrophage phagocytosis and direct effect on auto-antibody red blood cell affinity [2,3].

Such presentations of AIHA due to insect bites can pose a diagnostic challenge and can potentially be fatal. This case demonstrates the importance of a high level of suspicion to allow for timely recognition and intervention [2,4].

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Hereditary Non-Spherocytic Hemolytic Anemia (HNSHA): Four Children with Rare Hereditary Red Cell Enzymopathies

Hereditary red blood cell (RBC) enzymopathies, a group of non-immune, non-spherocytic hemolytic anemias, occur due to a defect in the genes encoding red cell enzymes. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency are the commonly reported red cell enzymopathies. Herein, we describe four children with rare red cell enzymopathies [1].

An 11-month-old girl child, the product of consanguineous marriage, presented with pallor, splenomegaly, and cardiac failure. Investigations were suggestive of hemolytic anemia (**Table I**). Direct Coombs test (DCT), hemoglobin electrophoresis, osmotic fragility test (OFT), isopropanol stability tests for unstable hemoglobins, HbH preparation, and G6PD assay were non-contributory. She had a history of neonatal hyperbilirubinemia needing exchange transfusion followed by a history of blood transfusion at 3 and 6 months of age. Next-generation sequencing (NGS) detected a homozygous missense variation in exon 12 of the *glucose-6-phosphate-isomerase (GPI)* gene.

An 11-year-old boy born to a consanguineous marriage presented with severe pallor, and splenomegaly. Laboratory workups were suggestive of Coombs negative hemolytic anemia (**Table I**). He had a history of neonatal hyperbilirubinemia warranting an exchange transfusion, followed by global developmental delay with sensory neural hearing loss (neurological sequelae of bilirubin encephalopathy). He also had a history of blood transfusion in infancy. A homozygous missense variant in exon 6 of the GPI gene was detected by NGS, which has also been previously reported to cause neurologic impairment and HNSHA [2].

A 9-year-old boy, product of consanguineous marriage, presented with severe pallor and splenomegaly. He had a history of exchange transfusion for hyperbilirubinemia in the neonatal period and also needed repeated blood transfusions for anemia. Laboratory workup (**Table I**) did not reveal a cause for hemolysis. NGS detected a homozygous nonsense variation in exon 4 of the *AK1* (adenylate kinase*)* gene, previously reported to cause hemolytic anemia [3].

A 9-month-old girl, product of consanguineous marriage, presented with severe pallor and splenomegaly. She had neonatal hyperbilirubinemia and required exchange transfusion. Her elder sibling had a history of neonatal exchange transfusion; he died at 1.5 years of age due to severe anemia with jaundice. Investigations were suggestive of Coombs negative hemolysis (**Table I**). A homozygous missense variant in exon 4 of the PKLR (pyruvate kinase L/R) gene was detected by NGS, which can lead to HNSHA.

Table I Clinical Profile and Laboratory Work-up of the Children With Red Cell Enzymopathies

Characteristics	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Age at presentation	11 mo	11 y	9 y	9 mo
Clinical features[a]	-	Developmental delay	-	-
Transfusion history	Once in 3 mo	During acute febrile illness	During acute febrile illness	Once in 3 mo
Consanguinity	3rd degree	3rd degree	3rd degree	2nd degree
Hb (g/dL), MCV (fL), Reticulocyte count (%), Indirect bilirubin (mg/dL)	2.1, 120, 39%, 3	5.2, 112, 11%, 4.5	6, 92, 7%, 3.9	5, 89, 12%, 3.5
Peripheral smear	Macrocytes, bite cells, polychromasia	Macrocytes, polychromasia	Polychromasia, elliptocytes	Polychromasia
Heinz body preparation	Positive	Negative	Negative	Negative

[a]Pallor, icterus and splenomegaly was present in all children. Other investigations (DCT: direct Coombs test, OFT: osmotic fragility test, HPLC: high performance liquid chromatography, HBH preparation (for alpha thalassemia), Isopropanol stability test (for unstable hemoglobinopathies), G6PD:Glucose 6 phosphate Dehydrogenase) were normal for all children. HB: hemoglobin, MCV: mean corpuscular volume. Bone marrow examination showed erythroid hyperplasia in all children.

All children are presently receiving nutritional supplementation and intermittent transfusions. RBC enzymopathies arise from mutations in genes coding for RBC metabolic enzymes. Deficiency of these enzymes leads to impaired cellular energy and/or increases the levels of oxidative stress, leading to premature removal of RBCs in the spleen and decreased red blood cell survival [1]. There are enzymes other than G6PD and PK, which are involved in nucleotide metabolism. The important ones are pyrimidine-5-nucleotidase (pyrimidine metabolism) and adenylate kinase and adenosine deaminase (purine metabolism) [1]. The clinical features of enzymopathies are highly variable, ranging from fully compensated hemolysis to severe transfusion-dependent hemo-lytic anemia. The severity of anemia may worsen during infec-tions, oxidant exposure any other physiological stress [2-4].

Enzymopathies pose a diagnostic challenge and patients may undergo repeated unsuccessful investigations over the years. Some clues include the presence of normocytic/macrocytic anemia with signs of hemolysis like indirect hyperbilirubinemia and reticulocytosis, along with a history of episodic/repeated blood transfusion for anemia. The diagnosis of a RBC enzymopathy is mainly based on exclusion; a negative DCT, a normal OFT, no specific RBC morphological abnormalities, and no evidence for abnormal hemoglobin [5]. Timely targeted NGS would help in the confirmation of diagnosis [2].

Treatment remains mainly supportive. Splenectomy is indicated in severe cases. Restoration of normal enzyme levels following bone marrow transplantation has been occasionally reported [5]. A novel treatment including enzyme activator is under development and this might provide a new option for the severe phenotype [6].

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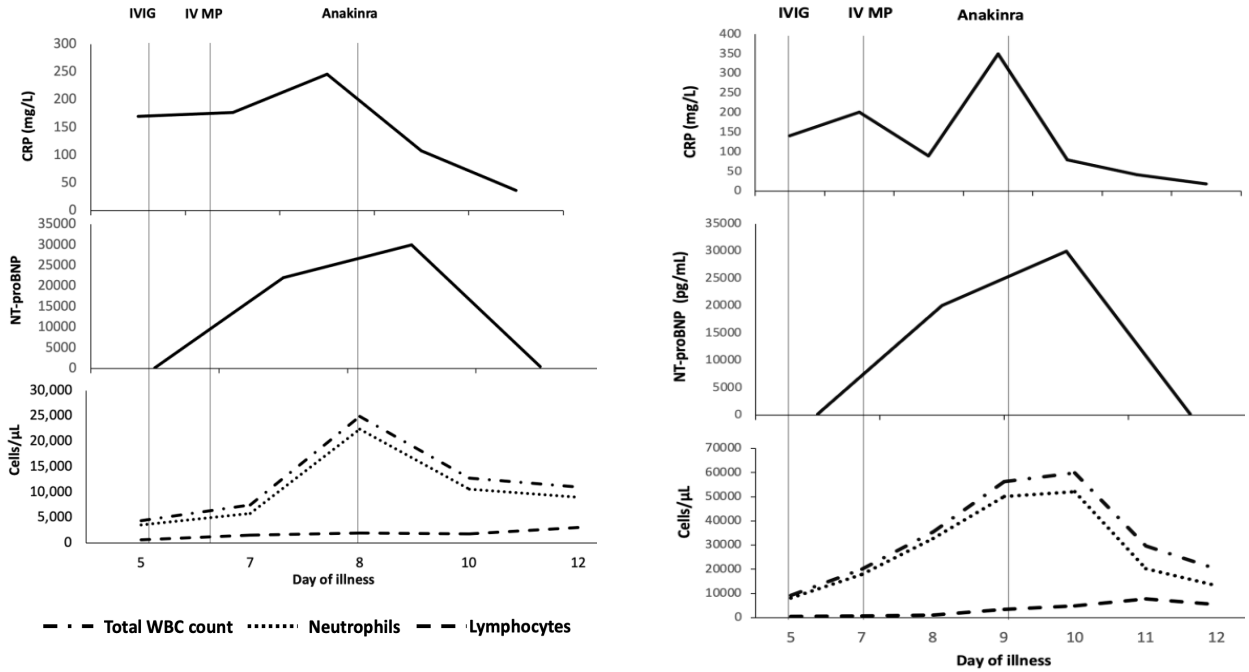
Anakinra in Refractory Multisystem Inflammatory Syndrome in Children (MIS-C)

A small proportion of children can develop a hyper-inflammatory condition 2 to 4 weeks following an infection or exposure to SARS-CoV2 virus termed interchangeably as multisystem inflammatory syndrome in children (MISC) or Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 virus (PIMS-TS) [1]. The patho-genesis of this novel condition remains elusive and treatment protocols are predominantly empirical. Intravenous immuno-globulin (IVIG) alone or with corticosteroids are the suggested first line agents [2,3]. In those with refractory disease (defined by the presence of persistent fever and/or significant end-organ involvement despite initial immunomodulation), second line treatment options include IL-1, IL-6, and tumor necrosis factor (TNF) blockers [2,3]. The PIMS-TS arm of the RECOVERY trial is currently evaluating tocilizumab and anakinra for refractory disease [5]. The experience with use of anakinra in India is sparse due to non-availability of the drug. We report our experience with the use of anakinra in two children with refractory MISC.

Case 1: A 11-year-old boy was referred for fever, abdominal pain and diarrhea of 5 days duration. At presentation he was hypotensive (BP 70/40 mm Hg) with bilateral non purulent conjunctival suffusion and an erythematous maculopapular rash over his trunk. Investigations revealed lymphopenia (total white blood cell count (WBC) 4,350/iL, lymphocytes 4%), elevated inflammatory markers (CRP 170 mg/L, ESR 72 mm/hour, LDH 359 U/L, ferritin 1,200ng/mL, d-Dimer 12,500ng/mL), hyponatremia (130mEq/L) and increased NT-proBNP levels (>20,000pg/mL). Serology was positive for IgG SARs-CoV-2 antibodies (Chemiluminescence, titer 74.9 AU/mL). An echocardiogram showed decreased left ventricular function (LVEF, 40%). A diagnosis of MIS-C was considered, and he was given IVIG (2 g/kg) with intravenous methylprednisolone (IVMP) (2 mg/kg). Noradrenaline infusion (0.15 µg/kg/min) for hypotension and empirical antibiotics were commenced simultaneously. The dose of methylprednisolone was increased (10 mg/kg, once daily for three days), and adrenaline infusion (0.15 µg/kg/min) was started for persistent hypotension. He



IVIG- intravenous immunoglobulin (2 g/kg), IVMP- intravenous methylprednisolone (10mg/kg once daily)

Fig. 1 Trend of inflammatory markers and therapeutic interventions in (*a*) Case 1 and (b) Case 2.

continued to be febrile and hypotensive with elevated inflammatory markers (**Fig. 1a**). Considering refractory disease, anakinra (5 mg/kg/day in two divided doses, subcutaneously) was initiated. There was a dramatic improvement in his clinical status with abrupt cessation of fever and normalization of blood pressure within 12 hours. LVEF increased subsequently (60%). Anakinra was discontinued after 48 hours, and he was discharged on a tapering dose of steroids and aspirin. On follow up at two- and six weeks, LVEF continued to be normal.

Case 2: A 9-year-old boy presented with fever and diarrhea of five days. On examination, he had bilateral conjunctival suffusion, red lips, strawberry tongue, erythematous maculo-papular rash, and pedal edema. Investigations revealed lymphopenia (WBC count 9,230/µL, lymphocyte 6%), elevated acute phase reactants (CRP 140 mg/L, ESR 60 mm/hr, ferritin 596 ng/mL, d-Dimer 9120 ng/mL), and hyponatremia (127 mEq/L). He tested positive for IgG SARs-CoV-2 anti-bodies (Biomerieux, Index 10.95). An echocardiogram showed dilatation of the right coronary artery (RCA, *z*-score 2.19). His presentation was consistent with Kawasaki disease like phenotype of MISC and he was given IVIG (2 g/kg) with IVMP (2 mg/kg/day). On day 3 of admission, fever recurred, and he developed hypotension necessitating inotropic support (noradrenaline, 0.15 µg/kg/min). Inflammatory markers and NT-proBNP levels had further increased (**Fig. 1b**). Repeat echocardiogram showed a decrease in LVEF (35%) and progression of RCA involvement (z-score 3.5). The dose of methylprednisolone was increased to 10 mg/kg once daily for 3 days. On day 5 of admission, his inotropic requirement (adrenaline, 0.5 µg/kg/min) and inflammatory markers progressively increased. Anakinra (6 mg/kg/day in two divided doses, subcutaneously) was commenced for refractory disease. Within 48 hours, he was off inotropic support with defervescence of fever, down trending inflammatory markers and normal LVEF (60%). He was discharged on a slow taper of oral steroids and aspirin. On follow up at two- and six weeks, coronary vessels and LVEF were within normal limits.

Anakinra is a recombinant IL-1R antagonist that blocks the binding of both IL-1α and IL-1β to IL-1R, thereby inhibiting the proinflammatory effects of IL-1. According to the American College of Rheumatology clinical guidance, anakinra (4-10 mg/kg/day) is the preferred monoclonal antibody in refractory MIS-C [4]. However, the United Kingdom national consensus guidance recommends tocilizumab, anakinra or infliximab depending on clinician preference [3]. In comparison to tocilizumab or infliximab, the short half-life of anakinra makes it more favorable for use in the Indian context where secondary infections are a cause of concern. In fact, anakinra was found to be beneficial in patients with severe sepsis, especially in the subset with macrophage activation syndrome [6]. The cost of treatment with anakinra compares favorably with tocilizumab. Our experience re-emphasizes that anakinra can be an effective therapeutic agent in children with MISC who do not respond to IVIG and corticosteroids.

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Acute Severe Heart Failure in a Child With Congenital Heart Defect and Multisystem Inflammatory Syndrome in Children (MIS-C)

Myocardial involvement is a known feature of multisystem inflammatory syndrome in children (MIS-C), with mild ventricular dysfunction being the commonest finding. We describe a child who had congenital heart defect with complete heart block (CHB), and presented to us with MIS-C, but due to a rare complication succumbed to intractable heart failure.

A 13-year-old boy was admitted with a history of high-grade fever, rash, body ache and vomiting for 4 days, and mild swelling over feet for 2 days. There was no history of dyspnea, cyanosis, syncope, loss of consciousness, or neurological symptoms. Hailing from a containment zone area for coronavirus disease 19 (COVID-19) two months back, neither the child, nor his family members had been symptomatic nor tested for severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection. He was a known case of corrected transposition of great arteries (CCTGA), moderate pulmonary stenosis (PS), intact interventricular septum, small ostium secundum atrial septal defect (ASD), and CHB, since infancy without any previous admissions.

On admission, he was conscious, irritable and febrile. Pulse rate was 80/min, respiratory rate 28/min, no distress, blood pressure 100/60 mmHg, and saturation 96% on room air. He was underweight (body mass index 12.4 kg/m^2; <-3 SDS) and had a petechial rash over the body with bilateral pedal edema. The first heart sound was normal and pulmonary component of second heart sound was soft. A grade III/VI ejection systolic murmur in the left upper parasternal area was present. Rest of the systemic examination was unremarkable. We considered MIS-C and dengue fever as the possibilities. Investigations revealed hemoglobin of 13.3 g/dL, total leucocyte count of 7.2×10^9/L, with relative neutrophilia (80%) and lymphocytopenia (14%), and thrombocytopenia (37×10^9/L). His C-reactive protein (CRP) was elevated (62.9 mg/L), D-dimer 4674 ng/mL was increased, NT-pro BNP 14352 pg/mL was highly elevated with hypoalbuminemia (2.9 g/dL). Renal function tests were normal. Anti-SARS-CoV-2 IgG antibody was positive, and IgM antibody was negative. Dengue serology was negative and chest *X*-ray was normal. ECG showed CHB with a ventricular rate of 78/min. Echocardiogram confirmed the anatomy of CCTGA with mild tricuspid regurgitation (TR), trivial mitral regurgitation (MR), mild right ventricular (RV) dysfunction, normal coronaries and no evidence of infective endocarditis.

We made a diagnosis of MIS-C [2]. Increased NT Pro-BNP and ventricular dysfunction on echocardiography reflected the myocardial involvement in MIS-C [2,3].

He was treated with intravenous immunoglobulin (IVIG) infusion (2 g/kg over 48 hours) along with injection methylprednisolone pulse therapy (10 mg/kg/dose), milrinone infusion and low molecular weight heparin. On day 3 of admission, he started complaining of severe abdominal pain, increased irritability, tachypnea but no tachycardia, and started desaturating (SpO_2 70%), despite being on high flow oxygen. Grade IV/VI pansystolic murmur was now audible over the left lower parasternal area and apex. Repeat chest *X*-ray showed cardiomegaly and pulmonary venous congestion, but no parenchymal involvement. Despite being electively put-on mechanical ventilation, the child remained hypoxic. Repeat echocardiogram showed severe MR due to ruptured chordae tendinae of the anterior leaflet, with the mobilized chordae giving an impression of a thrombus/vegetation attached to the edges of the flail leaflet. This caused gross coaptation failure and the regurgitant jet was eccentrically directed towards the ASD, through which there was now right to left shunting, causing cyanosis. The right atrium was dilated, right ventricle was dysfunctional and there was no thrombus/vegetation anywhere else. His heart rate did not show much variation, but inotropes doses were escalated in view of persistent hypotension. Extracorporeal membrane oxygenator (ECMO) and/or surgery was contemplated in view of persistent worsening but he went into sudden cardiac arrest and died.

Myocardial involvement is a known feature of MIS-C, and common cardiovascular complications reported are shock, cardiac arrhythmias, pericardial effusion, coronary artery dilatation, and reduced left ventricular ejection fraction [1-4]. Although the exact

mechanism of MIS-C is still unclear, it is treated with IVIG and/or steroids, anticoagulants, and inotropes depending upon the cardiac status. Irrespective of the cardiac involvement, response to treatment and prognosis is generally good in MIS-C. However, in children with comorbidities, course of MIS-C can be complicated [1-4]. Chordae tendinae rupture and severe regurgitation can be either iatrogenic (during intracardiac device implantation or myocardial biopsy), or in conditions like acute rheumatic fever and infective endocarditis [5]. There have been no reports of chordal rupture in MIS-C [1-4]. Whether presence of CHD predisposes to chordal rupture in myocardial involvement due to MIS-C, is open to speculation. However, it can be concluded that the myocardial involvement may be sufficient enough to cause chordal rupture, at least in some individuals.

To conclude, a high index of suspicion for diagnosis of MIS-C, and early proactive intensive and cardiac care management, with preparedness for rare complications, is recommended for children with congenital heart defect and MIS-C.

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Home Vaccination – The Way Forward in a Pandemic

When the coronavirus disease 2019 (COVID-19) pandemic struck in early 2020, the associated lockdowns and the fear of contracting the disease made parents miss their children's vaccinations. India saw a 70% reduction in routine vaccinations during early 2020, and concerns were expressed by World Health Organization (WHO) and United Nation's (UNICEF) that vaccine preventable disease (VPD) may make a comeback [1,2]. In this background, we introduced of home vaccinations [3]. We offered home vaccinations to parents who were afraid of coming out or could not come out due to various reasons.

The criteria for offering home vaccination were: parents to consult a pediatrician on video consultation or tele consultation – to discuss the vaccinations that are due there for child [4]; the pediatrician after detailed history would explain the vaccinations and possible common side effects and prescribe the vaccinations; and this prescription then be handled by a qualified pharmacist who will dispense the vaccines. The vaccines were delivered by a team of two experienced nurses, an ambulance officer and an ambulance driver capable of handling emergencies like anaphylaxis. This team visited the family in appropriate personal protective equipment (PPE), match the child's details with the prescription and administer the vaccines after taking parental consent. The team had provision of all emergency drugs, and observed the child for half an hour for any possible side effects.

This concept of home vaccination has gained good acceptance. In 2020, we carried out more than 25,000 home vaccinations for children. We feel that this concept is worth taking up on a wider scale by hospitals and non-governmental organizations so as to address the possibility of resurgence of VPDs during this pandemic.

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Unusual Complication of Hair Pulling in a Young Child

A 7-year-old girl, who was previously well, presented with complaints of scalp swelling. Two days prior to presentation, she had pain during combing of hairs, when her mother noticed swelling over the scalp and the swelling gradually increased in size over the next two days. There was no history of trauma, or family history suggestive of either bleeding disorder or coagulopathy. She was not on any medications, and had not undergone any surgical procedures.

On examination, she was conscious, alert, and had stable vitals. Neurologic examination and other systemic examinations were unremarkable. Local examination of the scalp revealed diffuse non-tender boggy swelling over the left parietal area. Skin over the swelling was normal. Computed tomography (CT) of head showed subgaleal bleed without skull fracture and intracranial pathology. Complete blood count, coagulation profile, factor XIII and VWF levels were normal.

As the child was hemodynamically stable, no neurosurgical intervention was required. Parents were counselled regarding the possible complications such as infections, calcification and further bleeding. The swelling was noted to decrease in size during follow up.

Subgaleal hematomas occurring beyond the neonatal period are rare and usually secondary to significant head trauma. Either tangential (blunt) or radial (pulling) forces cause shearing and rupture of emissary veins traversing the subgaleal space. Subgaleal hematoma has been reported following relatively minor trauma such as hair braiding or sudden hair pulling [1-3]. They are usually small, self-limiting in nature, remain localized, and resolve spontaneously and are usually conservatively managed. As this child presented with significant swelling, coagulation abnormality was considered as there was no history of trauma. As her investigations were unremarkable and she was hemodynamically stable, she was treated conservatively and the swelling resolved completely within two weeks. Edmondson, et al. [4] have previous reported a patient with delayed presentation of a massive subgaleal hematoma in an adolescent following a seemingly innocuous episode of hair pulling, in the absence of underlying hematological or anatomical abnormality [3].

In conclusion, although subgaleal bleed beyond neonatal period is rare, it can happen and the patient has to be investigated with neuroimaging to look for the skull fracture and hematoma extension, and investigated to rule out rare coagulation disorders, as subgaleal bleed due to hair pulling is a diagnosis of exclusion.

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Dental Caries in Children During COVID-19 Pandemic – Are We Doing Enough?

Dental caries is a common childhood disease of multifactorial origin and factors like dietary habits and carriage of oral cariogenic organisms play a major role in etiology [1]. Several other risk factors like oral hygine, malocclusion, socio-economic status, literacy, cultural factors and fluoride intake are also associated [1]. The recent COVID-19 pandemic has negatively modified many of these risk factors, and may increase the risk of dental caries.

The year-long curbs imposed due to COVID-19 pandemic has predisposed children to unhealthy lifestyle and altered behavioral profile [2]. The prolonged indoor stay due to lockdown restrictions has led to a sedentary lifestyle, reduced outdoor physical activity, altered eating patterns, especially increased snacking and junk food craving, and increased screen time [3]. Increased screen time also exposes children to commercials of caries-inducing foods and beverages. Several studies have linked these factors to increased incidence of obesity and dental caries among children [4]. However, unlike obesity, caries is often slowly progressive and sub-clinical, making early diagnosis challenging. The exact incidence of dental caries during COVID-19 pandemic may be underreported due to its sub-clinical progression and challenges in performing oral examination due to risk of aerosol transmission.

Children with dental caries often present to healthcare setups during acute exacerbations [3,4]. Since it is mostly asymptomatic, it can lead to delayed diagnosis, wherein a critical window time period for preventive interventions or slowing disease progression is missed. Disregarding routine dental care for long periods can predispose children to present with advanced disease. Moreover, during the first wave of COVID-19 pandemic, dental associations were the first to recommend postponement of elective dental procedures because of high risk of aerosol generation and were also the last services to resume [5].

Untreated tooth decay in children can lead to discomfort or toothache, increased chances of sepsis, malnourishment due to reduced food intake or obesity due to non-consumption of regular food and dependency on easily chewable carbohydrate-rich food, impaired cognitive development, disturbed sleep, reduced self-esteem and social acceptance among peers [1].

Health workers and parents need to be sensitized regarding the risk of dental caries during the lockdown period. 'Dental selfies', which can allow indirect oral examination via tele-dentistry, should be encouraged. Parents and children should be counselled on healthy lifestyle behaviors, measures to improve oral hygiene and need for scheduled hospital visits for dental caries screening.

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How did the Delta variant affect children in the US

There were two spikes of admissions in children with COVID-19 in the US in 2021. One was in January and the second was in August. The second spike was largely due to the Delta variant. A look at the admissions in the two peaks gives us some insight into whether the delta variant causes a more severe disease than the previous variants.

The peak admissions were similar with about 1.4/100000 children and adolescents being admitted in August. This was 5-times higher than the admission rate in June, 2021.Younger children between 0-4 years required more admissions with an admission rate of 1.9/100000 children. The severity of illness was also not different. In August, when the delta variant was predominant, 23% of children admitted required intensive care admission, 10% required ventilation and 2% died. In the pre delta variant period in January, about 27% required admission, 6% required ventilation and 1% died.

In the US two-dose vaccine coverage in adults is 53%, for adolescents 16-17 years it is 46%, and for those between 12-15 years, 37%. Hospitalizations were 10-times higher among the adolescents who were not vaccinated compared to those who had received both doses.

In summary, it appears the delta variant did not cause a more severe disease in children and adolescents and the role of vaccination in children appears significant in reducing severity of illness.
(*www.cdc.gov 10 September, 2021*)

How wildfires are contributing to mortality

In the last couple of years, there have been an unprecedented increase in the number of wildfires from many corners of the world. These have included Australia-where millions of acres were burnt down, California-which documented destruction of nearly 3 million acres, the Amazon rainforest and the Siberian forests. This appears to be due to the hotter drier climates which are becoming increasingly common with progressive climate change. Wildfire associated particulate matter PM 2.5 is considered particularly toxic since they enter the lungs and translocate through the alveolar epithelium.

An International study in 43 countries looked at the increase in all-cause mortality due to PM 2.5 released in wildfires. Overall, 0·62% (95% CI 0·48-0·75) of all-cause deaths, 0·55% (0·43-0·67) of cardiovascular deaths, and 0·64% (0·50-0·78) of respiratory deaths were annually attributable to the acute impacts of wildfire-related PM 2·5 exposure during the study period. Another article in the same journal found that children were more vulnerable to wildfire associated PM2.5 injury with highest impact in Nigeria, India, Congo, Uganda and Indonesia.

We live in an interconnected world and climate change is a huge challenge to world health which needs urgent action.
(*Lancet Planetary Health 1 September, 2021*).

How does immunity after natural infection compare with vaccination?

There is a huge global discussion about why someone who has had the COVID-19 infection needs a vaccine. There is good data to suggest that immunity after natural COVID-19 infection is robust and durable. However, the CDC still recommends that all people get vaccinated as soon as they are eligible citing that immune response was variable from person to person.

An NIH funded study from La Jolla Institute of Immunology found a good immune response upto 8 months in 95% of people who had previous infection with COVID-19. An influential paper in Science detected that though antibodies reduced over 8 months, memory B cells increased. Real-world data also suggests that immunity after natural infection parallels vaccination. Of the 50000 employees of Cleveland Clinic, infection rates were similar in those who had natural infection versus vaccine. A population-wide database from Israel also concluded that there was no difference to the risk of infection in those vaccinated versus those who had natural infection.

Some countries like Israel have suggested that after a natural infection one may take a single dose of the mRNA vaccine after 3 months. They are offering the vaccine passport to all those with anti-Covid antibodies irrespective of whether it is post-infection or vaccine.

It appears paradoxical to assume that someone exposed to the entire virus would have poorer immune response compared to someone exposed to just a portion of the spike protein. The decision to insist on two doses for all seems to be more related to administrative ease than anything else. The downside of insisting on vaccinating previously infected persons include a 56% higher rate of adverse effects post-vaccine, and a possible exhaustion of T cells as suggested by some researchers.

There is a lot to still understand about the best vaccine strategy in COVID-19!
(*BMJ13 September 2021*)

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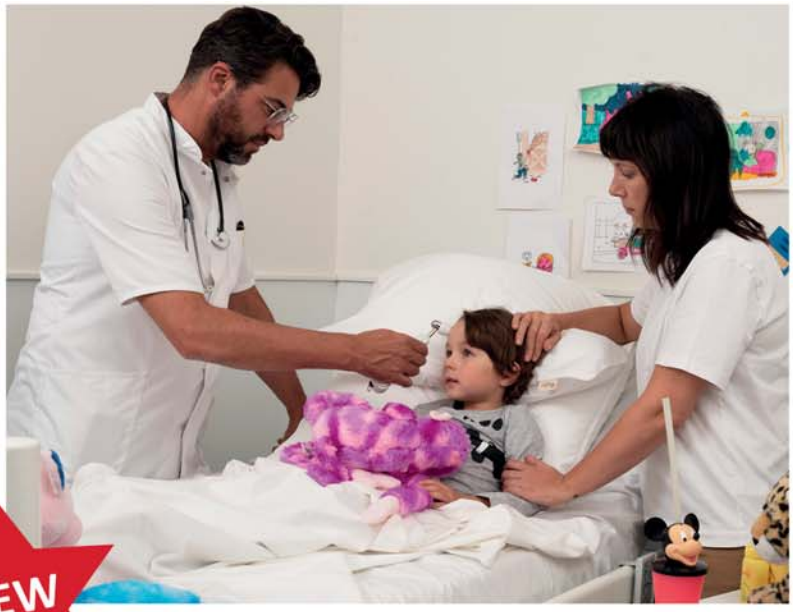

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