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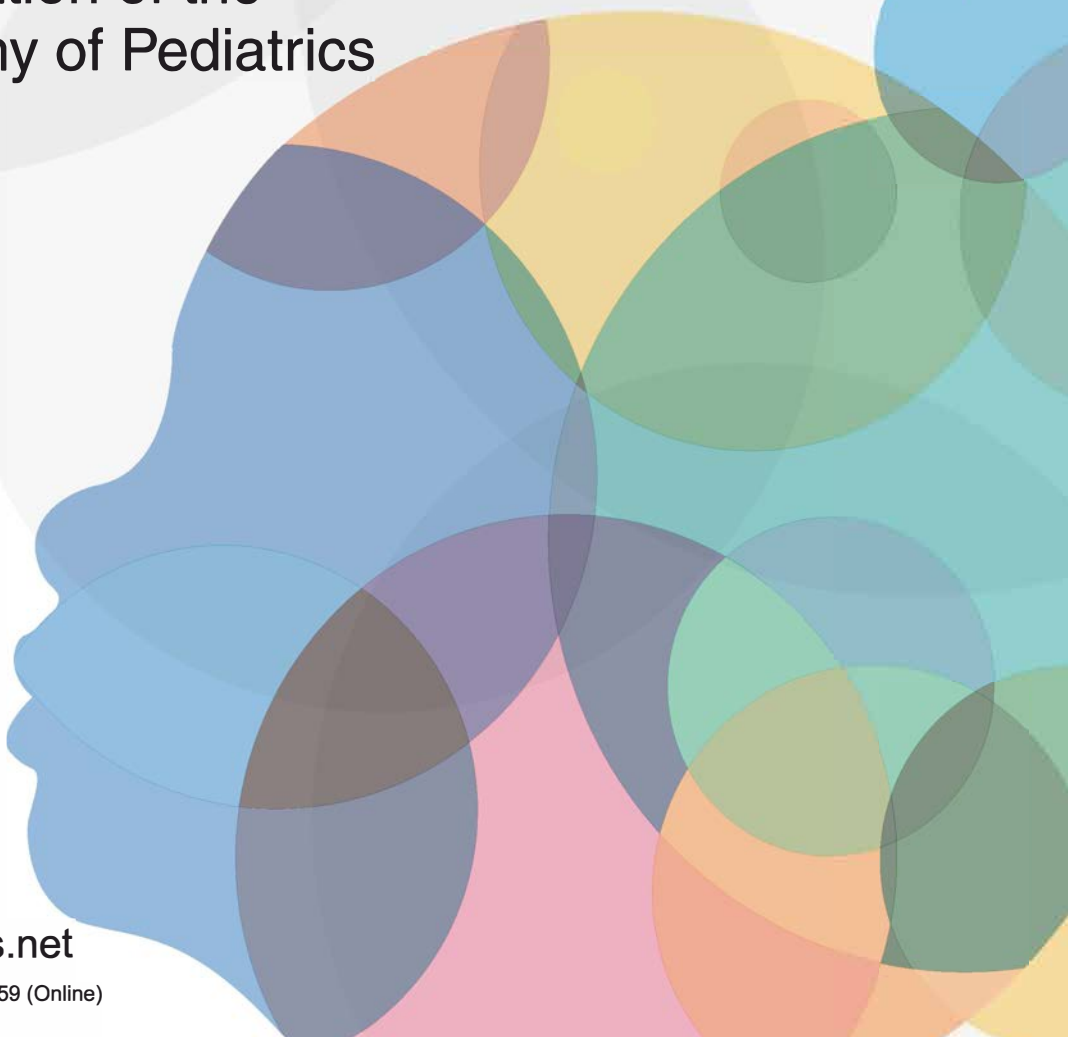

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The Need for Transformative Nutrition Initiatives

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All children and mothers in our country enjoy the constitutional right to food, and we have significantly progressed since 1947; through the green revolution and beyond, to become a food surplus country. From dependence on food aid until the 1960s, our godowns now are bursting at their seams. Our public distribution system now gives free grain to those who need support.

We still have to ensure that the food aid reaches all our people, and while there are many gaps, we continue to make progress. Food security is increasingly looking like a problem that our nation has solved and will soon solve the implementation issues.

NUTRITION SECURITY

There has been a lot of progress in reducing stunting and malnutrition numbers in the last few decades. But, with under-five stunting at close to 40%, we have a long way to go. India also has the peculiar problem of stunting across economic strata! Stunting is close to 20% even amongst the top economic quintile (the wealthiest one-fifth of the population). To add to the under-nutrition problem, we have over-nutrition to deal with amongst an increasing number of children and mothers, caused by excessive energy density.

What Can IAP Do to Solve These Problems?

IAP has two powerful levers: *Credibility* – IAP is an apex child health body in the country, and our recommendations are followed nationally; and, *Reach* – IAP's 32000 members treat over 100 million children annually.

We must deploy these levers in effective and efficient ways to empower all other stakeholders in the nation. All stakeholders; whether governments, schools, or others, must have the methodologies and solutions to effectively tackle maternal and child malnutrition.

IAP INITIATIVES

You will be glad to know that under the dIAP program and the guidance of nutrition experts in IAP, we have planned to pilot two solutions that can be adopted by all stakeholders.

The Reach Lever – The NAAP Solution

Our pediatricians are unable to spend the time needed to conduct ICMR recommended nutrition status evaluation protocols. Also, pediatric nutritionists are not readily available to serve the children visiting all our pediatricians.

There is a pressing need to deliver sustainable whole-food solutions to solve nutrition problems. Prescribing supplements is not a long-term solution. Processed food supplements are even worse as they are usually energy-dense foods that cause more damage. Mothers must have culture-/family- and kitchen-friendly whole food solutions, which are long term, sustainable nutrition solutions for the child, the mother, and the entire family.

IAP's NAAP solution will deliver nutrition assessment, along with sustainable, practical nutritional advice. This activity will be done *via* the pediatrician and in a manner that ensures high compliance. The NAAP pilot program will be conducted later this year. A successful pilot will be expanded nationwide and can become a large scale success template that can be adopted by the caregivers of the public sector and the rest of the private sector.

The Credibility Lever – The Chariot Solution

Our large scale public programs like mid-day meal scheme and maternal nutrition schemes reach millions of mothers and children. However, most are unable to deliver sufficient protein and micronutrients in the meal within the budgets available. A traditionally accepted whole food solution that can cover this gap within the available budgets has eluded us for long.

We have identified a whole food solution consisting of safety-certified nuts and leaves, which can solve this problem. The best part is that it is traditionally used in Indian homes since many centuries. We are working to pilot it under IAP Expert Committee supervision in a few

schools and urban slums. The Chariot program of IAP will do this. A successful pilot will deliver a solution that all government agencies and NGOs nationwide can adopt.

Repeating our mantra, "prevention is better than cure," I look forward to your blessings to make these programs successful.

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EDITORIAL COMMENTARY

Effect of Delayed Cord Clamping on Iron Stores in Infancy

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This issue of *Indian Pediatrics* has published a meta-analysis on the effect of delayed cord clamping in term infants on anemia in infancy by Fu, *et al.* [1]. The present systematic review included 12 studies which had 993 infants in the delayed cord clamping (DCC) group and 989 infants in early cord clamping group (ECC). The review concluded that the hemoglobin and serum ferritin were significantly higher in infancy in the DCC group, compared to the ECC group. The conclusions are not different from the review by McDonald, *et al.* [2], which included 5 studies (620 in DCC and 532 in ECC), and concluded that infants in the late clamping group were less likely to be anemic at 3-6 months of age. However, both reviews observed high heterogeneity in the reported results, which could be due several reasons – the way iron deficiency is defined, maternal iron status, type of feeding, proportion of low birth weight babies, etc. The review by Fu, *et al.* [1] has added two other possible variables that could potentially contribute to the heterogeneity *i.e,* ethnicity and timing of delayed cord clamping. Studies that use serum ferritin alone as a measure of iron deficiency, without concomitant hemoglobin measurement, are fraught with the risk of missing iron deficiency if serum ferritin is elevated due to infection (as an inflammatory response). This could be a potential confounding, especially in low-resource settings where infection rates tend to be high. Studies observing the effect of interventions on anemia in infancy should therefore include C-reactive protein to exclude concomitant infection, along with serum ferritin and hemoglobin measurements.

While there is evidence of the benefits of DCC on iron stores in term infants, its effect on iron stores in preterm infants beyond the neonatal period is limited. In a small trial in 37 preterm neonates over a decade ago, Ultee, *et al.* [3] observed that at 10 weeks, the DCC group had higher hemoglobin values. Trials of DCC *versus* ECC in preterm infants may not be easy in the present time, as clamping the cord late is increasingly being recommended and practiced as the norm, and thus could pose an ethical challenge for the conduct of such trials. The only possibility could be varying the timing of cord clamping beyond 60 seconds. The appropriate timing of cord clamping when benefits could cease to occur or harm (if any) could manifest, is unknown and hence should be explored. One of the reasons to examine such questions could be the need to validate observations such as by Fu, *et al.* [1] that benefits of increased iron stores may not accrue if cord is clamped beyond 120 secs.

There have been reports that low cord ferritin could be a potential biomarker to predict brain iron deficiency and dysfunction as evidenced by lower psychomotor scores at 1 year with iron deficiency due to maternal gestational diabetes [4]. Gupta and Ramji [5], in a randomized trial, observed that term infants born to anemic mothers who underwent DCC were at lower odds for anemia at 3 months compared to those in the ECC group. Thus, in regions of the world with high burden of maternal anemia, DCC has the potential to positively impact iron stores in infants and their neurodevelopment outcomes as has been demonstrated by Andersson, *et al*. [6] in term infants in Sweden. To see its effect in low-resource settings, the same authors had designed a trial comparing DCC and ECC on neurodevelopment to be conducted in Nepal [7]; the trial was registered in 2014 but is apparently not recruiting as per information available at the trial registry site.

While trialists continue in their endeavor to untangle the influence of the effects of confounding on the timing of cord clamping and iron stores, current practice guidelines to delay cord clamping to atleast 60 seconds should be vigorously pursued given the available evidence of its benefits, which possibly goes beyond improving iron status in infancy and more importantly no harm having been demonstrated.

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

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EDITORIAL COMMENTARY

Early Childhood Care and Education

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Early childhood years are the most crucial period for the development of physical and cognitive growth. Both genetic endowment and environmental factors determine the achievement of the ultimate developmental potential. Healthcare and nutrition, appropriate education, shelter and protection constitute the critical requisites for optimal growth and development. The measures to provide healthcare are well established, but education and learning during the early formative years have not been addressed adequately. In that context, the consensus statement by the Indian Academy of Pediatrics (IAP) on early childhood development (ECD) is a welcome effort [1]. It focuses on brain development and interventions for ECD that should begin early and be inclusive and available for all, especially for high risk and marginalized families.

It is important to be aware of the governmental plans toward provision of healthcare and education during early childhood.

GOVERNMENT POLICIES AND PROGRAMS

The National Early Childhood Care and Education (ECCE) policy [2] mentions the government's commitment, and describes various measures to provide ECCE to all children in the 0-6 age group. The National plan of action for children focuses on the four key areas of survival, health, nutrition and education, and development [3].

Healthcare

Various programs concerning antenatal and perinatal care, immunization, infant feeding, subsequent nutritional support, and care of children with disability are widely known. The Integrated Child Development Scheme (ICDS) program and primary health centers deliver health care services. However, the prevalence of malnutrition and anemia in young children still remains alarmingly high. Furthermore, their adverse impact on physical and intellectual attainment is irreversible.There are considerable difficulties in healthcare delivery to children in underprivileged rural and urban communities that must be tackled by better micro-management and informing and educating the caregivers. Indeed, children must be given the 'right to health' (similar to the right to education), and the government must provide sufficient inputs to make it a reality [4]

Early Childhood Education

The ECCE policy document [2] reiterates the government's commitment to promote inclusive, equitable and contextualized opportunities for promoting optimal development and active learning capacity of all children below 6 years. Early childhood is referred to as the first 6 years of life with sub-stages: conception to birth, birth to 3 years and 3 to 6 years, that have age specific needs. ECCE encompasses the inseparable elements of care, health, nutrition, play and early learning within a protective and enabling environment. As per 2011 census, India has 158.7 million children in the 0-6 year age group. Providing ECCE to them, especially those in the low income segments, is a formidable undertaking. The document mentions that the contribution of national programs that provide basic services, such as national rural health mission, total sanitation and drinking water campaign and several others is required towards providing an enabling environment. Various institutes that provide training for early childhood development will be strengthened. The policy document gives details of how ECCE is to be implemented through the ICDS program. The role of Non-governmental organizations is also mentioned.

IAP RECOMMENDATIONS

The IAP recommendations are directed towards pediatricians and the consensus document is envisaged to guide the pediatric fraternity to improve practices and advocacy in ECD [1]. It explicitly identifies the first 2000 days of life as being crucial for brain development and the factors eligible for prompt actions. It takes cognizance of WHO and UNICEF statements, sustainable development goals (SDGs) and the relevant wide database. It mentions appropriate interventions and identification of specific

needs of the vulnerable, integration with other sectors including obstetrics, education, civil society, government agencies, preschool learning advice and use of digital devices, and daycare crèche policies (guideline and training). It calls for necessary modifications in undergraduate and postgraduate medical training, and promoting research and developing innovative methods in ECD. Importantly, it mentions that "anganwadis need an additional trained worker in early stimulation and care for child development." Most of these suggestions are; however, not elaborated.

The recommendations in neonatal period, interventions in the neonatal unit and postnatal period, identification of high risk newborn and stratification, described in great length, can only be practiced by neonatologists or experienced pediatricians at nurseries having adequate expertise, which may not be widely available. Neonatal developmental interventions asked to be performed by family members would be difficult to carry out among the poor socioeconomic communities. The two extensive tables list the scope of the pediatrician's role in areas of ECD and checklist for working in pediatric clinics. Although important; it is doubtful that the busy pediatrician would have sufficient time for their application. Ideal neonatal care will reduce neonatal and infant mortality, but is unlikely to make a substantial contribution to ECD.

CHALLENGES AND THE WAY AHEAD

An Expert Group consultation that included government participation describes various measures to meet the challenges of early ECD [4]. ECCE training modules designed by UNICEF and Ambedkar University, Delhi, which outline the learning activity for children aged between 3-4, 4-5 and 5-6 year are available. Universal access to integrated child development including ECCE for all young children remains the primary responsibility of the government. It is to be provided through the ICDS with its network of 1,37,700 anganwadi centers in the country [6]. The governmental schemes and programs for providing healthcare require better micromanagement and supervision. Early education for all children presents greater difficulties, but it can be carried out at anganwadis by adequately trained workers, helped by Accredited Social Health Activists (ASHAs), and given the necessary requirements by the government and support of the civil society. The anganwadi worker is presently overwhelmed with various forms of work. An additional anganwadi worker, trained in the provision of ECCE and other problems of children (*e.g*, detection of disability, maltreatment and exploitation) will be extremely beneficial. Pediatricians should support and supervise various childcare programs. The IAP can provide its expertise, advise the policymakers, and advocate and demand on behalf of the children.

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

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RESEARCH PAPER

Correlation of Aortic Intima-Media Thickness With Birthweight in Healthy Term and Near Term Neonates

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Submitted: August 19, 2019; Initial review: November 14, 2019; Accepted: March 14, 2020.

Objectives: The primary objective was to correlate aortic intima-media thickness (aIMT) measured at L1-L2 with birth weight in neonates born at ≥35 week of gestation. The secondary objective was to compare aIMT in small for gestational age (SGA) and appropriate for gestational age (AGA) babies in this cohort. **Methods:** Prospective observational study enrolling 200 newborns. aIMT was measured on day 3 of life using 10-12 MHz ultrasound probe. Relevant maternal and baby details were collected and analyzed. **Results:** Mean (SD) aIMT was 0.43 (0.15) mm. There was a negative correlation between aIMT and birthweight (r= -0.64). Mean (SD) aIMT in AGA was significantly lesser than in SGA babies (0.36 (0.11) *vs*. 0.64 (0.08) mm; P<0.0001). **Conclusion:** aIMT progressively decreases with increase in birthweight.

Keywords: *Atherosclerosis, Barker hypothesis, Outcome, Small for gestational age*.

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Most of adult onset cardiovascular diseases and stroke are end result of atherosclerosis; which, contrary to prior belief, begins during fetal life itself [1,2]. The first atherosclerotic lesion begins in the abdominal aorta [3]. Ultrasound based measurement of aortic intima-media thickness (aIMT) is a feasible and accurate marker of atherosclerotic risk [4,5]. Studies in developed countries have demonstrated a difference in aIMT between small for gestational age (SGA) and appropriate for gestational age (AGA) babies but absolute aIMT values are conflicting [6-8]. There is a paucity of data on normative values of aIMT in various birthweight cohorts and data on aIMT values in SGA and AGA babies in Indian population. We conducted this study to correlate aIMT with birthweight in term and near-term babies and compared its value between AGA and SGA babies.

METHODS

This prospective study was conducted at Apollo BGS Hospital, Mysore from December, 2017 to November, 2018, after clearance from institutional ethics committee. After informed parental consent, babies of 35 to 41 weeks gestation were included in this study. Babies with congenital anomalies and babies who were discharged within two days of birth were excluded. Pre-pregnancy weight of mother was obtained from antenatal card. Mother's weight at the time of delivery was recorded using standard electronic weighing machine, and weight gain during pregnancy was calculated. Gestational age was calculated from last menstrual date, if not known, dating scan during first trimester or modified New Ballard scoring of neonates was used to ascertain gestational age. Birthweight was measured using a calibrated electronic weighing machine, and length was measured with an infantometer using standard methodology [9].

Intergrowth-21 charts were used to plot anthropometric details of the baby [10]. Ultrasound examination was done for all the enrolled babies on day 3 of life to measure aortic intima-media thickness. All the ultrasound scans were carried out by a single radiologist who was blinded to birthweight and weight group of the baby. High resolution B mode measurement was performed using linear high-resolution probe of 10-12 MHz at L1-L2 *i.e.* supra renal aorta using Philips HD 11xe ultrasound system (Koninklijke Philips NV). Intima-media thickness was defined as distance from the leading edge of first echogenic line to the second line. The first line represents lumen-intima interface, and second line represents collagen containing upper layer of the adventitia. The image was focused on the dorsal wall of the aorta, and a gain setting was used to optimize image quality.

Statistical analyses: All the data were entered in a Microsoft excel sheet and analyzed using SPSS 22.0. Pearson correlation coefficient was calculated for

continuous variables and ANOVA was used to compare aIMT across different birthweight categories. All the tests of significance were carried out at 5% level of significance.

RESULTS

A total of 200 (94 females) babies were enrolled in the study. Mean (SD) pre-pregnancy weight of the mothers was 55.32 (7.05) kg, mean (SD) height was 158 (4.67) cm and mean (SD) weight gain during pregnancy was 14.12 (2.62) kg. The mean (SD) birth weight of enrolled babies was 2.79 (0.60) kg, mean (SD) length was 48.75 (2.76) cm and mean (SD) head circumference was 33.03 (1.47) cm.

The mean (SD) aIMT observed in our study was 0.43 (0.15) mm. aIMT showed a negative correlation with birthweight and length of the baby with correlation coefficient (*r*) of –0.64 and –0.61 (***Fig.* 1**). However, there was a poor correlation of aIMT with gestational age (*r*= –0.31), maternal weight (*r*= –0.03), maternal height (*r* = –0.12) and weight gain during pregnancy (*r*= –0.29). There was no significant difference in mean (SD) aIMT in male and female babies [0.45 (0.16) and 0.43 (0.14)].

Value of aIMT was significantly more in SGA babies than their AGA counterparts (***Table* I**). For every given gestation, SGA babies had significantly higher aIMT than AGA babies (***Table* II**).

DISCUSSION

In this study, we enrolled 200 healthy neonates of 35-41 weeks of gestation and aIMT was measured on dorsal wall of aorta between L1-L2, and this was correlated with birth weight. aIMT was higher in babies with lower birth weight irrespective of gestational age. Similar correlation was found between length and aIMT. SGA babies in our study had significantly higher aIMT than their AGA counterparts. Mean aIMT value was fairly static across gestation age of 35-41 weeks within SGA and AGA categories.

Table I Aortic Intima-Media Thickness in Different Birthweight Groups (*N*=200)

	AGA (n=136)	*SGA (n=54)*	*LGA (n=10)*
Birthweight, kg	2.99 (0.35)	2.07 (0.36)	3.91 (0.37)
Gestational age, wk	38.2 (1.3)	37.3 (1.5)	38.9 (1.1)
aIMT,* mm	0.36 (0.08)	0.64 (0.11)	0.36 (0.08)

Values in mean (SD); *aIMT*: *aortic intima media thickness; *P<0.001; AGA: appropriate for gestational age; SGA: small for gestational age; LGA: large for gestational age.*

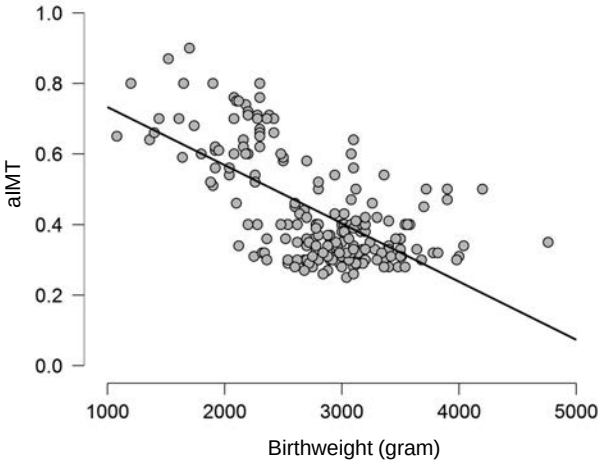

Fig. 1 *Scatter diagram of correlation of aortic intima-media thickness (aIMT)*

We had a relatively large sample size, and all the aIMT measurements were done by a single radiologist blinded to birthweight cohort, hence eliminating the possibility of any inter observer variation. However, we did not look into risk factors for SGA and possible differential effect of these risk factors on aIMT.

Our value of mean aIMT of 0.44 mm is comparable to the data reported from India [11,12]. AGA babies in our study had a mean aIMT of 0.36 mm which is lower compared to most of other reported values, and SGA babies had a mean aIMT of 0.64 mm which is higher than most other values reported from the Western population [1,6,7]. This difference could be either due to racial variation, or due to different nutritional and medical illness profile in Indian mothers.

Even though, aIMT has been investigated in newborn period, the natural history of these lesions and possible reversibility of these lesions has never been evaluated. Long term follow up of these babies for confirming evolution of these lesions into atherosclerotic plaques is needed.

Table II Aortic Intima-Media Thickness among Infants With Different Gestational Age (*N*=200)

Gestational age	*Aortic intima-media thickness, mm*			
	*AGA**		*SGA*	
	n	*mean (SD)*	*n*	*mean (SD)*
35-36 wk	16	0.41 (0.13)	17	0.66 (0.11)
37-38 wk	59	0.35 (0.07)	23	0.64 (0.12)
39-40 wk	61	0.36 (0.08)	14	0.62 (0.1)

AGA: *appropriate for gestational age; SGA: small for gestational age; P<0.001 for aortic intima-media thickness between SGA and AGA babies in different gestational age groups; *P=0.03 for comparison between different gestational age groups among AGA babies.*

WHAT THIS STUDY ADDS?

A negative correlation exists between birthweight and aortic intima-media thickness, with small for gestational age babies exhibiting higher values than appropriate for gestational age counterparts

Ethical clearance: Institutional ethics committee, Apollo BGS hospital; No. 11/2018. April 21, 2018.
Contributors: RD, VV, GG: formulated the study, drafted the protocol and involved in final writing of the article; RD, GG: collected and analyzed the data; VV: did the sonographic measurement of all cases.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Urinary Intestinal Fatty Acid Binding Protein for Diagnosis of Necrotizing Enterocolitis

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Objective: This study was conducted to compare the urinary levels of intestinal fatty acid binding protein (I-FABP) and I-FABP: Cr (creatinine) between neonates with necrotising enterocolitis and gestation matched healthy controls. **Methods:** 24 neonates with stage 1, 25 with stage 2 and 3 necrotizing enterocolitis, and 25 gestation matched (32.9 wk) controls were compared. Single spot urine sample was collected for estimating the IFABP and creatinine levels. **Results**: Median (IQR) value of urinary I-FABP were higher in those with stage 2, 3 NEC [2773 (2417.7- 2820)] than stage 1 NEC [1164 pg/mL (1341.5 – 2213.4)] and controls [413 (113 – 729.7); pg/mL] (P<0.001). Urinary I-FABP: Cr levels of 3.6 pg/mmoL had a sensitivity and specificity of 96% and 99.5%, respectively in diagnosing stage 2/3 NEC. **Conclusion**: Urinary IFABP: Creatine ratio of 3.6 pg/mmoL is highly specific for stage 2 and 3 NEC.

Key words: *Diagnostic marker, Necrotizing enterocolitis. Newborn, Bell criteria, Preterm*

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Necrotizing enterocolitis (NEC) has a reported incidence of 5-10% in very low birth weight babies [1]. Clinical signs and abdominal *X*-ray in early stages are nonspecific, resulting in a diagnostic challenge.

Intestinal fatty acid binding protein (I-FABP) is a sensitive and specific biochemical marker for NEC [2-5]. I-FABP is an intestinal mucosal protein, which escapes into circulation upon enterocyte injury in trauma, infection or ischemia [7-9]. It gets filtered into urine which can be measured to compare the urinary levels of I-FABP and I-FABP clearance between neonates with suspected NEC and gestation matched controls.

METHODS

This study was conducted in a tertiary care unit in India between February, 2015 and December, 2016. Both preterm and term babies with NEC as per modified Bell's criteria were included as cases. Asymptomatic babies with corrected gestational age within 3 days of the cases formed the control group. Babies with surgical problems and cyanotic heart disease were excluded.

Cases were recruited separately in two groups, suspected (stage 1) NEC and established (stage 2 and 3) NEC, for a single control. This study was approved by institutional ethics board. Informed written consent was taken from the parents prior to obtaining urine sample.

Five milliliters of urine sample was collected within 12 hours of diagnosis and stored after centrifugation at –80°C under sterile condition. Sample from an appropriate control was collected and similarly stored. Human I-FABP was quantified using commercially available enzyme linked immunosorbent assay (ELISA) (Hycult Biotech, the Netherlands). Urinary creatinine (Cr) was measured at the same time for estimation of I-FABP: Cr. The incidence of NEC in our unit was 3.7%. Considering specificity of 94% and alpha error of 5%, a total of 75 subjects were needed.

Statistical analysis: Statistical analysis was done using Microsoft Excel 2016 and Analyse-it v4.65.2. Kruskal Wallis test was used to compare the medians and chi-square for proportions. ROC curve was plotted to calculate the sensitivity and specificity of the test.

RESULTS

A total of 74 babies (25 control group, 24 with suspected NEC group and 25 with established NEC) were recruited. Two babies were of 38 weeks gestation and rest were preterms. The baseline characteristics are depicted in ***Table* I**. Ten babies (6 with established NEC) received CPAP/ventilator support and none had birth asphyxia.

Median (IQR) urinary I-FABP value and urinary IFABP: Cr in various groups is depicted in ***Table* II**. Urinary IFABP value of 900 pg/mL had a sensitivity of

WHAT THIS STUDY ADDS

- Raised urinary intestinal fatty acid binding protein (I-FABP) and I-FABP: Creatinine ratio are sensitive and specific for the diagnosis of necrotizing enterocolitis in neonates.

Table I Baseline Characteristics of the Study Population

	Control (n=25)	*Suspected NEC (n=24)*	*NEC stage 2 or 3(n=25)*
#Gestation (wk)	32.9 (2.3)	32.8 (2.3)	32.9 (2.3)
*Birthweight (kg)	1.7 (1.45-1.9)	1.56 (1.36-1.89)	1.54 (1.17-1.81)
Male, *n* (%)	14 (56)	13 (54.2)	18 (72)
Breast milk	23 (92)	24 (100)	24 (96)
Normal delivery	9 (36)	6 (25)	9 (36)

*P>0.05 for all inter-group comparisons; All values in no. (%) except #mean (SD) *median (IQR).*

91.8% and specificity of 92% in diagnosing stage 1 NEC and a value of 1800pg/mL had a sensitivity of 88% and specificity of 82% in diagnosing stage 2 and stage 3 NEC.

Urinary I-FABP: Cr ratio of 2.1pg/mL had a sensitivity of 83.3% (95% CI 66.4, 95.3%) and specificity of 96% (95% CI 87, 99.8%) for the diagnosis of stage 1 NEC. True positive rate, true negative rate, positive likelihood ratio and negative likelihood ratio were 91.8% (79.5-97.3%), 96% (77%-99.7%), 11.3 (4.4-28.9), 0.04(0.006-0.28), respectively. A higher ratio of 3.6 pg/mmoL had a sensitivity of 96% (95% CI 69.7, 97%) and specificity of 99.5% (95% CI 87.2, 99.8%) for diagnosis of stage 2 and 3 NEC; area under the curve was 0.99%. True positive rate, true negative rate, positive likelihood ratio and negative likelihood ratio were 96% (77.6-99.7%), 93.8% (82-98.4%), 24 (3.5-164), 0.06 (0.02-0.19), respectively.

DISCUSSION

A reliable marker for intestinal injury can be helpful in clinically challenging situations. Our study showed a significant increase in urinary excretion of I-FABP in babies with NEC.

Several earlier studies have shown that both plasma and urinary I-FABP are useful markers in neonatal NEC [8-13]. Serial urinary and plasma IFABP values predicted the progression and complication within 8 to 16 hours after onset of symptoms, and the highest level was seen by 24 hours [8]. Neonates with higher baseline values had developed NEC unlike others with lower values [11].

Urine I-FABP levels were also found specifically elevated in NEC and not in sepsis [14]. A urinary IFABP value of 1000 pg/mL was found to have a sensitivity of 100% and specificity of 83% for diagnosis of bowel ischemia [15], similar to our study.

Earlier studies have reported cut-off values of IFABP: Cr ratio ranging from 2 to 5 pg/mmoL for diagnosis of NEC [19,14]. The variations in cut-off values is due to different priorities regarding sensitivity and specificity, and the sample size. Our study showed high specificity, and has good sensitivity for urine IFABP: Cr level of 3.6 pg/mmoL for stage 2 and 3 NEC. As diagnostic tests are done on clinical suspicion, even if the pre test probability is about 50%, the post test probability would be greater than 98%.

The present study did not prospectively collect data with regard to respiratory support, sepsis or asphyxia, which may be considered as a study limitation.

To conclude, urinary I-FABP is significantly elevated in neonates with NEC. Urinary I-FABP: Creatine ratio performed better than urinary I-FABP alone for diagnosis of NEC and can serve as a quantitative marker for assessment of severity of the illness.

Contributors: Contributors: AS: recruited the subjects, collected the data, carried out literature review and prepared the initial draft of manuscript; DD: conducted the biochemical test and contributed to manuscript writing; SMD: conceived and designed the study, analyzed the data, and finalized the manuscript. All authors have approved the manuscript submitted.

Table II Urinary I-FABP levels and I-FABP: Creatinine in Neonates with Necrotizing Enterocolitis (*N*=74)

	Control (n=25)	*Suspected NEC stage 1(n=24)*	*NEC 2 or 3 (n=25)*
Urinary IFABP, pg/mL	413 (113-729.7)	1164 (1341.5-2213.4)	2773 (2471.7-2820)
Urinary IFABP: Creatine, pg/mmoL	1.23 (0.56-1.57)	2.78 (2.32-3.36)	4.84 (4.67-5.34)

Data in median (IQR); I-FABP: intestinal fatty acid bindings protein; data in median (IQR); P<0.001 for inter group comparisons.

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RESEARCH PAPER

Pharmaceutical Excipient Exposure in a Neonatal Intensive Care Unit

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Objective: To study the excipients exposure among neonates in a neonatal intensive care unit. **Method:** Prospective observational study was conducted from January, 2017 to June, 2019**.** Details of administered drugs were collected from the hospital case files. List of excipients of formulations and their quantities were collected from package insert leaflets or by contacting the manufacturers. Excipients were grouped into four categories based on available safety data. Calculated daily exposures to the excipients (mg/kg/day) were compared with adult acceptable daily intake. **Results:** More than half of the included 746 neonates were exposed to harmful excipients. 12.3% and 12.7% of neonates received higher than acceptable daily intake of sodium metabisulphite and sunset yellow FCF, respectively. **Conclusion:** There is a high risk of exposure of neonates to harmful excipients, and clinicians need to be aware of this during neonatal care.

Keywords: *Additives, Harm, Medications, Sodium metabisulphite*.

Excipients play a major role in converting medicinal agents to acceptable dosage forms [1]. Neonates are a vulnerable population and their drug handling, pharmacokinetic and pharmacodynamic aspects are different from older children. Neonates may be exposed to risks and unwanted effects of excipients when they are administered drug formulations. The reason could be immature physio-logical functions leading to inadequate metabolism and excretion of such excipients from body [2-4].

In the 1980s, ten neonatal gasping syndrome and death were reported in a study as a result of toxicity of benzyl alcohol (preservative) used in intravenous solutions [5]. Parabens, ethanol and propylene glycol are other examples of excipients having harmful effects in neonates [1]. Therefore, this study was conducted to assess types and amount of exposure to excipients among neonates in neonatal intensive care unit (NICU).

METHODS

This prospective observational study was conducted in the NICU of a tertiary care teaching hospital in Bangalore for duration of 2.5 years (January, 2017 to June, 2019) after approval from institutional human ethics committee. Valid consent was given by the parents/guardians of included study subjects who received at least one drug. Neonates dying within 24 hours of birth were excluded. Demographic details (gestational age, birthweight, gender, date of birth, post natal age), length of stay, daily clinical progress of neonates, information about prescribed medicines for all neonates (indication, dose, frequency, route of administration, dosage form and brand names) were recorded. Diagnoses were classified according to ICD-10 (International statistical classification of diseases and related health problems, 10th revision, 2016). Administered drugs were classified according to WHO Anatomical Therapeutic and Chemical (ATC) classification system.

Lists of excipients and their quantities present in each prescribed formulation were collected by referring to package insert leaflets (PIL) of drugs or contacting the manufacturers. Excipients were categorized into four groups as per Lass, *et al.* [1] *viz.*, (*a*) known to be harmful to neonates (adverse reactions reported in neonates); (*b*) potentially harmful (adverse reactions reported); (*c*) no safety data found (no data found in the literature on human exposure and toxicity); and (*d*) description of the excipient in PIL non-specific (description does not allow a specific literature search).

Statistical analyses: Daily exposure to excipients (mg/kg/day) were calculated based on available data on quantity of excipients in formulations, and were compared with acceptable daily intake (ADI) [6-8] for those which data of ADI was available.

RESULTS

Of the 790 cases admitted to NICU during the study period, 41 were excluded as they had received only phototherapy (no medications), and 3 babies died within 24 hours of birth. The baseline characteristics of 746 included neonates

are described in ***Table* I**. The most frequent diagnoses were respiratory distress of newborn, neonatal sepsis and congenital heart disease.

The total number of prescribed drugs was 5535, and 77 different drugs were given. Systemic anti-infectives, blood and blood forming organs, and alimentary tract and metabolism class were the most commonly prescribed classes of drugs. Intravenous (49, 63.6%) and oral (18, 23.3%) were the most common routes of administration.

The qualitative and quantitative information on excipients were available only for 35 and 15 drugs, respectively. Total of 27 different excipients were identified. Of all excipients, 4 (14.8%) and 10 (37%) were grouped under category a and category b, respectively. These excipients were present in 26% (20/77) of prescribed formulations, details of which, including safety concerns [1,6,9], are given in ***Table* III**. It was found that the highest proportion of above mentioned excipient were present in systemic anti-infectives.

Emulsifier 472 C was the only identified excipient of category c. Remaining excipients (8, 29.6%) including yellow and red oxides of iron, caramel colour and flavours were classified under category d. Daily exposure to excipients of 8 injections (vitamin K, adrenaline, amikacin, gentamicin, dexamethasone, heparin, midazolam and ranitidine), oxymetazoline hydrochloride nasal solution and paracetamol syrup were assessed and compared to ADI (***table* II**).

Table I Characteristics of Neonates (*N*=746)

Characteristics	*Value*
Male sex	424 (56.8)
Inborn babies	576 (77.2)
Gestational age, wk	
Term (≥37)	408 (54.7)
Moderate to late preterm (32 to <37)	274 (36.7)
Very preterm (28 to <32)	55 (7.4)
Extremely preterm (<28)	9 (1.2)
**Length of stay, d*	
Term	5.7 (0.91)
Moderate to late preterm	8.4 (0.80)
Very preterm	19.27 (4.90)
Extremely preterm	27.33 (4.16)
*Birthweight, g	2480 (700)

*All values in n (%) except *mean (SD).*

DISCUSSION

This study on qualitative and quantitative excipient exposure among hospitalized neonates in India found that 86.9% and 53.8% of neonates were exposed to at least one excipient known to be harmful or potentially harmful, respectively. Previous studies conducted in Brazil and Estonia found that almost all neonates were prescribed drugs containing at least one harmful excipient [1,3]. We found that harmful and potentially harmful excipients were present in formulations that were administered frequently and simultaneously. Hence neonates could be at greater risk of toxic effects. Similarly, Fister, *et al*. [10] reported that 51.6% of added excipients in formulations were potentially harmful and harmful ones.

Coloring agents (ponceau 4R, sunset yellow FCF, erythrosine and titanium dioxide) present in oral dosage forms were included in potentially harmful category. Regulatory status on colorants in different countries are not similar; in the European union, medicines containing sunset yellow and ponceau 4R must carry warning label concerning possible allergic reactions [6]. In our study, Ponceau 4R was most frequently observed colorant, though its use is banned in some countries due to its effect on neurocognitive development and behavior [2].

The use of category a or b excipients in intravenous/ oral formulations was much lesser in our study than findings of Lass, *et al*. [1]. However, in another study carried out in Spain [11], 32% of intravenous formulations

Table II Amount of Exposure to Excipients in Neonates (*N*=746)*

Excipient	*Adult ADI [6-8]*	*Daily dose exposure range*	*Comparison with adult ADI*
Sodium metabisulphite	0.7 mg/kg/d	0.09-2.1 mg/kg/d	‡Higher than ADI
Benzalkonium chloride	0.1 mg/kg/d	0.02-0.09 mg/kg/d	Within ADI range
Methyl paraben	10 mg/kg/d	0.03-1 mg/kg/d	Within ADI range
Propyl paraben	10 mg/kg/d	0.0003-0.09 mg/kg/d	Within ADI range
#Benzyl alcohol	5 mg/kg/d	0.016-1.3 mg/kg/d	Within ADI range
Phenol	<50 mg in 10 h period	0.1-0.8 mg in 12 h	Within ADI range
Sunset yellow FCF	2.5 mg/kg/d	0.3-4.2 mg/kg/d	^Higher than ADI

**Based on available data on quantity of excipients present in drugs; ADI: Acceptable daily intake; #should not be used in neonates; ‡12.3 % of exposures with use of adrenaline injection; ^12.7 % of exposures with use of paracetamol syrup.*

Table III Classification of Excipients to Which Neonates were Exposed*

Excipient category	*Functional category*	*Safety concern*	*Formulations containing excipients*
Known to be harmful to neonates			
Methyl paraben, *n*=713	Antimicrobial preservative	Hyperbilirubinemia in neonates, hypersensitivity reactions	Amikacin inj (*n*=405); Gentamicin inj (*n*=235); Dexamethasone inj (*n*=73)
Propyl paraben, *n*=713	Antimicrobial preservative	Hyperbilirubinemia in neonates, hypersensitivity reactions	Amikacin inj (*n*=405); Gentamicin inj (*n*=235); Dexamethasone inj (*n*=73)
Benzyl alcohol, *n*=108	Antimicrobial preservative, solvent	Fatal toxic syndrome in premature infants, metabolic acidosis, hypersensitivity, seizure, gasping	Heparin inj (*n*=93); Midazolam inj (*n*=15)
Benzalkonium chloride, *n*=5	Antimicrobial preservative, solvent	Skin irritation and hypersensitivity broncho-constriction in asthmatics	Oxymetazoline hydrochloride nasal solution
Potentially harmful			
Sodium metabisulphite, *n*=236	Antimicrobial preservative, antioxidant	Paradoxical bronchospasm, wheezing, chest tightness in asthmatic children	Adrenaline inj (*n*=74); Vitamin K inj (*n*=162)
Sodium carbonate, *n*=202	Alkalizing agent, buffering agent	Irritation to skin, eye, mucous membrane	Meropenem inj (*n*=202)
Sunset yellow FCF, *n*=74	Coloring agent	Anaphylactoid reactions, urticaria, angioedema	Paracetamol syp (*n*=71) Ibuprofen and paracetamol syp (*n*=3)
Ponceau 4R, *n*=114	Coloring agent	Anaphylactoid reactions, urticaria, angioedema	Domperidone susp
Phenol, *n*=188	Antimicrobial preservative, disinfectant	Hyperbilirubinemia, nephrotoxicity, anemia and may result in death	Ranitidine inj
Sodium bicarbonate, *n*=55	Alkalizing agent	Exacerbation of chronic heart failure in elderly, skin and eye irritant	Imipenem and cilastatin injection
Sodium deoxycholate, *n*=19	Detergent	Bradycardia, jaundice, lysis of red and white blood cells	Amphotericin B inj
Titanium dioxide, *n*=21	Coating agent, opacifier, pigment	Possibly carcinogenic	Sildenafil tablet (*n*=11); Paracetamol suppository (*n*=9); Clarithromycin granules for susp (*n*=1)
Erythrosine, *n*=67	Coloring agent	Concerns about carcinogenicity, toxic to human lymphocytes *in vitro*	Vitamin D and calcium syp (*n*=67)
Calcium chloride, *n*=44	Antimicrobial preservative, water absorbing agent	Stomach and heart disturbance, dermatitis	Lung surfactant

**According to available safety data [1,6,9]; Inj-injection; Susp-suspension; Syp-syrup.*

and 62% of oral formulations contained at least one harmful excipient. These differences can be explained by the availability of information of excipients present in formulations in different countries. We found high rates of exposure (higher than ADI) to sodium metabisulphite and sunset yellow FCF. Similar findings were reported by Akinmboni, *et al*. [12] that 11% of neonates were exposed to a higher amount of an excipient than the FDA/WHO recommended adult dose.

Daily exposure to phenol (in ranitidine injection) was within the adult ADI range. However, literatures show that use of ranitidine in very low birth weight neonates can increase incidence of necrotizing enterocolitis, mortality and infection [13]. Safety concern regarding use of ranitidine was reported to the neonatologist. Daily exposure to benzyl alcohol did not exceed the adult ADI. However, as per FDA recommendation and label of the heparin injection, benzyl alcohol containing formulations

WHAT THIS STUDY ADDS?

- It is advisable that excipient exposure be assessed while selecting medicinal formulations for neonates.

should not be used for neonates and premature infants due to risk of fatal toxic syndrome in neonates [6,14-16]. Unfortunately, 14.5% of neonates were exposed to benzyl alcohol containing formulations. For 12.5% of exposures, alternative preservative free formulation with the same concentration of heparin sodium injection and similar cost was available, which were suggested to the neonatologist. Another study conducted in Netherlands showed that oral liquid medicines without potentially harmful excipient were available for 22% of medicines [17].

An important limitation of the present study was the lack of data on neonatal ADI of excipients due to barriers to conduct such studies. Another limitation was lack of information about list of excipients and their quantities present in each formulation. So, we could not assess the extent of exposure to all excipients of formulations. However, our findings with limited available data show that exposure to harmful excipients is high, and awareness regarding their risks needs to be raised.

Substitution of those medications with excipient (harmful) free formulations, at least in high risk conditions, will avoid unwanted risks. It is also important that manufacturers disclose detailed qualitative and quantitative information of excipients of formulations to clinicians and clinical pharmacists, for risk/benefit assessment of selection of drugs for neonates.

Ethical clearance: VIPS Human Ethics Committee; IEC/2016-14 dated December 09, 2016.
Contributors: SN: collected the data, analyzed the data and wrote the manuscript; NKM: designed, monitored and supervised the study and approved the final manuscript; SB: was the neonatologist who co-supervised the study.
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RESEARCH PAPER

Use of Point of Care Ultrasound for Confirming Central Line Tip Position in Neonates

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Objective: To assess feasibility of ultrasound (USG) evaluation of tip position of central catheter in neonates and to determine agreement between radiograph and USG-based assessments. **Methods:** This prospective observational study was conducted in a tertiary neonatal intensive care unit from April, 2019 to August, 2019. Point of care USG and radiograph were performed on infants who underwent central line placement. Agreement between the two was determined using Kappa statistics. **Results:** Of the 141 central catheters insertions performed, USG was performed for 65 central catheters. On USG, catheter tip position could be assessed and defined in 62 (95%) of cases. Of these 62 central lines, 24 (38.7%) were defined as optimally placed on radiograph and 20 (32.2%) were defined as optimally placed on USG. There was excellent agreement between radiographic and USG assessment of catheter tip position [K (95% CI) = 0.86 (0.73-0.99), *P* <0.001]. All 38 lines found to be mal-positioned on radiograph were assessed as sub-optimal on USG as well. **Conclusion**: Point of care USG has excellent agreement with radiography for confirming central line tip position.

Keywords: *Bedside*, *Central catheters, Long line, Radiograph*.

Trial Registration: CTRI/2019/01/017282

Preterm infants and sick, term infants frequently require central venous or arterial canulation. However, central lines are advanced blindly to a predetermined length based on an external anatomic measurement of the estimated catheter pathway. Optimality of catheter tip position is confirmed with chest or abdominal radiographs. Frequently, position of these catheters may be sub-optimal, necessitating manipulation of catheters followed by further radiographs for reconfirmation [1]. This involves handling of critically ill infants, and carries a significant risk of dislodgement of lines, radiation exposure and unacceptable delay in confirmation of central catheter position.

Point of care ultrasound (USG) is an emerging bedside tool in management of sick neonates. It may be used to locate catheter position during and immediately after procedure, reducing the time lag and radiation exposure. Whereas few studies [2] in the past have evaluated the utility of USG in locating umbilical catheters, there is re-emergence of interest amongst neonatologists to evaluate the tip position of various central catheters in neonates [3-7]. We conducted this study to determine the agreement between radiological and USG-based assessment of central line tip position.

METHODS

This was a prospective observational study conducted at the neonatal intensive care unit of a tertiary care centre in India from April, 2019 to August, 2019. All infants admitted to the NICU who underwent central line placement were eligible for enrolment. A written informed consent was obtained from parents of eligible infants. Central catheters [umbilical arterial and venous catheter (UAC, UVC), peripherally inserted central venous catheter (PICC) and femoral venous catheter] were placed by the attending neonatologist using standard techniques. The length of insertion for PICC in the upper and lower limb was measured from point of insertion along the venous pathway till suprasternal notch to right third intercostal space and till level of xiphisternum, respectively. For UAC and UVC insertion, Dunn shoulder umbilical length normogram was used [8]. After placement of central catheter, USG assessment of position of catheter tip was done by a neonatologist, trained in ultrasound. A radiograph was also performed to assess catheter position as the standard of care. The ultrasonologist was blinded to the radiological findings.

Ultrasound was done using Sonosite M Turbo

machine with curvilinear probe with frequency of 8-4 MHz. A sub-xiphoid right parasagittal view was used to assess tip position of UVC, femoral venous lines and lower limb PICC, with additional complementary windows (long axis, apical, modified views) as needed. Once inferior vena cava (IVC) was visualized, probe head was moved back and forth, until catheter tip was clearly seen. For visualization of UAC, a sub-xiphoid left parasagital view, high parasternal view and suprasternal view were used with similar approach. Tip position of upper limb PICC was assessed using the high parasternal view. If catheter tip was not visible using standard techniques, 0.5-1 mL of normal saline was flushed through catheter to locate the tip, which was seen as a point of origin of jet. Optimal position for UVC, femoral venous catheter, and PICC inserted through lower limb, was defined as catheter tip at IVC/right atrium (RA) junction or 0.5-1 cm proximal to it. For PICC inserted through upper limb, optimal position was defined as catheter tip at superior vena cava (SVC)/RA junction or 0.5-1 cm proximal to it. For UAC, optimal position was defined as catheter tip located in lower half of thorax, between diaphragm below and aortic isthmus above.

On radiograph, UVC, femoral venous line and lower limb PICC catheter position was considered optimal if tip was at the level of diaphragm or slightly above, or at level of vertebral bodies T8-T9 [9,10]. For upper limb PICC, catheter position was considered optimal, if tip was found to be vertically within the SVC within 1-2 vertebral units below the carina [11]. An UAC was said to be optimal if catheter tip was located in thoracic aorta at vertebral bodies T7 and T9 [3]. Radiograph was ordered immediately after insertion of central catheters to confirm tip position and USG was initiated as per method described above. Time elapsed between completion of central line insertion to completion of USG and to availability of *X*-ray film was noted.

For a disagreement of 10% between the two methods, as reported in a recent study [6], alpha error of 0.01 and power of 80%, the sample size was estimated to be 60.

Statistical analyses: Statistical analyses were performed using SPSS version 19. Catheter tip position was defined as optimal or suboptimal, both on USG and *X*-ray, as per predefined criteria. Agreement between USG and *X*-ray defined tip positions was determined using kappa statistics. A *P* value <0.05 was considered significant.

RESULTS

Of the 141 central catheters insertions performed during the study period, USG was performed for 65 central catheters (refusal of consent in 13, and investigator not available in 63). On USG, catheter tip position could be assessed and defined in 62 (95%) of cases. In three neonates, central lines (2 PICC and 1 UV) were misplaced at aberrant locations and not visualized on USG. Of the 62 catheters, 25 were PICC, 4 were femoral venous catheters, 16 were UVC and 17 were UAC.

The median (IQR) gestation and weight of the enrolled infants were 28 (26, 34.2) weeks and 1060 (860, 2120) g, respectively. Twenty four (38.7%) central lines were defined as optimally placed on radiograph and 20 (32.2%) were defined as optimally placed on USG. There was excellent agreement between radiographic and USG assessment of catheter tip position [K (95% CI) = 0.86 (0.73 – 0.99); *P*<0.001] (***Table* I**). All 38 lines found to be mal-positioned on radiograph were assessed as sub-optimal on USG as well. Four lines, 3 PICC and 1 UVC, which were deemed to be optimal on radiograph were detected to be suboptimal on USG, all entering RA. The mean (SD) time from completion of central line insertion to completion of USG was less than time required for obtaining *X*-ray film [6.11 (2.7) min *vs* 122.46 (45.45) min; MD (95% CI) -116.35 (-128.11 to -104.58); *P* <0.001].

DISCUSSION

In this study, we could identify catheter tip position in 95% of cases and there was excellent agreement between USG and *X*-ray for optimal catheter tip position. In three cases, catheter tip was not visualized as it was mal-positioned in aberrant pathways, two in the neck veins both being upper limb PICC lines and one UV being coiled in the liver. Till date, few studies have reported utility of USG for placement of central catheter in neonates. Ohki, *et al*. [12] assessed the ability of USG to detect the tip of a percutaneous central venous catheter in neonates and reported a consistency of 87% between USG and radiography. Simanovsky, *et al*. [13] measured the distance of UVC tip from the diaphragm on USG and *X*-ray and reported no significant difference in the distance measured by using the two modalities. Greenberg, *et al*. [2] also demonstrated feasibility and safety of USG for assessment of umbilical venous catheter position. Other authors have also suggested high agreement coefficients between point of care USG and *X*-ray with respect to overall central venous tip, UVCs and PICCs [14,15].

Although radiograph is considered a gold standard for defining optimal tip position, it has certain limitations. It is difficult to precisely identify junction of RA to IVC or SVC on plain *X*-ray, which could lead to misinterpretation of correct tip position. We found that 4/24 (16.6%) central lines that were deemed to be appropriate on radiograph were actually lying inside the cardiac chambers on USG

WHAT THIS STUDY ADDS?

- Point of care ultrasound and radiograph have excellent agreement in confirmation of central line tip position in neonates.

assessment. Tauzin, *et al*. [5] have also described limitation of *X*-ray assessment for PICCs in low birth neonates. They reported that, of all PICCs deemed to be in good position on plain radiographs, 25% were within the heart [5]. Similarly, another small study found that 41% of PICC lines that were deemed to be correctly placed on *X*-ray were found to be malpositioned on USG [4].

Our study evaluated degree of agreement between USG and radiograph in locating the tip position of different central lines across wide range of weights and gestation. All USGs were performed by a single trained operator. We, therefore, emphasize that USG is a skill-based operator dependent technology and competency training is required before non-radiology users can evaluate central line tip positions at various locations. Sometimes examiners may find it difficult to visualize catheter tips within the liver, outside of IVC or SVC, especially if they are in aberrant pathways. The limitation that point of care ultrasound is performed for specific clinical purpose to answer a clinical question, and it may not mandate a detailed comprehensive examination is also acknowledged.

Ethical Clearance: Ethics Committee, Sir Ganga Ram Hospital; EC/12/18/1454, dated December 18, 2018.
Contributors: AT: conceptualized the project and developed the protocol; AT: had primary responsibility of patient screening, enrolment and data collection; AT: performed the data analysis; AT,VK: wrote the manuscript; NK, PG: participated in protocol development, supervising enrolment, outcome assessment and in writing the manuscript; AT, MM: participated in planning of project and writing of manuscript.
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RESEARCH PAPER

Epidemiology and Clinical Features of Coronavirus Disease 2019 in Moroccan Children

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Objectives: This study aims to analyze the epidemiological and clinical features of coronavirus disease 19 (COVID-19) in a Moroccan pediatric population. **Methods**: A retrospective study of a cohort of 74 children with RT-PCR confirmed COVID-19. We collected information on clinical and laboratory features of all children (age <18 years) admitted between 2 March, 2020 and 1 April, 2020. **Results**: The mean (SD) age of the 74 children (40 girls) was 7 (1.5) years. The mean (SD) time from illness onset to diagnosis was 2 (1) days. 54 children were asymptomatic, while eight had fever, and five cases had cough. Recovery was after a mean (SD) of 12 (1) days. **Conclusions**: COVID-19 was mostly mild in the pediatric population in Morocco.

Keywords: *Outcome, Pandemic, RT-PCR, SARS-CoV-2.*

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Emergence of coronavirus disease 2019 (COVID-19) has attracted global attention, and the WHO has declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as a pandemic. As of May 25, 2020, a total of 7756 cases, which 9% of them are children, occurred in Morocco [1]. Worldwide, it has been reported that the disease is mostly asymptomatic, or mild-moderate in nature in children [2-4]. To date, not much information is available about COVID-19 in Moroccan pediatric population. Our study aims to detail clinical features and outcome in Moroccan children infected with SARS-CoV-2 virus.

METHODS

We retrospectively reviewed records of 74 children confirmed with SARS-COV-2, who were managed in Mohammad VI university hospital of Marrakesh from March 2, 2020, to April 1, 2020. The ethics committee of our hospital approved this study. COVID-19 pediatric cases were defined as follows: Possible case: when a history of contact with a confirmed case of SARS-COV-2, and/or an acute respiratory infection of unknown etiology are present; and confirmation of infection was obtained from all patients at admission by detection of SARS-COV-2 nucleic acid on nasopharyngeal swab specimens using RT-PCR.

All confirmed COVID-19 cases <18 years were included except from newborns. Parents or guardians of all participants provided informed consent enrolled in this study. We collected data regarding epidemiological, demographical, clinical symptoms, laboratory measurements, imaging findings, management, and outcome. Laboratory workup carried out in all patients at diagnosis included complete blood count, CRP, procalcitonin, urea, creatinine, AST, ALT, PTT, aPTT, D-Dimer, ferritin, LDH, CPK, fibrinogen, and serum electrolytes. Computed tomography (CT) scan was done in those with severe manifestations. Patients were classified as follows: Asymptomatic infection (children without manifestations of clinical symptoms of COVID-19 testing positive to SARS-COV-2); Acute upper respiratory tract infection (children with fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia or discomfort, and without signs of pneumonia by chest imaging or sepsis); Mild pneumonia (when children have a fever, respiratory symptoms such as cough, and chest imaging indicating pneumonia, but not reaching the criteria of severe pneumonia); Severe pneumonia (when any of the following criteria are present: (*i*) increased respiratory rate: ≥60 breaths/min (<2 years), ≥40 breaths/min (between 2 and 5 years), ≥30 breaths/min (≥5 years); (*ii*) oxygen saturation <94%; (*iii*) hypoxia; (*iv*) disturbance of consciousness; and, (*v*) food refusal or feeding difficulty, with signs of dehydration);

and, Critical cases (who meet any of the following criteria and require ICU care: respiratory failure requiring mechanical ventilation, shock, or with other organ failure).

Treatment was prescribed according to the Moroccan Ministry of Health recommendations [5]. RT-PCR tests were done on the ninth, 14th, 21st, and 28th days from diagnosis. Recovery was declared when there was clinical improvement, child was afebrile for more than three days, and at least one negative RT-PCR result was obtained. All statistical data were processed using the Excel professional 2016 software.

RESULTS

Out of 74 children with confirmed COVID-19 included in our study, 34 (46%) were boys. The median age was 7 years (range, 2 month – 17 year). Medical history was marked by two cases of mild intermittent asthma, one case of type 1 diabetes, one case of epilepsy, and one case of Down syndrome with intraventricular shunt. All the cases exhibited familial aggregation and had a history of close contact with their adult relatives who were diagnosed with COVID-19, except for one child who contacted the disease from a housemaid, and a second one who contacted from a neighbor. All our patients had satisfactory nutritional state, as well as normal growth parameters.

Fifty-four (73%) children were asymptomatic. The remaining twenty patients had mild symptoms (***Fig***. **1**), mainly symptoms of flu, with a mean (SD) time from illness onset to diagnoses of 2 (0.5) days. Most frequent signs were fever (10.8%), cough (6.7%), rhinorrhea (6.7%), and diarrhea (5.4%). Hematological abnor-malities were marked by lymphocytosis in 8% of cases, while the rest were characterized by high creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and mild hepatic transaminitis (<1.5 times normal) (***Table* I**).

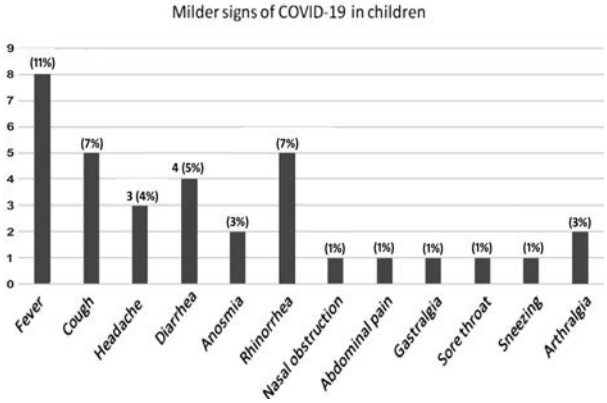

Fig. 1 *Symptoms in children with confirmed COVID-19.*

Management consisted of supportive care: hydration, antipyretics and nutritional support. The 15-year-old girl was started on chloroquine 5 mg/kg/12h for five days (after documenting a normal electrocardiogram) with azithromycin (10 mg/kg the first day; then 5 mg/kg/day for five days) along with vitamin C (1g twice a day for ten days) and zinc (90 mg twice a day for ten days). By the third day, evolution was marked by severe side effects (diplopia, nausea, epigastric pain), when we switched to hydroxychloroquine (5 mg/kg/12h to complete a total of ten days). Subsequently, improvement was noted and no new side effects were seen. Breastfeeding was maintained in a two-months-old infant while respecting airborne and contact protection measures. No case was hospitalized in the intensive care unit or needed respiratory assistance. No patient died.

Resolution of symptoms occurred by the seventh day in most (80%) cases. The average (SD) hospital stay was of 13 (3) days (range, 10-21 days). Negative RT-PCR results were obtained after a mean (SD) time of 14 (2) days (50% by ninth day, 75% by the 14th day, 94% by the 21st day), while four cases remained positive until the 28th day.

DISCUSSION

In Morocco, till date, approximately 600 children have been affected with COVID-19. Marrakesh is at the heart of the epidemic, with 19% of nationwide cases. All the pediatric cases are admitted to our center. Retrospective study of these cases found that our series agrees with those previously published, suggesting that most

Table I Laboratory Abnormalities in Pediatric Patients with Coronavirus Disease-2019 in Morocco (*N*=74)

Laboratory test	*Number (%)*
Complete blood count	
Anemia	4 (5)
Hyperleucocytosis	2 (3)
Leucopenia	1 (1)
Lymphopenia	2 (3)
Lymphocytosis	6 (8)
AST (≥40 IU/L)	22 (30)
ALT (≥40 IU/L)	22 (30)
Ferritin (>150 ng/mL)	2 (3)
LDH (>290 IU/L)	32 (43)
CPK (>25 IU/L)	10 (13.5)
Procalcitonin (>0.5 ng/mL)	9 (12)

AST - Aspartate aminotransferase; ALT - alanine aminotransferase; LDH - lactic dehydrogenase; CPK - creatinine phosphokinase.

WHAT THIS STUDY ADDS?

- Our study describes the North African experience with COVID-19 in children.

pediatric COVID-19 cases are females [6]. Children of all ages were susceptible to COVID-19 similar to other studies [7,8]. The most affected proportion of children were aged between 10 and 14 years, with a mean age similar to a Korean report [9], while a Spanish series found that most affected children were younger [6]. A Chinese series reported that over 90% of children were either asymptomatic or with mild-moderate manifestations [4]. The majority of our cases were asymptomatic because these infections were recognized mostly through contact tracing. Median time from illness onset to diagnosis was similar to the Chinese series [4]. All the symptomatic cases were upper respiratory infections, while other series found more severe cases [9-11]. Lymphopenia has been reported in COVID-19 previously also [9], and was seen in 3% of our children.

The Moroccan ministry of health approved in early April, 2020, a nationwide protocol using chloroquine or hydroxychloroquine associated with azithromycin in all COVID-19 severe pediatric cases [5]. We used this protocol in only one case with an immunocompromized condition (type 1 diabetes). Finally, we were well aware of the impact of the psychological state on the well-being of our children, so as recommended by Massimo, *et al.*, [12], we organized various activities such as anniversary parties, as well as providing hospitalized children with toys and books to alleviate loneliness.

In conclusion, COVID-19 in Moroccan children seems to be mild, with non-specific clinical and biological findings, and with a rare need of specific treatment. Other studies are necessary to verify these findings from this preliminary report.

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Contributors: KF: concept and designed the study, analyzed data and drafted the manuscript; HN: helped in data analysis and writing; GD, MB, IS: supervised data analysis. All authors approved the final manuscript.
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RESEARCH PAPER

Iodine Deficiency Disorders in Children in East Khasi Hills District of Meghalaya, India

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Objective: To assess the prevalence of iodine deficiency disorders among school-going children in Meghalaya. **Methods:** Multi-stage 30 cluster sampling with probability proportionate to size (PPS) method was used. Children (age 6-12years) were examined clinically for goiter. Urinary iodine excretion (UIE) was performed by spectrophotometric method. Iodine content in the salt was analyzed using iodized salt test kits. **Results:** A total of 195 (7.22%) out of 2700 children had goiter on examination. Goitre prevalence was significantly associated with wasting (P<0.05) and stunting (P <0.001). The median (IQR) UIE level was 150 (108.05 - 189.37) µg/dL. Nineteen (9.74%) children had severe iodine deficiency (UIE<20µg/L). Iodine content was above the recommended level of 15 ppm in 95.9% salt samples. A positive correlation was observed between household salt consumption and UIE levels (r=0.25; P<0.001). **Conclusion:** Iodine deficiency disorder is a public health problem in Meghalaya, which needs to be addressed.

Keywords: *Urinary iodine excretion, Goiter, Iodized salt.*

Iodine deficiency disorder (IDD) has been a major nutritional health problem in India. Sample surveys have shown 263 out of 325 districts in India to be IDD-endemic with a goiter prevalence of more than 10% [1]. Urinary iodine excretion (UIE) and goitre are the most common indicators to assess iodine status in a population. Urinary iodine is a good marker of recent dietary iodine intake whereas goitre reflects past iodine status [2]. The median UIE levels were 100 mcg/L in 86% districts surveyed in India [3]. The Coverage Evaluation Survey, 2009 reported 91% population coverage of iodized salt in India [4]. Even though use of iodized salt is high in Meghalaya at 98% [5], no district level or state level surveys have been conducted to assess the prevalence of goiter or to monitor the impact of iodized salt.

The present study was conducted to obtain baseline prevalence of IDD among school-going children (age 6-12 years) in Meghalaya, and to estimate the percentage of households consuming the recommended level of iodized salt.

METHODS

This cross sectional study was conducted among school going children of East Khasi Hills district of Meghalaya from June, 2016 to December, 2018. The sampling strategy was a multi-stage 30 cluster sampling method. The list of all the villages/ wards in the East Khasi Hills district was collected. A sample of 30 villages in the form of clusters was selected from the district using probability proportionate to size (PPS) systematic sampling. Thereafter, we selected one school present in each cluster randomly for data collection after getting the list from the Inspector of schools. Consent was taken from the Director of mass education and Inspector of schools, East Khasi Hills district. Written consent was taken from the school authorities and the parents of all the children who participated in the study, and assent from the children. Ethical clearance to conduct the study was taken from the Institutional ethics committee.

The estimated sample size was 2700 *i.e.*, 90 children per cluster. All children in the age group of 6-10 years were taken from school as the gross enrollment was 100%. Children with known chronic diseases or thyroid disorders were excluded from the study. Systematic random sampling was used to select children from each class. In the age group of 11-12 years, four children per cluster were taken from the community considering the gross enrollment around 70%. One lane was randomly identified as the starting point in the respective cluster. Children in the specific age groups were then selected by visiting the household next to the random start following the right hand rule till the required sample size was fulfilled.

Children were examined as per standards prescribed by National Iodine Deficiency Disorder Control Programme (NIDDCP). All children were examined clinically for goiter by the standard palpation method and the score for goiter was recorded using WHO criteria of grade 0, 1 and 2 [6]. All the goiter cases reported clinically were verified by the principal investigator. The district was considered as endemic district if the total goiter rate was above 5% in children aged 6-12 years [6]. Weight and height of each child was recorded and *Z* scores were interpreted as per the WHO child growth standards. Moderate and severe underweight were defined as weight-for-age SDS ≤-2 and -3, respectively, and moderate and severe stunting as height-for-age SDS ≤-2 and -3, respectively.

Urine samples were collected from all the children in labeled plastic bottles (50 mL capacity with screw cap and thymol crystal as preservative, and transported to the laboratory in cold chain for spectrophotometric estimation of iodine in urine. A median UIE level of >99 µg/L was taken as the cut-off for adequacy for the population. Severe iodine deficiency was defined at a level of <20 µg/L [6]. Every fifth child selected in the class for goiter survey was instructed to bring approximately 20 grams of household salt in auto seal plastic pouches, which were distributed to the children a day ahead of sample collection. The test kit produced by MBI chemicals and procured from National Institute of Nutrition, Hyderabad was used for estimation of iodine in the salt sample. The salt samples were tested in the school as per manufacturer's instructions and iodine concentration was recorded as 0, <15 and >15 ppm [7].

Statistical analyses: Data were entered in MS Excel and analyzed using SPSS 19.0 version . Pearson correlation coefficient and chi square test was used to find out the association between continuous variables and categorical variables.

RESULTS

A total of 2700 (1365 boys) children were examined. The total goiter prevalence was 195 (7.22%) [grade 1 in 175 (6%) and grade 2 in 20 (0.7%) children], similar in both genders. The prevalence was higher in the age group 9-12 years (12.2%) than in younger children (5.5%); (*P* <0.001). Ninety three (3.9%) and 631 (25.1 %) children were severe and moderate underweight, respectively; 389 (16.8%) and 641 (31%) children had severe and moderate stunting, respectively. ***Table* I** shows the goiter prevalence with respect to clinical and laboratory variables. The median (IQR) UIE levels were 150 (108.05-189.37) µg/L.

A total of 518/540 (95.9%) salt samples tested had iodine content >15 ppm. Most (97.9%) of the children with goiter had salt iodine content >15 ppm. A positive correlation was observed between household salt consumption and UIE levels (r=0.25; P<0.001). Only 8 (0.3%) families consumed open salt, while rest consumed packaged iodized salt. Sixty (2.07%) families stored salt in open containers.

DISCUSSION

The present study reported a 7.22% prevalence of goiter in school-going children, which was more than 5% cut-off, signifying that IDD was a public health problem in this region.

A variable goiter prevalence of 2-12% has been reported earlier from Madhya Pradesh [8], Karnataka [9] and Jammu [10], respectively. The present study did not observe any significant difference in goiter rates among males and females, unlike earlier studies [11,12], which reported a higher prevalence in females. This may be due to socio-cultural factors and a positive attitude towards the girl child in this region. A higher prevalence of goiter was seen in the 9-12 year age group in this study, similar to an earlier Indian study [11]. A significantly higher goiter prevalence was seen among underweight and stunted children in the present study, as also noted in other studies [13-15].

Table I Clinical and Biochemical Characteristics of Goiter in Meghalaya, 2016-2018 (*N*=2700)

	Goiter present (n=195)	*Goiter absent (n=2505)*
#Age		
6-<9 y	91 (3.4)	1655 (61.3)
9-12 y	104 (3.8)	850 (31.5)
‡UIE level (µg/L)		
>200	22 (0.8)	412 (15.2)
100-200	89 (3.3)	1627 (60.2)
50-99	53 (1.9)	357 (13.2)
20-49	12 (0.4)	59 (2.2)
<20	19 (0.7)	50 (1.8)
Gender		
Male	101 (3.7)	1264 (46.8)
Female	94 (3.5)	1241 (45.9)
**Weight-for-age*		
Normal	83 (3.1)	1319 (48.8)
Underweight	112 (4.1)	1186 (43.9)
#Height-for-age		
Normal	101 (3.7)	841 (31.1)
Stunted	94 (3.5)	1664 (61.6)

*Values in n (%); *P<0.05 and #P<0.001 for inter-group comparison among those with goiter; ‡P<0.001 for comparison between those with and without goiter.*

WHAT THIS STUDY ADDS?

- The goiter prevalence in Meghalaya was 7.22%, with adequate urinary iodine excretion levels and consumption of adequately iodized salt in most households.

A significant association between goiter and UIE levels was seen in this study. However, there may be some discrepancy between UIE and goitre prevalence by the palpation method, as UIE reflects the current iodine concentrations and goiter indicates a chronic situation of iodine deficiency [16]. The median UIE levels were above the adequate cut-off level in the study. Variable UIE levels (96.5-200 µg/L) have been reported from other parts of India [8,10,17]. High goiter incidence with normal median UIE, as in this study, has been observed from some other regions in India as well [3]. This may result as the thyroid size reflects previous iodine nutrition and goitre may take years to shrink even after attaining iodine sufficiency [18].

The iodine content of salt was optimum in the present study, as reported earlier [9,10]. At the national level, the household coverage of iodized salt was 91.7% with 77.5% of households consuming adequately iodized salt [19]. A study from Mandya district of Karnataka showed higher iodine content in more than 90% of the salt samples [20]. However, a quarter of households were consuming inadequately iodized salt in Madhya Pradesh [8].

The confirmation of iodine deficiency for those with goiter could not be done by thyroid function tests due to difficulty in obtaining serum samples from school-going students. It was also difficult to predict the iodine status of an individual by a spot sample of UIE instead of a 24-hour sample, which was difficult to obtain due to technical reasons.

To conclude, the total goiter prevalence was 7.22% which suggests IDD as a significant public health problem in this region. IDD control program in the region needs to be strengthened with strong advocacy from the health sector.

Contributors: CKN: analysis of urine samples, biochemical analysis; SP: finalization of concept proposal, execution of project in field; GKM: critical review of proposal, expert advice on data analysis and interpretation; HC: storage of samples and biochemical analysis. HB: Study concept, planning, supervision and preparation of manuscript. All authors approved the final manuscript.
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SYSTEMATIC REVIEW

Effect of Delayed *Versus* Early Cord Clamping on Improving Anemia in Term Infants Aged Two Months or Older - *A Meta-analysis*

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Objective: To assess the effects of delayed cord clamping (DCC) on hemoglobin (Hb), mean corpuscular volume (MCV) and ferritin level in infants 2 months or older.

Evidence acquisition: Meta-analysis of randomized control trials searched systematically from PubMed, Cochrane and Web of science. Trials published from Jan 1,1975 to Mar 12, 2018, no language and country restrictions. Twelve studies were included in this meta-analysis. In total, 993 infants were treated with DCC, while 989 cases received early cord clamping. Delayed cord clamping was defined as umbilical cord clamping time greater than 60s after delivery. Outcomes assed were (*i*) hemoglobin (Hb), (*ii*) mean corpuscular volume (MCV) and ferritin level.

Results: The results show that DCC increased hemoglobin level (SMD=0.4678 95%CI: [0.1515, 0.7841]), Ferritin level (SMD=2.1450 95%CI: [1.0431, 3.2470]) and MCV (SMD=0.5751 95%CI: [0.1637, 0.9865]) in infants between 2-12 months compared to ECC subject analysis noted the effects of Hb increase was greater in Asian infants.

Conclusions: Delayed cord clamping improved the Hb, MCV and ferritin level of infants after birth.

Keywords: *Hemoglobin, Infant, Meta-analysis, Umbilical cord*.

The appropriate timing of umbilical cord clamping has been a matter of debate for long. Early umbilical cord clamping (ECC) was standard practice but with emerging evidence it has started to shift to delaying cord clamping (DCC) to beyond 30-60 secs. In term infants, placental transfusion contributes between one-quarter and one-third of total potential blood volume at birth [1]. At 1-minute, newborn infants receives about 80 mL of blood while at 2-3 minutes it is about 100 mL [2].

The American Association of Obstetricians guideline, 2017, states that DCC can increase hemoglobin levels at birth, and early iron stores [3]. The guideline also recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30–60 seconds after birth. In addition, it can also benefit the preterm infants by decreasing the need for blood transfusion, lowering incidence of necrotizing enterocolitis and intraventricular hemorrhage. Previous systematic reviews [4,5] have reported the advantages of DCC, but mainly as a dichotomous variable, and mainly during the neonatal period [6]. The present systematic review and meta-analysis reports change in hemoglobin between ECC and DCC in infants 2 months or older.

METHODS

All relevant studies published between January 1, 1975 and March 8, 2018 were identified by searching PubMed, Cochrane reviews and Web of science. The Search strategy used the terms (((delayed cord clamping [Title/Abstract]) OR delayed cord ligation [Title/Abstract])) OR ((late cord clamping [Title/Abstract]) OR late cord ligation [Title/Abstract]))) Filters: Randomized Controlled Trial. There was no language limitation in the selection.

Accompanying commentary: Pages 791-92.

Studies were screened and selected by the following criteria: (*a*) randomized controlled trials (except quasi randomized study); (*b*) singleton newborns, no developmental deformity, no gestational age limit; (*c*) clinical trial data included hemoglobin, mean corpuscular volume (MCV) and ferritin; (*d*) delayed cord clamping was in intervention group, and early cord clamping was in control group; (*e*) the outcomes' were measured at 2 months or more after birth. Articles were excluded if it was a conference summary; had Incomplete data; presence of maternal complications (antepartum blood loss, pregnancy-induced hyper-tension, pre-eclampsia and gestational diabetes); history of post-partum hemorrhage (PPH), there was need for neonatal resuscitation, or history of fetal distress.

The following data were extracted from each selected study: Region where study was performed, total number of participants, gestational age, follow-up time, and the effect of DCC versus ECC beyond 2 months were also compared; hemoglobin as the main outcome, MCV or ferritin as a secondary outcome.

For meta-analysis, RevMan 5.3 of the Cochrane Collaboration and stata 12.0 was used [6]. The Cochrane risk bias assessment tool was used to assess the bias in the included studies. Clinical and methodological heterogeneity of the included studies were analyzed, and subgroup analysis were conducted according to clinical and methodological heterogeneity. The I^2 index was calculated to assess the degree of heterogeneity. In the absence of heterogeneity ($P \geq 0.05$; $I^2 \leq 50\%$), a fixed effect model was used; if there was heterogeneity between studies ($P < 0.05$; $I^2 > 50\%$), a random effects model was used. Sensitivity analysis was used to assess the stability of the results. Continuous data were expressed as Standard mean difference (IV, Random, 95% CI). Funnel plots was used to analyze for possible publication bias. Funnel plot asymmetry was assessed using Egger tests, and significant publication bias was defined as a P value<0.1. If publication bias existed, the trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results.

The entire process was completed by two independent investigators, and the disagreement if any, was resolved by a third investigator.

RESULTS

A total of 325 studies was identified, with 13 publications fulfilling eligibility for inclusion. [7-19] (***Fig.* 1**). Two articles written by Andersson, *et al*. [9,19] have the same patients but the follow-up time and outcomes were different. So these two articles were regarded as one trial and outcomes extracted accordingly. The characteristics of all included trials is presented in ***Table* I**. Follow-up time was between 2 months and 12 months. The effect of ECC and DCC on hemoglobin was assessed in 12 trials, ferritin in 10 trials and MCV in 5 trials. In total, 993 infants were treated with DCC, while 989 cases received

Table I Characteristics of Included Studies Comparing Early and Delayed Cord Clamping

Study; place, year	*Sample (DCC/ECC)*	*Gestational age (DCC/ECC)*	*Intervention method DCC/ECC*	*Outcomes*
KC, *et al.* [7]; Nepal, 2017	212/188	38/38 median	≥180s/≤60s	Hb and ferriten level at 8-mo
Tiemersma, *et al*. [8]; South Africa, 2015	35/38	38/38 median	120-180 s/≤30s	Hb level at 2-3 mo
Andersson, *et al*.* [9]; Sweden, 2011-2014	168/175 150/144	40.0/40.1 mean	≥180s/≤10s	Hb and MCV level at 4-mo Ferritin level at 12-month
Ceriani Cernadas, *et al*. [10]; Argentina, 2010	83/86	39/39 median	180s/<15s	Hb and MCV level at 6-mo Ferritin level at 6-mo
Chaparro, *et al*. [11]; Mexico, 2006	171/157	38.8/39.0 mean	120s/around 10s	Hb and MCV level at 6-mo Ferritin level at 6-mo
Geethanath, *et al*. [12]; India, 1997	59/48	Term infants	Placenta into vagina/ICC	Hb level at 3-mo Ferritin level at 3-mo
Li, *et al*. [13]; China, 2012	64/94	38.6/38.7 mean	60s/15s	Hb and MCV level at 4-mo Ferritin level at 4-mo
Nesheli, *et al*. [14]; Iran, 2014	30/30	40/40 mean	50-60s/ICC	Hb, ferritin and MCV level at 6-mo
Venâncio, *et al*. [15]; Brazil, 2008	115/109	39.3/39.3 median	60s/ICC[h]	Hb level at 3-mo Ferritin level at 3-mo
van Rheenen, *et al*. [16]; Zambia, 2007	39/39	40/40 mean	>60s/20s	Hb level at 4-mo
Gupta, *et al*. [17]; India, 2002	29/29	39.1/39.4 mean	Placenta into vagina/ICC	Hb level at 3-mo
Grajeda, *et al*. [18]; Guatemala, 1997	26/21	38.8/38.5 mean	Cord stopped pulsating/ICC	Hb level at 2-mo Ferritin level at 2-mo

**Includes two articles with the same patients, the sample 168/175 at 4-month, the other at 12-month; DCC-delayed cord clamping; ECC-early cord clamping; ICC-cords clamped immediately after the birth ; Hb-hemoglobin; MCV-mean corpuscular volume.*

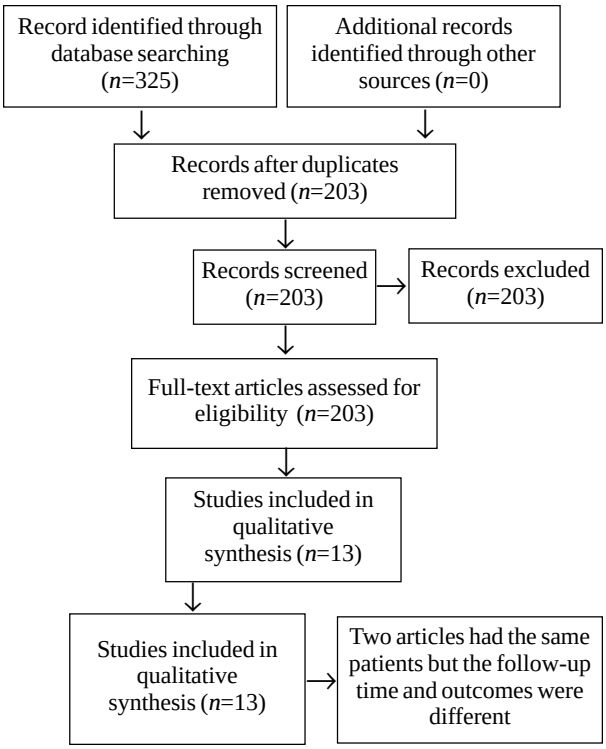

Fig.1 *Study selection for the meta-analysis.*

ECC. All of these infants were term infants. These trials used different definition of DCC, but all were pooled, and DCC was redefined as umbilical cord clamping time greater than 60s after delivery.

***Web Fig.* I** depicts the assessment of risk of bias in the included trials. Eight studies [7-12,13,16,17] clearly indicated the method of randomization, 9 studies [7,8,12-18] did not indicate if the study was blinded.

There was little publication bias on funnel plot (***Fig.* 2**) and Egger test (P=0·073) in this analysis. However, further analysis with trim-and-fill test indicated that this publication bias could not impact the estimates (no trimming done because data was unchanged).

To study the effect of DCC compared to ECC on hemoglobin level the sample size varied significantly among the included studies and there was heterogeneity (I^2=91%), so a random effects model was used to analyze the results. One trial in our study did not mention the unit [16], so outcomes have taken SMD to analyze. The results obtained show that DCC resulted in higher hemoglobin levels compared to ECC (SMD=0.47; 95% CI: 0.15, 0.78) (***Fig.* 3**). DCC resulted in significantly higher ferritin levels compared to ECC (SMD=2.14; 95% CI: 1.04, 3.25) (***Fig.* 3**). Similarly DCC resulted in significantly higher MCV levels compared to ECC (SMD=0.57; 95% CI: 0.16, 0.99) (***Fig.* 2**).

Subgroup analysis on effect of DCC and ECC on hemoglobin was performed by race (***Web Fig.* 2.1**), timing of DCC (120s as the critical value) (***Web Fig.* 2.3**) and the follow-up time of DCC (6 months as the critical value) (***Web Fig.* 2.2**). DCC improved Hb significantly compared to ECC in Asian studies, when follow-up was more than 6 months and when timing cord clamping was not beyond 120 secs. Accordingly, the race of participants, timing and follow-up time of DCC can be regarded as a source of heterogeneity.

DISCUSSION

The results obtained show that DCC could increase the level of hemoglobin, MCV and especially ferritin when compared with ECC. The influence could be different based on participants' regional distribution, timing of umbilical cord clamping and the age of infants. The optimal time to delay umbilical cord ligation which impacted hemoglobin levels is about 60-120s.

Some studies have indicated that the differences in hematologial variables between DCC and ECC became smaller with the increased follow-up time [7,9]. A randomized controlled trial in Sweden demonstrated that DCC significantly increased stored iron at 4 months, but the effect on hemoglobin was not significantly different from ECC. When the follow-up reached 12 months, the beneficial effect on iron storage disappeared. This might be related to the postnatal iron supplementation. A previous study [11] showed that during the three-month follow-up, hematologic improvement was enhanced in iron-deficient mothers, infants with infant birth weights between 2500 and 3000 grams, and infants who did not receive infant formula or iron fortified milk. A previous meta-analysis including 6 trials about hemoglobin level showed no significant difference in the hemoglobin levels within 6 months.

The study has some limitations. Firstly, the timing of cord clamping varied from 60 seconds till descent of placenta into vagina or cord stopped pulsating, and in the latter the means used were approximate estimates. Secondly, all studies had loss to follow-up. Since acute inflammatory process could increase the ferritin concentration, there might be an error in the result of ferritin.

There is also a long way to go in the optimization of umbilical cord ligation. In addition, countries should develop DCC guidelines based on race, gender, and physical status of pregnant women in order to improve the blood volume and iron storage of newborns more effectively.

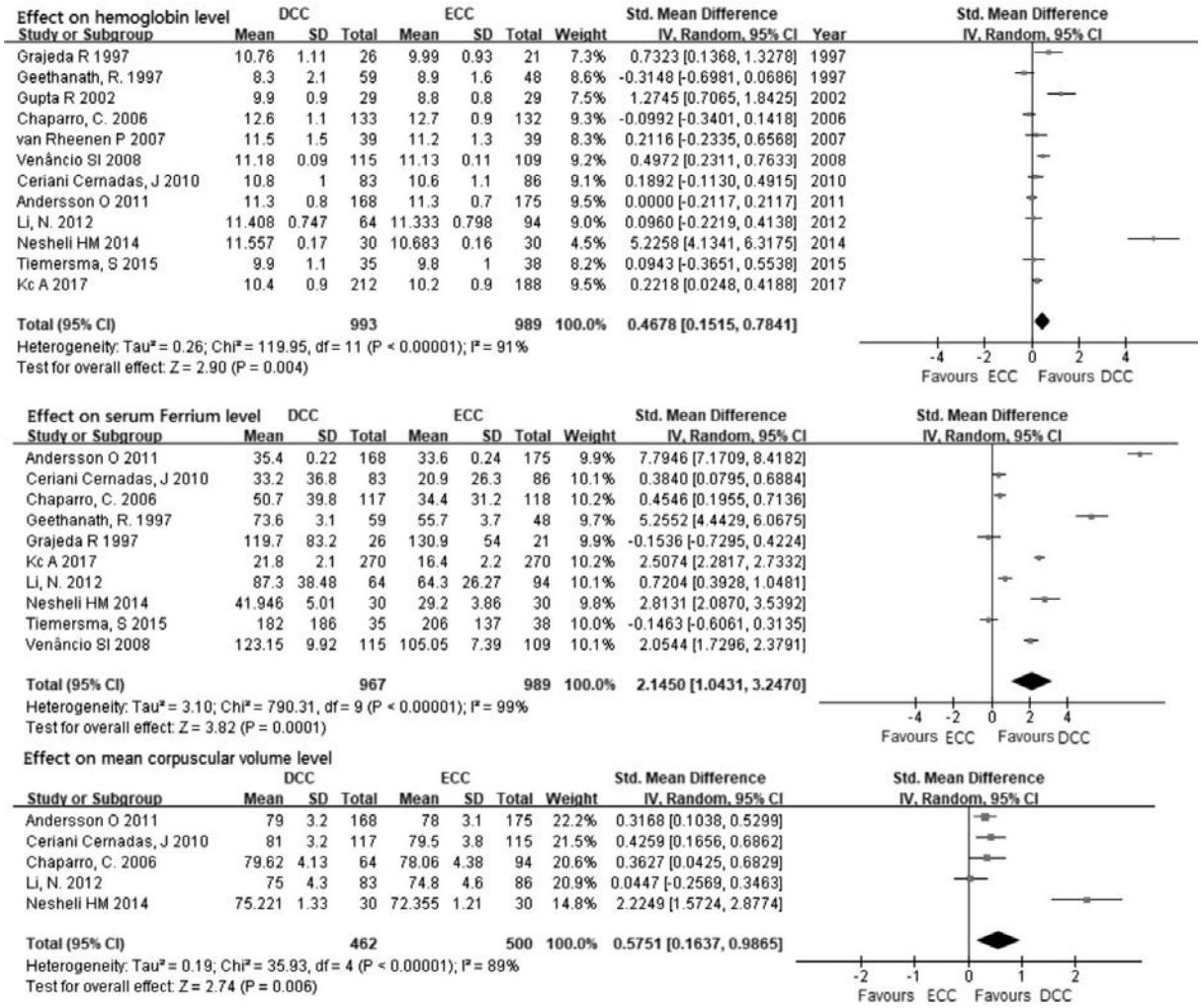

Fig. 2 *Forest plots comparing effect of early and delayed cord clamping on various hematological parameters.*

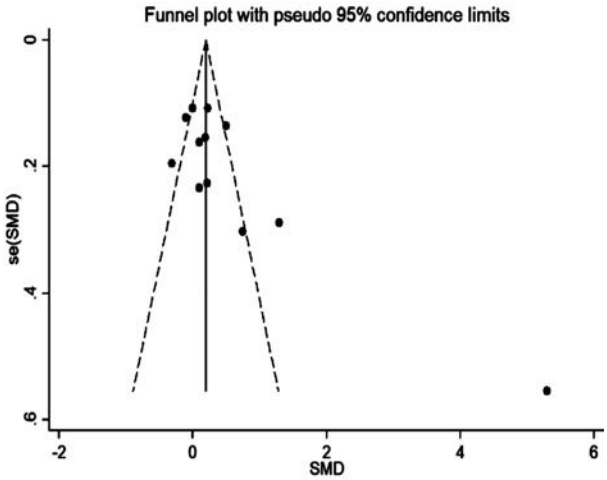

Fig. 3 *Funnel plot of studies comparing early and delated cord clamping.*

As there is a high incidence of anemia and low iron stores in Asian and African infants [7,12,16], DCC might be an effective intervention to prevent anemia and iron deficiency in developing countries.

Contributors: XF: contributed to conception and design, acquisition, analysis, and interpretation; DD: contributed to conception and design, acquisition and interpretation; SL: contributed to conception and design, acquisition; ZX: contributed to conception and design, analysis; HW: contributed to conception and design, acquisition, analysis, and interpretation. All authors drafted manuscript, critically revised manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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WHAT IS ALREADY KNOWN?

- Delayed cord clamping provides adequate blood volume and birth iron stores, thus decreasing the risk of iron deficiency anemia during infancy

WHAT THIS STUDY ADDS?

- The optimal time to delay umbilical cord ligation is about 60-120s and it will be more conducive to the growth of hemoglobin than the longer umbilical clamping time. In contrast, Asians might gain more benefits from delayed umbilical clamping.

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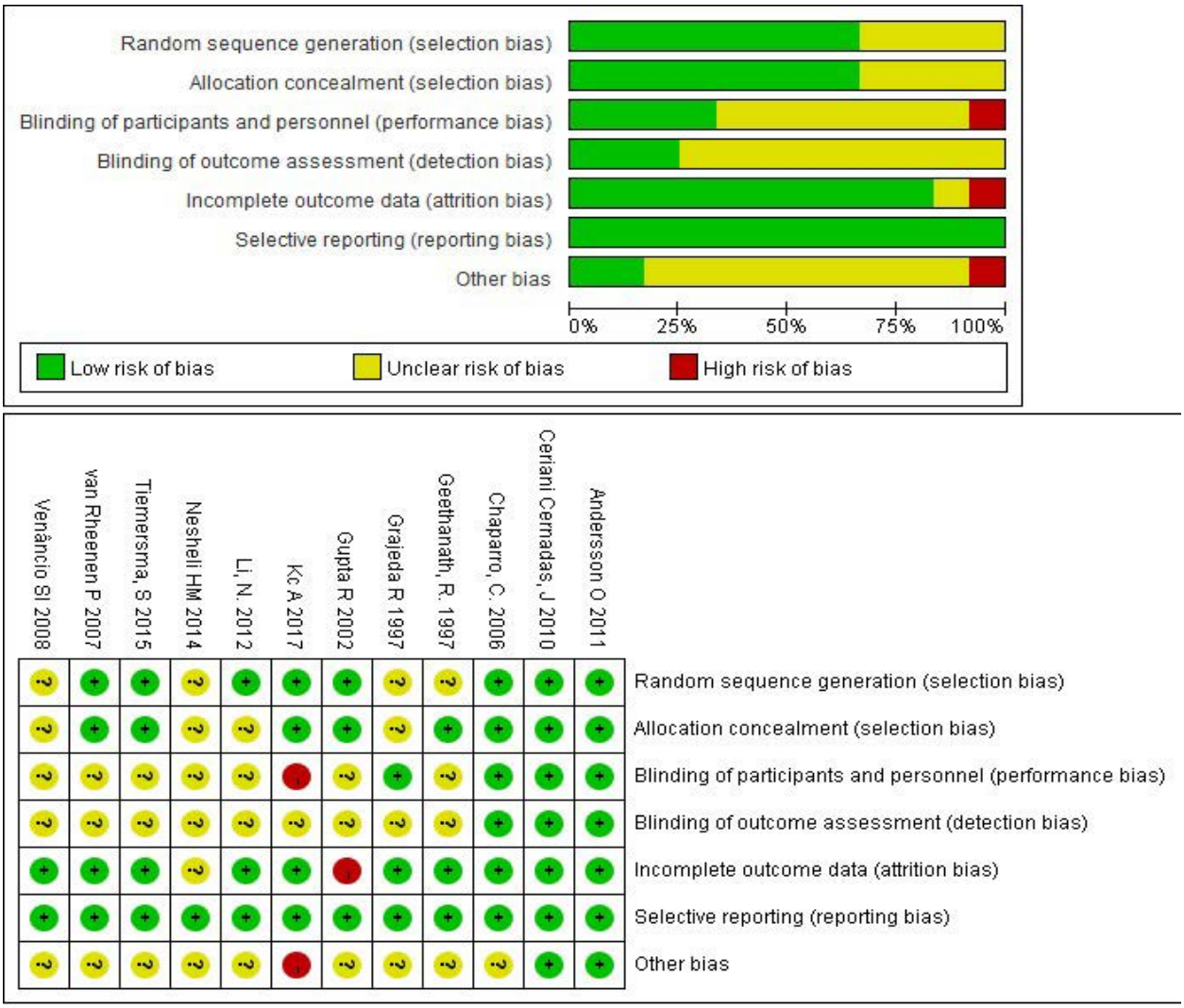
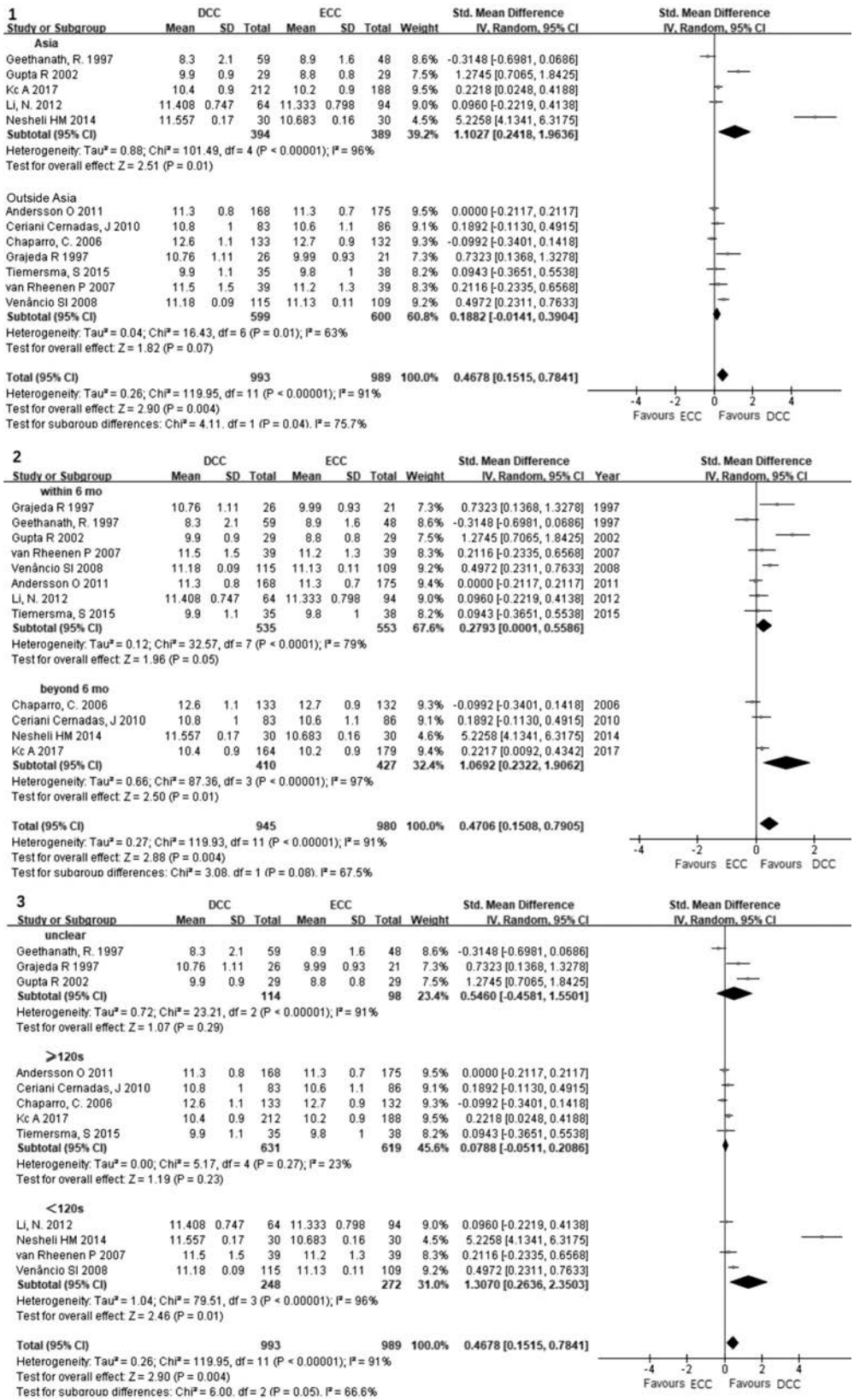


Web Fig. 1 *Assessment of Risk Bias.*



Web Fig. 2 *Subgroup analysis on effect of delayed (DCC) and early cord clamping (ECC) on hemoglobin.*

SYSTEMATIC REVIEW

Clinical Features and Outcome of SARS-CoV-2 Infection in Children: *A Systematic Review and Meta-analysis*

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Objective: Knowledge about COVID-19 in children is limited due to the paucity of reported data. The pediatric age group comprises only less than 5% of total COVID-19 worldwide, therefore, large studies in this population are unlikely in the immediate future. Hence, we planned to synthesize the current data that will help in a better understanding of COVID-19 in children.

Evidence acquisition: Four different electronic databases (MEDLINE, EMBASE, Web of Science, and CENTRAL) were searched for articles related to COVID-19 in the pediatric population. We included studies reporting disease characteristics and outcomes of COVID-19 in patients aged less than 19 years. We performed a random-effect meta-analysis to provide pooled estimates of various disease characteristics.

Results: 27 studies (4857 patients) fulfilling the eligibility criteria were included in this systematic review, from a total of 883 records. About half of the patients had each of fever and cough, 11% (6-17%) had fast breathing, and 6-13% had gastrointestinal manifestations. Most of the patients had mild to moderate disease, and only 4% had a severe or critical illness. Leukopenia was the commonest reported laboratory abnormality.

Conclusion: Even among the symptomatic COVID-19 cases, severe manifestations are seen in very few children. Though fever and respiratory symptoms are most common, many children also have gastrointestinal manifestations.

Keywords: *COVID-19, Gastrointestinal symptoms, Mortality, Severity.*

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With the rapidly evolving severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) pandemic, the knowledge about the disease manifestations and severity has also evolved quickly. Due to its resemblance to SARS, influenza, and other respiratory viruses, children were initially thought to be more susceptible than adults. However, less than 5% of total coronavirus disease (COVID-19) cases belong to the pediatric age group, and the severity has been milder as compared to adults [3,4]. Information regarding clinical manifestations and outcomes of COVID-19 in adults is available due to a huge number of reported cases, but the scenario for the pediatric population is different as our knowledge about clinical and laboratory characteristics as well as prognosis of COVID-19 is very limited.

Due to this difference in the manifestations of COVID-19 among pediatric patients from adults, there is a need to clarify the disease manifestations and course among children. We performed this systematic review to synthesize the information on clinical manifestations, laboratory findings, and outcome of COVID-19 among the pediatric population.

METHODS

We performed this systematic review to describe the currently available literature on clinical features and outcomes of COVID-19 in children between 1 month-19 years. Our primary aim was to provide a pooled estimate of various clinical manifestations, disease severity, and outcomes in children with SARS-CoV-2 infection.

This study was conducted following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [5]. A predefined search strategy was developed, and three investigators independently performed a literature search in MEDLINE, EMBASE, Web of Science, and CENTRAL (Cochrane central register of controlled trials) for the original articles published between December 01, 2019, to May 10, 2020. The search strategy was targeted for patients aged less than 19 years with SARS-CoV-2 infection or COVID-19 and was based on two basic groups of terminologies: study population [pediatric / children / child / infant/ adolescent], and terms related to or describing COVID-19 and novel coronavirus (nCoV) infection. Terms used for literature search were: COVID-19, coronavirus, SARS-CoV-2, 2019 nCoV, severe acute respiratory syndrome

coronavirus 2, pediatric, children, adolescent, and infant. Specific search strategies were created for each search engine, by using the MeSH term and above-described terms. The electronic search was also supplemented by a hand search of bibliography of the included studies and relevant review articles. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [6]. No language restrictions were used.

Study selection: A predefined set of the criteria were used for study selection for this systematic review. Studies enrolling children and clearly reporting data on their clinical features were considered eligible for the review. Initially, two researchers independently screened the title and abstract for the eligibility. Later all the authors examined full-text articles for inclusion and exclusion criteria. Studies were included if they met the following criteria: (*i*) Patients aged less than 19 years with confirmed SARS-CoV-2 infection, (*ii*) the study reporting clinical manifestations, disease severity, and/or laboratory investigations and/or outcome of SARS-CoV-2 in children, and (*iii*) all types of study design: cohort, cross-sectional studies, case-control studies, and case series. Correspondences or letters fulfilling the above criteria were also included. We excluded: (*i*) case series reporting nine or fewer cases, (*ii*) studies reporting only neonatal data, (iii) studies reporting about other serotypes of coronavirus, (*iv*) narrative or systematic review, (*v*). Conference proceedings, (*vi*) editorial, perspective, etc. not meeting the inclusion criteria.

Data extraction and quality assessment: A well-structured, standardized proforma was used for data extraction. Four investigators independently extracted data from the full text of the eligible studies. Extracted data included first author name, year, country, journal, study design, study population information for risk of bias assessment of the study, method, and type of sample used for confirmation of SARS-CoV-2 infection, age and gender distribution of cases, clinical and laboratory manifestations, major radiological abnormalities, the severity of the disease, and reported outcomes in studies. Any disagreement between two investigators was resolved through discussion with another investigator. An independent researcher rechecked the extracted data for its accuracy and completeness. Every effort was made to avoid duplicity of data by screening full-text articles of the included studies for author name, location, setting, date and duration of the study, number of participants, and baseline data. There is a possibility that the small case series/case report might be a part of larger retrospective cohort. To address this issue, we excluded case reports and small case series (up to nine patients). The quality of the included studies in this systematic review was assessed using the Newcastle Ottawa scale [7]. We used the following scoring system: Good quality: 3 or 4 stars in selection domain, and 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; fair quality: 2 stars in selection domain and 1 or 2 stars in comparability domain, and 2 or 3 stars, in outcome/exposure domain; and poor quality: 0 or 1 star in selection domain or 0 stars in comparability domain or 1 star in outcome/exposure domain. Three investigators independently assigned an overall risk of bias to each eligible study, and if they disagreed, another researcher resolved the discrepancy.

Data synthesis and statistical analysis: We present the data with descriptive statistics and provide pooled estimates of various parameters, wherever it was feasible to meta-analyze the data. We categorized the disease severity into five categories (asymptomatic, mild, moderate, severe, and critical) as described by Dong, *et al*. [8]. We provid the pooled estimates of various categories of disease severity from studies in which severity classification was reported. Percentages and mean values were calculated to describe categorical and continuous variables, respectively.

Meta-analyzed parameters were presented as pooled estimates with a 95% confidence interval (CI). Meta-analysis was performed using STATA version 14.2 (Stata Corp LLC, College Station, Texas, USA).

We pooled data from individual studies using a random effect model with the assumption that the frequency of clinical features and other parameters will be variable across the studies. Heterogeneity in studies was explored by inspection of forest plot as well as using the chi-square test on Cochran's Q statistics. Study heterogeneity was assessed by using the Higgins and Thompson I^2 method [9]. Publication bias was assessed by Egger's test.

RESULTS

Using the above-described search strategy we found 883 articles, out of which 27 studies (4857 patients) (***Fig.* 1**) that met inclusion and exclusion criteria were included for final qualitative synthesis, and 25 studies for quantitative synthesis (***Web Table* I**). A publication bias was found [bias (95% CI) = –2.9 (–4.5 to -1.3); P = 0.01].

Among 27 included studies, 21 were from China [8,10-29], two each from Italy [30,31] and the Republic of Korea [32,33], and one each from the United States of America [4], and Spain [34]. Among the included studies, five were good, thirteen were fair, and nine were of poor quality as assessed by the Newcastle Ottawa scale [7].

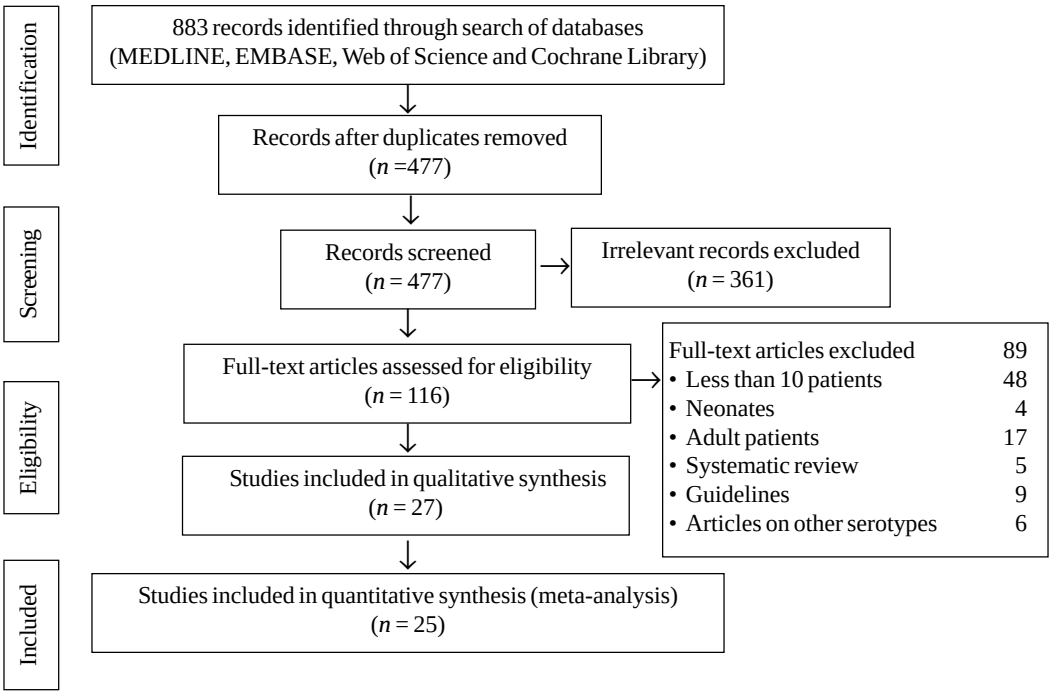

Fig. 1 *Flow diagram of the study selection process.*

A total of 4857 pediatric cases were reported in 27 eligible studies. The mean (SD) age of the participants was 6.4 (3.4) years (reported in eight studies) whereas the range varied from one month to 19 years. Twenty-three studies [8,10-25,27-32,34] (1777 patients) reported separate data for gender; 1014 (57%) of all the patients were male. Twenty-three studies [4,10-16,18-25,27-32,34] described the frequency of specific symptoms in patients, of which only seventeen reported disease severity.

Clinical manifestations and disease severity: Sixteen studies reported data on the history of exposure to a SARS-CoV-2 infected patient and 91% (87-95%) of children had a history of contact [10,11,14,15,17-25,27,28,30,34]. Among the included studies, only 17 studies reported data on asymptomatic SARS-CoV-2 infection [8,11,12,15,16,19,21-25,27-32]. Almost one-fourth, 23% (17-30%) of patients were asymptomatic. Since we included studies describing clinical features, this number is not representative of the overall proportion of asymptomatic cases in COVID-19 children. Twenty-three studies (*n*-1330) reported data on specific symptoms [4,10-16,18-25,27-32,34].

Fever was the commonest clinical feature and was seen in almost half of the patients (***Table* I**). Similarly, 45% of symptomatic patients had cough, 11% had fast breathing, and 4-9% had gastrointestinal manifestations.

Of the all included studies, fifteen (*n*=1666) provided specific information on disease severity [8,11-13,15-20,22,24,25,30,31] (***Table* II**). Most of these patients had mild to moderate disease (96%), with a very small proportion of patients having a severe manifestation (3%) like hypoxia, dyspnea, and cyanosis **(*Table* I)**. Only 1% of all the symptomatic pediatric cases were critically sick (acute respiratory distress syndrome, respiratory failure, shock, encephalopathy, myocardial injury or heart failure, acute kidney injury *etc*).

To explore high heterogeneity, we did sensitivity and subgroup (only for the quality of the studies) analysis and we did not find any meaningful significant difference in the pooled estimates of any of the clinical or laboratory feature. None except one study provided data on relationship of severity of the illness with the age of the patients. Dong, *et al*. [35] assessed the severity of illness by age and reported that the young children, particularly infants are more vulnerable to SARS-CoV-2 infection and had more severe disease. Data on relationship of disease severity and gender was not reported in children.

Laboratory and radiological abnormalities: Among the laboratory findings (***Table* III**), leukopenia was the most commonly detected abnormality and was seen in almost one-fifth of the patients. Twelve percent also had lymphopenia. On the other hand, leucocytosis was

Table I Clinical Features in Children with SARS-CoV-2 Infection

Symptoms	*Studies (patients)**	*Pooled estimates#*	*Heterogeneity‡*	*P value*
Fever	23 (1330)	49 (41-58)	90	<0.001
Cough	23 (1330)	45 (39-51)	79	<0.001
Fast breathing	10 (966)	11 (6-17)	87	<0.001
Coryza	15 (1095)	20 (13-26)	87	<0.001
Sore throat	15 (1012)	14 (7-21)	92	<0.001
Vomiting	13 (1067)	6 (4-9)	48	0.03
Diarrhea	15(1102)	9 (6-13)	80	<0.001
Abdominal pain	7(604)	4 (1-6)	52	0.05
Myalgia	6(418)	10(1-18)	83	<0.001
Headache	6(546)	10(1-19)	92	<0.001
Hypoxia	6(405)	2 (1-3)	0.0	0.84

**Number of studies (patients); #in % (95% CI); ‡in I^2%; P value for I^2.*

Table II Severity of COVID-19 in Children

Disease severity	*Studies (patients)**	*Pooled estimates#*	*Hetero-geneity‡*
Mild	10 (1224)	40 (26-52)	94
Moderate	10 (1224)	56 (40-72)	95
Severe	19 (1677)	3 (1-5)	68
Critically sick	19 (1677)	1 (0.1-2)	31

**Number of studies (patients); #in % (95% CI); ‡in I^2%; P value for I^2.*

detected in 12% (6-17%) patients. A significant proportion (9-25%) of the cases had raised inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and procalcitonin). From the 15 studies which reported data on organ dysfunction, seven patients had acute kidney injury and deranged liver function was documented in 10-15% of patients [10-16,18,20-23,27,28,30]. Thirteen studies reported data on radiological imaging (*X*-ray, Computerized tomography scan), and the common radiological findings on CT scan were ground-glass opacity (41%) and consolidation (16%) [12,14-16,19-25,28,29,32].

Outcomes: Due to low event rate of outcome in studies we did not meta-analyze this data. Mortality data was provided in twenty-two studies (4476 patients) and overall, five deaths have been reported [4,8,10-16,18-21,24-28,30,32-34] in these studies. Nineteen studies [4,10-14,16,18-22,24,25,27,30-32,34] reported details on hospital stay in 1670 children and of these 35 (2.1%) patients required intensive care support for management and mechanical ventilator support was needed for twelve patients (0.7%).

DISCUSSION

This review summarizes the clinical features, laboratory findings, disease severity and prognosis from the available studies about pediatric COVID-19 in the age group of one month to 19 years. The total number of reported pediatric cases is much less than that reported in adults.

Similar to adults, the commonest clinical features are fever and cough; however, their frequency is much lower in children (60-100% in adults *vs*. 40-60% in children) [37,38]. On the other hand, features like dyspnea, hypoxemia, and sputum production are more frequently seen in adults. Like adults, the gastrointestinal manifestations (diarrhoea, vomiting) are frequently seen in children and sometimes may be the sole manifestation of COVID-19 [37-39]. Overall, respiratory symptoms followed by gastrointestinal symptoms are the predominant manifestations in children as well as adults [37,38]. These findings play an important role in devising a screening strategy for COVID-19 in children. The screening algorithms in adults rely primarily upon fever and cough as these are present in more than 80% of the patients; however, the same approach for the pediatric population is likely to miss out 40-50% of the cases. Therefore, the screening strategy for children should incorporate both respiratory and gastrointestinal features.

Similar to adults, one-third of children with COVID-19 children will have abnormal complete blood count [37,38]. Unlike other infections, leukopenia is more frequently encountered than leukocytosis even in milder cases and should raise a high index of suspicion for cases being evaluated for COVID-19. Around 15-25% of pediatric cases may have raised C-reactive protein and

Table III Laboratory Findings in Children with COVID-19

*Laboratory parameter**	*No. of studies (patients)*	*Pooled estimates % (95% CI)*	*Heterogeneity (I^2%)*	*P value for I^2*
Leukopenia	17 (743)	16 (11-22)	81	<0.001
Leucocytosis	17 (743)	12 (7-17)	71	<0.001
Lymphopenia	19 (808)	12 (8-17)	75	<0.001
Elevated aspartate transaminase	14 (665)	15 (9-21)	70	<0.001
Elevated alanine transaminase	14 (665)	10 (7-12)	0.0	0.71
Elevated C-reactive protein	13 (620)	16 (10-22)	79	<0.001
Elevated procalcitonin	9 (476)	25 (9-42)	97	<0.001
Elevated erythrocyte sedimentation rate	4 (125)	9 (4-14)	0.0	0.47

**The normal values of the laboratory parameters were as per the authors of the given study.*

procalcitonin in alike other infections, and therefore inflammatory markers may not differentiate COVID-19 from other infections. Serial procalcitonin measurements in COVID-19 are shown to be useful in predicting disease severity in adults, but similar data for the pediatric population is lacking [40]. Like adults, 10-25% of pediatric COVID-19 cases may have elevated liver enzymes (AST, ALT), however, its impact on disease severity is unknown [41].

Most of the infections are asymptomatic in children as well as adults and many of them are not reported. Therefore, we confined ourselves to symptomatic cases only. Unlike other influenza-like viral infections (MERS-CoV, H1N1) the children have less severe COVID-19 affection as compared to adults [42]. Among the symptomatic ones, mostly have a mild cough, cold, fever, and upper respiratory tract infections only. The severe disease and the critical disease (acute respiratory distress syndrome, respiratory failure, shock, myocardial failure, and multiorgan dysfunction) are less frequent in children (1-3%) as compared to adults (10-30%) [37,38-43]. Similarly, the mortality associated with COVID-19 is much lower in the pediatric population (less than 0.1 %) than that reported in adults (5-15%).

We excluded neonates to avoid clinical heterogeneity as the clinical manifestations, mode of transmission, and outcome in the neonatal population are quite different from the pediatric population and are difficult to differentiate from the other neonatal illness. We included studies published until May 10, 2020 and enrolled patients tested positive for SARS-CoV-2 by RT-PCR. Also, it comprises information from observational studies done in six different countries and is likely to be the true representation of the clinical picture. The studies included in previous reviews were exclusively from China and were primarily case reports and small case series due to the non-availability of larger studies at that time [36,44,45].

This study had several limitations. The pandemic is still spreading and the available data are derived over a short duration. The clinical features, laboratory abnormalities, and radiological findings are limited to the studies describing symptomatic patients admitted in the hospital. Therefore, it may not fully characterize mild/asymptomatic patients not requiring hospitalization. Also, we did not evaluate the impact of pre-existing comorbidities over the clinical outcome; however, this is likely to be significantly less than adults. As most of the studies are small, retrospective with lot of heterogeneity and publication bias, the overall evidence (GRADE) is very low. Therefore, the results should be interpreted cautiously.

Most of the children with COVID-19 were asymptomatic. Amongst the symptomatic patients, the majority will have a mild infection with very few requiring intensive unit care. Though fever and other respiratory symptoms make up the commonest clinical presentation, many may present with gastrointestinal symptoms. Therefore, a comprehensive screening strategy including respiratory as well as gastrointestinal features may be more useful.

Contributors: JM: conceptualized and designed the study, formulated search strategy, collected data and analyzed the data, and drafted the manuscript; JY: Acquisition and analysis of the data, and critically revised the manuscript; LS: Acquisition and analysis of the data, and critically revised the manuscript; AY: Supervised the search strategy, data retrieval, and completeness of the data. Performed hand search of the bibliographies and critically revised the manuscript; JK: Conceptualized and designed the study, formulated search strategy, collected and analyzed the data, and drafted the manuscript. All the authors

WHAT IS ALREADY KNOWN?

- Most children with COVID-19 present with mild symptoms, and carry good prognosis.

WHAT THIS STUDY ADDS?

- Though fever and cough are the most common clinical presentation, many children may present with gastrointestinal symptoms.
- A comprehensive screening strategy including respiratory as well as gastrointestinal features (diarrhea and vomiting) may be more useful.

approved the final version of the manuscript and will be accountable for all aspects of the work.

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Web Table I Details of Studies Included in the Systematic Review

Author	*Country*	*Patients (n)*	*Study design*	*Age (range)*	*Study quality*
CDC COVID-19 Response Team [4]	United States of America	2572	Retrospective case series	0-18 y	Good
Chen, *et al.* [43]	China	12	Retrospective case series	6 mo-17 y	Poor
Cai, *et al.* [14]	China	10	Retrospective case series	3 mo-10.9 y	Poor
Dong, *et al.* [35]	China	728	Retrospective case series	4-15 y	Good
Du, *et al.* [11]	China	14	Retrospective case series	0-16 y	Fair
Garazzino , *et al.* [31]	Italy	168	Retrospective cohort	1 d -17 y	Good
Kai, *et al.* [32]	Republic of Korea	15	Retrospective case series	4-14 y	Poor
Korea CDC [33]	Republic of Korea	480	Retrospective case series	0-19 y	Poor
Li B, *et al.* [29]	China	22	Retrospective case series	2-8 y	Fair
Li H , *et al.* [13]	China	40	Retrospective cohort	16 d -14.2 y	Poor
Lu , *et al.* [16]	China	171	Retrospective case series	1d to 15 y	Fair
Ma , *et al.* [12]	China	50	Retrospective case series	0-16 y	Fair
Parri , *et al.* [30]	Italy	100	Cohort	0-17.5 y	Fair
Qiu , *et al.* [15]	China	36	Retrospective cohort	1-16 y	Good
Shi , *et al.* [17]	China	10	Retrospective case series	7 mo-11y	Fair
Shen, *et al.* [26]	China	28	Retrospective case series	1mo-17y	Poor
Song , *et al.* [19]	China	16	Retrospective case series	11mo-14 y	Poor
Tagarro, *et al.* [34]	Spain	41	Case series	0-15 y	Poor
Tan, *et al.* [28]	China	10	Retrospective case series	13 mo- 11y 8 mo	Fair
Wang , *et al.* [27]	China	31	Retrospective case series	6 mo-17 y	Fair
Wu, *et al.* [25]	China	74	Retrospective case series	1mo -15 y	Good
Xia , *et al.* [20]	China	20	Retrospective case series	1d-14 y	Fair
Xin, *et al.* [24]	China	13	Retrospective case series	2-17 y	Fair
Xu , *et al.* [21]	China	10	Retrospective case series	2 mo-16 y	Poor
Yaoling, *et al.* [22]	China	115	Retrospective case series	1 mo-15 y	Fair
Zheng, *et al.* [18]	China	25	Cross-sectional	1mo -14 y	Fair
Zhang, *et al.* [23]	China	46	Retrospective cohort	7 mo-18 y	Fair

REVIEW ARTICLE

COVID-19 Associated Hemophagocytic Lymphohistiocytosis and Coagulopathy: Targeting the Duumvirate

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Context: Preliminary data on coexistence of secondary hemophagocytic lymphohistiocytosis syndrome (HLH) and disseminated intravascular coagulation (DIC) in critically ill children with novel coronavirus disease (COVID-19) are emerging. Herein, we summarize the available literature and fill-in the gaps in this regard.

Evidence Acquisition: We have performed a literature search for articles in PubMed, EMBASE and Google Scholar databases till May 12, 2020, with following keywords: "COVID-19", "SARS-CoV-2", "HLH", "HScore", "coagulopathy", "D-dimer", "cytokine storm", "children" and "pediatrics" with interposition of Boolean operator "AND".

Results: Children presenting with moderate-severe COVID-19 and Kawasaki disease shock-like syndrome exhibit peripheral blood picture analogous to HLH. HScore, a validated tool to diagnose HLH, has been suggested to screen severe COVID-19 patients for cytokine storm. However, HScore faces certain limitations in this scenario. It may be more pragmatic to use 'high D-dimer' (> 3 µg/mL) instead of 'low fibrinogen' to facilitate early detection of cytokine storm. COVID-19 associated coagulopathy resembles hypercoagulable form of DIC with bleeding being rarely reported. Although the International Society on Thrombosis and Haemostasis (ISTH) interim guidance recommends low molecular weight heparin in all hospitalized patients, data is lacking in population below 14 years of age. However, in the presence of life-threatening thromboembolic event or symptomatic acro-ischemia, unfractionated heparin (UFH) should be used with caution.

Conclusions: HScore can be used as a complement to clinical decision for initiating immunosuppression. Children with moderate-to-severe COVID-19, especially those with documented thrombocytopenia or chilblains, should be regularly monitored for coagulopathy.

Keywords: *Cytokine storm, Disseminated intravascular coagulation, Immunosuppression, Management, SARS-CoV-2.*

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Novel coronavirus disease 2019 (COVID-19) has emerged as a pandemic, claiming over 350,000 lives worldwide. Disease mortality has been mostly attributed to viral pneumonia, complicated by acute respiratory distress syndrome (ARDS) and/or sepsis. A cytokine storm like picture in peripheral blood, as evident by significantly higher plasma levels of interleukin (IL)-2, IL-7, tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein-1 (MCP-1), inducible protein 10 (IP 10) and macrophage inflammatory protein 1-α (MIP-1α), has been shown in severe COVID-19 illness [1]. Albeit uncommon, but biochemical findings like C-reactive protein, D-dimer, liver enzymes and ferritin in high concentration along with increase in IL-6, IL-10 and interferon (IFN)-γ are being reported in critically ill children with COVID-19 [2]. This points towards a coexistence of possible secondary hemophagocytic lymphohystiocytosis (HLH) syndrome and a form of disseminated intravascular coagulation (DIC). Although biochemical diagnosis of DIC is straightforward, it is often challenging to diagnose HLH in an early evolving stage irrespective of the underlying conditions.

COVID-19-Associated HLH: A Distinct Entity?

HLH is a hyperinflammatory state characterized by development of fulminant multi-organ damage (including ARDS), which can also occur secondary to viral infections [3]. Of note, virus-associated secondary HLH (sHLH) was considered in the differential diagnosis of life-threatening pneumonia and SARS-CoV infection during 2003 epidemic [3]. In a recently published series of eight cases [4], authors suggested presence of new entity affecting previously asymptomatic COVID-19 children. A refractory vasoplegic shock like presentation with peripheral edema, pleuro-pericardial effusion, ascites and myocardial involvement was noted.

Additional presence of variable rash, conjunctivitis, extremity pain along with coronary aneurysm in one child, made authors to consider Kawasaki disease shock syndrome or toxic shock syndrome as differential diagnosis [4]. SARS CoV-2 was only identified in one child post mortem, who died of major ischemic cerebrovascular accident [4]. Although no pathological organism was identified on bronchoalveolar lavage or nasopharyngeal aspirates in seven children; positive antibody tests were later found in ten cases out of more than 20 children presenting in a similar fashion in that center (including eight children of published series). All these eight children, described in the series, had evidence of cytokine storm/HLH like picture in peripheral blood with high D-dimer level (range, 3.4-24.5 µg/mL) [4]. Subsequent data regarding this phenomenon are still awaited. Nevertheless, clinicians need to be extremely vigilant to diagnose cytokine storm/HLH in evolving phase in children during this pandemic.

HScore, a widely used tool for diagnosing HLH, was first validated in adult population [5]. Later on, HScore was also found to be more sensitive than adapted HLH-2004 guidelines for HLH diagnosis in pediatric population. However, a different cutoff value of the HScore was given for children [6] (***Table* I**). Recently, owing to non-availability of expensive cytokine assays in clinical practice, HScore has been suggested to screen critically ill COVID-19 patients to ensure timely immunosuppression [7]. However, it has certain limitations in this scenario.

Temperature rise, heavily weighted in HScore, does not seem to differ significantly according to the severity of COVID-19 [2,8]. In contrast to most forms of HLH, few studies [1,8] including one study in children [2], reported rather a lower incidence of leukopenia (mostly due to concomitant neutrophilia) in severe cases with cytokine storm. Lymphopenia, the striking hematological abnormality of adults with COVID 19, is an independent predictor of mortality [9,10]. Severe lymphopenia, with absolute count of less than 0.6×10^9/L, was also found to be an important indicator for intensive care support in patients [11]. Lymphopenia in critically ill children is reported to be less common in comparison to adults with COVID-19 [12]. However, clinicians should keep in mind that higher neutrophil count has also been shown to be associated with increased risk of ARDS and death [10].

Hepatosplenomegaly, seen in other HLH syndromes due to direct infiltration of macrophages and lymphocytes [3], has not yet been reported in COVID-19 patients. Likewise, there are no reports of hemophagocytosis in bone marrow aspirate in these patients. Notably, hemophagocytosis is not a specific finding for sHLH and it can be seen in viral infections as well [13]. Hypertriglyceridemia, believed to be due to inhibition of lipoprotein lipase by TNF-α, has not been documented in studies on adults, but it has been found in children [4]. Viral infections *per se* can also lead to hyperferritinemia suggesting a very low positive predictive value for diagnosing HLH with ferritin values [14]. Extremely high ferritin level (>10,000 ng/mL), which can detect sHLH/cytokine storm with around 95% sensitivity and specificity [3], has not been reported in adults or children [1,2,8].

Low fibrinogen level, with its high specificity for HLH diagnosis, helps to distinguish HLH subset from critically ill patients with sepsis. Interestingly, a recent study in COVID-19 pneumonia patients showed that D-dimer was significantly higher in non-survivors on admission than in survivors, but fibrinogen was not significantly different between two groups [15]. Fibrinogen was found to decline very late during hospitalization in non-survivors [10,15]. There is increased production of fibrinogen, an acute phase reactant, in hyper-inflammatory condition. Fibrinogen level can remain normal despite increased consumption by circulating microthrombins in early hypercoagulable state of severe COVID-19. Hence, rather than the finding of low fibrinogen level, rising D-dimer value is more likely to detect the hyper-inflammatory state in COVID-19 early in its course. Nonetheless, regular monitoring of fibrinogen would help guide clinicians to initiate cryoprecipitate infusion in case of bleeding with a drop in fibrinogen below 1.5 g/L.

A prospective study to diagnose sHLH subset in COVID-19 patients is underway using modified HLH-2004 guidelines (NCT04347460). HScore, being a more sensitive tool, has advantages over HLH-2004 criteria for early detection of COVID-19 hyperinflammatory state. In absence of bone marrow examination in critical care setting, it is also pragmatic to consider a lower HScore threshold (see table 1) in case of strong clinical suspicion to avoid delay in interventions. In fact, use of intravenous immunoglobulin in children with severe COVID-19 looks promising [2]. At the same time, over diagnosing HLH and treating them with steroids may be counterproductive. Thus, HScore should only be used as a complement to clinical judgment on immunosuppression in severe COVID-19.

Immunosuppression: A Word of Caution For Glucocorticoids

Due to lack of efficacious antiviral therapies, timely administration of glucocorticoid therapy, as in other sHLH

syndromes, indeed holds the promise to prevent development or further progression of ARDS and multi-organ dysfunction in COVID-19 with impending cytokine storm. The World Health Organization (WHO) does not advocate adjunctive use of steroids in critically ill COVID-19 patients till now, unless indicated for other reasons, such as adrenal insufficiency [16]. 'Surviving sepsis guideline' has suggested (weak recommendation) the use of short course of low dose glucocorticoids in mechanically ventilated moderate-to-severe ARDS in adults apart from its usual recommendation in refractory septic shock [17]. However, there is no recommendation regarding use in children. Glucocorticoids for long duration in high doses can lead to increased ventilator dependence, osteonecrosis and poor cognitive outcomes in children. Hence, in early ARDS with suggestion of cytokine storm, the protocol of using glucocorticoids in lower doses (less than methylprednisolone equivalent dose 1-2 mg/kg/day) and short duration (5 days) is acceptable [18]. RECOVERY is a randomized trial currently in recruitment phase that aims to investigate whether treatment with lopinavir-ritonavir, hydroxy-chloroquine, azithromycin, corticosteroids or tocilizumab prevents mortality in children and adults with severe COVID-19 (NCT04381936). Of note, corticosteroid in the form of oral (liquid or tablets) or intravenous low dose dexamethasone daily for maximum 10 days is being administered in this trial (prednisolone in case of pregnant or breastfeeding mothers). Interim analysis of this trial has found significant mortality benefits with low dose dexamethasone in patients requiring oxygen or ventilator support; although, complete data is still awaited.

Nonetheless, delayed viral clearance, worsening of preexisting diabetes and poor outcomes in severe ARDS remain the concerns for glucocorticoid use in COVID-19 illness with severe ARDS [19]. Glucocorticoid use may further interfere with the ability to replenish lymphocyte pool in patients with severe lymphopenia and compromise on chances of survival. Hence, individualization depending on lymphocyte count is warranted with regular monitoring for dyselectrolytemia, hyperglycemia and serial differential count. Clinicians also need to be vigilant about the possibility of unmasking of Critical illness-related corticosteroid insufficiency (CIRCI) following treatment withdrawal in these patients [20].

Intravenous immunoglobulin alone or in combination with glucocorticoids or plasma exchange may also be beneficial in children with this infection-associated HLH/cytokine storm [3]. IVIG has been recommended as a part of trials with variable doses, including, 1.0 g/kg/d for 2 days, or 400 mg/kg/d for 5 days, 0.2 g/kg/d for 3-5 days, or 2 g/kg/d infusion for 1-3 days. Data is still insufficient to recommend its use in HLH/cytokine storm with ARDS. Although recent prospective series on critically ill children has shown good outcomes with IVIG, randomized controlled trials are needed to draw validated conclusions [2]. However, for children with hyper-inflammatory vasoplegic shock like presentation in recovery phase resembling atypical Kawasaki disease, IVIG 2 g/kg within 24 hours of admission is warranted with vasopressor support and intravenous antibiotics cover [4].

Since significantly higher IL-6 was found in non-survivors compared to COVID-19 survivors [9], tocilizumab (anti-IL6 receptor antibody) has been widely used in many countries; but clinical evidence is still insufficient to recommend its use [16,17]. Clinical outcomes of tocilizumab administration will also be evaluated in hospitalized cancer patients of all ages with severe COVID-19 disease (NCT04370834). Other immunosuppressive drugs, eculizumab (anti-C5), siltuximab (anti-IL6), sarilumab (anti-IL6 receptor), anakinra (IL1 receptor antagonist), ruxolitinib & baricitinib (JAK1-2 inhibitors), adalimumab (anti-TNF), meplazumab (anti-CD147) and ixekizumab (anti-IL 17A) had also been included in various clinical trials, mostly for patients above 12 years of age [21].

COVID-19-ASSOCIATED COAGULOPATHY

Apart from the cytokine storm, another distinctive feature noted in severe COVID-19 cases was development of COVID-19-associated coagulopathy (CAC). Unlike acutely ill patients with decompensated form of disseminated intravascular coagulation (DIC) who have high risk of bleeding, this coagulopathy resembles hypercoagulable state of compensated chronic DIC [22]. This can be attributed to the distinct thrombo-elastography findings of high fibrinogen and high factor VIII activity in these patients [23]. Tang *et al*. [12] reported that 71.4% of non-survivors had overt DIC based on ISTH DIC diagnostic criteria **(*Table* I)** in contrast to 0.6% of the survivors. Notably, in one recent large case series, none of the patients with thromboembolic events developed overt DIC [24]. Hence, it is important to screen these patients for a new category, namely sepsis induced coagulopathy (SIC), which is believed to precede overt DIC; therapeutic anticoagulant use is more likely to yield benefits in this early phase [25]. In support of this rationale, in a cohort of 183 patients with age range 14-94 years, prophylactic heparin use for ≥7 days has been shown to be associated with significant reduction in 28-day mortality in patients with SIC score ≥4 (40.0% *vs.* 64.2%) or D-dimer >3 µg/mL, that is, 6-fold of upper limit (32.8% *vs*. 52.4%) [26].

Table I Scoring Systems for COVID-19-associated HLH and Coagulopathy

*HScore** [5]	*ISTH DIC score*[#] [25]	*SIC score*[‡] [25]
Temperature	–	Total SOFA score[$]
< 38·4°C: 0		1: 1
38·4°C-39·4°C: 33		≥ 2: 2
>39·4°C: 49		
Organomegaly	–	–
None: 0		
Hepato/splenomegaly: 23		
Both: 38		
Cytopenias^	*Platelet count*	*Platelet count*
1 lineage: 0	>100 × 10^9/L: 0	> 150 × 10^9/L: 0
2 lineages: 24	50-100 × 10^9/L: 1	100-150 × 10^9/L: 1
3 lineages: 34	<50 × 10^9/L: 2	< 100 × 10^9/L: 2
Triglycerides, mmol/L	*PT prolongation*	*INR*
<1.5 : 0	<3 s: 0	1.2-1.4: 1
1.5-4 : 44	3-6 s: 1	>1.4 : 2
>4·0 : 64	>6 s: 2	
*Fibrinogen, g/L***	*Fibrinogen*	–
>2·5: 0	>1.0 g/L: 0	
≤2·5: 30	≤1.0 g/L: 1	
Ferritin, ng/mL	*D-dimer*	–
<2000: 0	No increase: 0	
2000-6000: 35	Moderate increase: 2	
>6000: 50	Strong increase: 3	
SGOT, IU/L		
<30: 0		
≥30: 19	–	–
Bone marrow aspiration[##]		
Hemophagocytosis: 35		
No: 0	–	–
Immunosuppression[‡‡]		
Yes: 18		
No: 0	–	–

**HScore >169 is 93% sensitive and 86% specific for HLH in adults [5]. To obtain similar specificity, HScore cut-off >131 had 94% sensitivity, whereas HScore >120 was 100% sensitive and 80% specific to detect HLH in children at initial presentation [6]. ^Cytopenias - (hemoglobin ≤9·2 g/dL, white blood cell ≤5000/mm³ or platelet ≤110,000/mm³); **More emphasis on high D-dimer (>3 µg /mL) may be given instead for COVID-19 associated hyper-inflammatory state; ##In the absence of BMA in critical care setting, it is prudent to consider a lower HScore threshold based on clinical judgement to avoid delay in immunosuppression; ††HIV positive or on long term immunosuppressive therapies (i.e. glucocorticoids, cyclosporine, azathioprine); #ISTH DIC score ≥5 is 88% sensitive and 96% specific for overt DIC; ‡SIC score ≥4 is diagnostic for SIC; $Total SOFA (pediatric sequential organ failure assessment) score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA). Validated pediatric SOFA (pSOFA) score with age-adjusted variables should be used in children [39]; ISTH: International Society on Thrombosis and Haemostasis; DIC: disseminated intravascular coagulation; SIC: Sepsis induced coagulopathy; PT: Prothrombin time; INR: International normalized ratio; SGOT: Serum glutamic oxaloacetic transaminase.*

International Society on Haemostasis and Thrombosis (ISTH) interim guidance recommends measuring D-dimers, prothrombin time (PT) and platelet count in all patients for risk stratification and subsequent management plan [27].

Anticoagulant Use: Where Do We Stand?

ISTH interim guidance has recommended only prophylactic low molecular weight heparin (LMWH) to all hospitalized patients with COVID-19 in absence of active bleed or thrombocytopenia (platelet count <25×10^9/L) [27]. Anti-inflammatory properties of heparin are believed to offer an additional benefit in this pro-inflammatory milieu. Based on existing literature regarding severe hypercoagulable state of non-survivors with COVID-19, Barrett, *et al*. [28] have strongly advised to consider therapeutic anticoagulation with unfractionated heparin to prevent life threatening micro and macro-vascular thrombosis [28]. It is to be noted that one child with SARS CoV-2 infection did succumb to extensive ischemic cerebro-vascular stroke in a recent case series [4]. Chinese expert groups had issued guidance regarding therapeutic unfractionated heparin use (UFH at a rate of 3-15 IU/kg/h) based on high fibrin degradation product (FDP ≥10 g/mL) or D-dimer concentration (≥5 µg/mL), even in absence of documented thromboembolism [29]. As an alternative, LMWH in higher than normal prophylactic doses is also being used as thrombo-prophylaxis in adults with critical COVID-19 illness in many hospitals around the world.

Current evidence must be extrapolated with caution in the pediatric population. Data on LMWH use in population below 14 years of age is lacking in the large study that guided the interim recommendations [26]. Based on preliminary data from children who recovered from critical illness, none of them received prophylactic heparin during hospitalization [2]. In the case series presenting with Kawasaki shock syndrome-like picture with cytokine storm and high D-dimer, six children were rather advised high dose anti-platelet (aspirin 50 mg/kg); only one patient received heparin [4]. Heparin is generally avoided in children with hypercoagulable phase of DIC due to its potential adverse effect of bleeding, except for incident 'symptomatic' thrombi or acral ischemia [30]. Of note, skin manifestations resembling chilblains involving acral parts ('COVID toes') have appeared to be frequent among children and young population in recent literature [31]. This could be due to a direct virus-mediated endothelial damage, vasculitis or micro-thrombosis. Skin lesions in four children recovered without any sequelae in one case series [31]. Although elevated D-dimer along with the

clinical features in one child did suggest vaso-occlusion owing to micro-thrombus, it was not symptomatic enough to warrant anticoagulant use [31].

In absence of data on prophylactic anticoagulant use in children, timely immunosuppression remains the key to halt the immune-thrombosis model of multi-organ dysfunction. In persistent hyperinflammatory state with high fibrinogen and increasing D-dimer trend, a course of IVIG or tocilizumab should be strongly considered as per standard pediatric intensive care protocol [32]. A recent case-report from India [33] reported the successful use of tocilizumab (8 mg/kg intravenous over 2 h) as second line agent following single dose of IVIG (2 g/kg) in an 8-year-old child with COVID-19-associated hyperinflammatory syndrome. Plasma exchange may also be considered to salvage the situation in this setting.

Even if the clinical decision is made to administer anticoagulation in suspicion of thrombosis in persistent hyperinflammatory state and DIC, continuous intravenous infusion of UFH should be started with a low dose (5-10 U/kg/hour) and up-titrated slowly if required [30]. In addition to its advantage due to ease of titration, the anticoagulant effect also wears off quickly with stoppage. Activated partial thromboplastin time (aPTT) should be regularly monitored. UFH should be stopped in case of bleeding or high aPTT (more than 1.5 times upper normal level) [29]. For children with DIC, loading doses of heparin are generally avoided [30]. There is controversy regarding the type of heparin to be used in adults, since high fibrinogen and anti-thrombin deficiency in COVID-19 may lead to resistance to UFH [34]. Although LMWH has been used in adults with DIC, there is limited data to assess its efficacy in children with DIC [30]. Nonetheless, in case of symptomatic 'documented' thrombotic event or acro-ischemia, UFH is the ideal agent to use in pediatric intensive care setting, especially for those with renal insufficiency. For reasons unknown, heparin-induced thrombocytopenia seems to occur rarely in children [35].

One large-scale study on recombinant activated protein C (drotrecogin alpha) in patients with sepsis and DIC led to its abandonment from clinical use due to multiple reasons, notably, timing, dosing, efficacy and significant bleeding as a side effect [36]. However, studies are ongoing to evaluate other potential molecules in patients with sepsis induced coagulopathy or DIC. The preliminary success of recombinant soluble thrombomodulin in DIC and clinical states associated with endothelial dysfunction has shown promise with its tolerable side effect profile [37]. SARS CoV-2 enters the pulmonary epithelium by binding to ACE2; ACE2 in turn is cleaved and activated by host transmembrane serine protease 2 (TMPRSS2). Nafamostat, a TMPRSS2-inhibitor that also potently inhibits thrombin and plasmin, has been identified as a potential therapy in patients with COVID-19 and DIC [38].

Even though bleeding is rare in COVID-19 associated coagulopathy, stringent monitoring of surgical sites and orifices is needed for patients on invasive ventilation or extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT). If bleeding ensues, similar transfusion principles for DIC/SIC as per ISTH guidelines should be followed to keep platelet count above 50×10^9/L, fibrinogen above 2 g/L and PT ratio below 1.5 [27].

CONCLUSIONS

COVID-19-associated coagulopathy resembles hypercoagulable state of DIC with rare reports of bleeding. All moderate-to-severe COVID-19 patients, especially with documented thrombocytopenia (platelet count $<150\times10^9$/L) or acral manifestations, should undergo regular screening with SIC score, followed by screening for overt DIC. Unfractionated heparin infusion should be used in children with symptomatic thrombotic event under intensive monitoring. Although the presence of distinct COVID-19-HLH syndrome remains debatable, it is evident that a systemic hyper-inflammatory state has a significant role to play in 'immunothrombosis' model of multi-organ dysfunction and Kawasaki disease shock syndrome-like presentation in children. Interim analysis of RECOVERY trial has recently found mortality benefit with low dose dexamethasone for patients requiring oxygen or ventilator support. Immunosuppression with intravenous immunoglobulin has also shown favorable outcomes in critically ill children in preliminary studies. However, patient selection for immunosuppression should be done judiciously due to absence of well-characterized criteria for early identification of COVID-19-related cytokine storm. In view of the limitations of HScore in this context, it may be prudent to consider using 'high D-dimer' (>3 µg/mL) instead of 'low fibrinogen' to facilitate early diagnosis. HScore should only used as a complement to clinical judgment for instituting immunosuppressive therapies in severe COVID-19.

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Consensus Statement of Indian Academy of Pediatrics on Early Childhood Development

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Justification: Early Childhood Development (ECD) has lifelong impact on learning, education, productivity, socio-emotional functioning, health and disease. A Consensus Statement for promoting ECD is needed to improve patient care and promote research. **Process:** Indian Academy of Pediatrics convened a National Consultative Meeting on 20 September, 2019 at Surat to discuss the way forward for pediatricians in ECD and form a consensus advisory statement. Experts from Chapters of Infant and Young Child Feeding, Neurodevelopmental Pediatrics, Neonatology, Growth Development and Behavior, Adolescent Health Academy, Parenting for Peace and UNICEF participated. **Objectives:** To formulate, endorse and disseminate a consensus advisory statement of working at current levels of resources and to build future framework for ECD from Indian perspective. **Conclusions:** Interventions for ECD should begin from conception to adolescence, prioritized in first 3 years, inclusive and equitable for all, especially for high risk, vulnerable and marginalized families. Pediatric clinics can play a pivotal role as cost effective delivery points for guidance and interventions. Age appropriate approaches, active care giver's involvement, advocacy and integration with different sectors, community and policy makers should be done to enable supportive environment. Research should be promoted into finding cost effective novel scalable interventions.

Keywords: *Intervention, Management, Screening, Surveillance.*

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Early Childhood (up to 6 to 8 years) is the time of formation of base of all lifetime learning, education, productivity, socio-emotional functioning, health and disease. A slight shift in trajectory of child development in its initial journey can make a huge drift in its adulthood outcomes. Adversities and support during pregnancy, early childhood to adolescence have potential to change the whole life of the individuals and the society.

The first 1000 days (conception to 2 years age) are most sensitive and crucial in development [1]. Neuroplasticity declines after early childhood. Thereafter less stimulated synapses during first 1000 days get pruned and will be lost for a life time [2]. Science has also begun to decipher the impact of environmental factors and parenting quality on genetic expressions spreading over more than one generation [3]. Children's developing brain needs nurturing care [4] in the form of: good healthcare; enriching nutrition with responsive feeding [5]; stimulating experiences with responsive positive parenting (prompt, consistent and appropriate child-caregiver interactions with play, talk and love); early learning provided by parents and family members [6]; and security and safety. They should be supported by an environment enabling such needs. It is also evidenced that deficits in ECD (Early Childhood Development) cannot be effectively repaired when interventions are done after 24 to 36 months age [7,8].

Accompanying commentary: Pages 793-94.

The prevalence of improper child development is much higher than generally estimated. The four risk factors

are recognized as eligible for prompt actions are: stunting, low cognitive stimulation, iodine deficiency, and iron deficiency anemia. With majority childhood adversities being manageable and preventable the interventions in ECD are far more warranted as cost effective. ECD has far reaching implications in development of nation and inactions in ECD are very costly [9].

IAP has long recognized the importance of a focus on brain development. There are dedicated chapters to the cause of specific areas of ECD. Assimilation of currently published guidelines related to ECD and bridging the gaps in view of needs of ECD should be done as a detailed module. From amongst these some guidelines are already in place and published by IAP and its sub-chapters on topics of neonatal resuscitation, different aspects of nutrition and feeding, child safety, immunization, disabilities, etc [10-22].

Pediatric clinics and hospitals are point of care opportunities for ECD care. High risk assessment, anthropometric monitoring, treatment of illnesses, immunization, diet counseling and therapeutic ties with families are routine for them. Busy practices frequently miss developmental surveillance and screening, anticipatory guidance including safety and tips for responsive nurturing parenting care. They can be developed to work comprehensively for ECD to improve patient care and promote research **(*Web Table I*)** [23].

OBJECTIVES

Increasing importance and evidences of ECD mandates the need for formulation of consensus guideline statement on it for the Indian pediatric facilities to work comprehensively, based on WHO (World Health Organization) - UNICEF (United Nations Children's Fund) framework on Nurturing Care for ECD. To gather the currently available resources published by IAP (Indian Academy of Pediatrics) backing up the ECD; and gaps where pediatric facilities can work better or do advocacy or liaison with other faculties in improving ECD. To formulate and disseminate a comprehensive advisory for pediatric facilities in contributing to ECD, and to make a framework for future actions in ECD. The consensus guideline would help achievement of Sustainable Development Goals (SDGs) and global targets set in Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition; and The Global Strategy for Women's, Children's, and Adolescents' Health.

PROCESS

IAP organized a National consultative meeting of experts on 20 September, 2019, during the West zone PEDICON at Surat. Experts from United Nations Children's Fund and Indian Academy of Pediatrics from fields of developmental pediatrics, neonatology, nutrition and feeding, neurology, public health, child safety and general pediatrics from different parts of India were present at the discussion. Discussion took place for development in different age groups. Detailed articles were submitted later on them to formulate a module. This consensus statement is formed as an excerpt of the discussions and contents of the draft module. Search was made in databases of MEDLINE through Pubmed, Google Scholar, Cochrane library, and recent systematic reviews using combination of keywords *viz.*, early childhood development, stimulation, early intervention, nurturing care, responsive feeding, child nutrition, child safety, parenting, care for development, preschool learning. Child development, infant and young child feeding, parenting nurturing care, india, first 1000 days, and further expanded through related articles and reference lists of the articles.

RECOMMENDATIONS

General Recommendations

- WHO-UNICEF guidelines on Care of development [24,25] be adapted as reference for care development frame, till new Indian research-based evidence is available.
- IAP should join global partnership for ECD –The ECD Action Network (ECDAN).
- Psychosocial interventions to support maternal mental health should be integrated in early childhood health and development services [25]. All mothers should be screened for depression between 1 and 3 months postnatally. Parenting interventions improves maternal depression also [26]. During routine visits for child, mothers should be guided and reminded to take iron and calcium supplements and healthy diet; and visit obstetrician/family physician for general health, contraception, family planning, reproductive and sexual health.
- Pediatricians should lead awareness generation in care givers and the development of training module for frontline workers.
- Family focused care with adequate involvement of fathers is a must. The health and leave policies should be family friendly [24].
- Gender equity and female education should be propagated.
- Identification and attention to specific needs of vulnerable, at risk and marginalized children during routine care should be done with extra efforts [24].

- Promote early responsive caregiving (positive parenting) and early learning. Support for it should be included as part of interventions for optimal nutrition of infants and young children as responsive feeding strategies. Parents and other caregivers should be supported in doing so [5,24,25]. Encourage and support combined play times, life skill education and emotionally healthy home and school environments. Promote age-appropriate play and cultural toys. In resource-poor settings delivery of parenting interventions by trained non-professionals through local community organizations should be promoted [26].
- Pediatricians should routinely talk to parents and caretakers of children under 5 years of age regarding adequacy of physical activity, sedentary behavior and sleep [27].
- Care takers should be routinely guided about regulations and guidelines for use of screens and digital devices right from the delivery rooms, to TV programs and internet availability for children in school and homes, especially background running of television before the age of 2 years [28].
- ECD needs a structured approach at pediatricians' clinics using a comprehensive checklist.
    - Age group-wise single page content health file should be made in line of MCP (mother child protection) card to include each domain of ECD viz., standardized nutrition, development, parenting tips, stimulation, preschool learning and safety advices.
    - Display of public information of ECD domains in waiting rooms including audio visual formats should be done.
    - A parent friendly IAP digital app for comprehensive approach to ECD should be made and disseminated.
- Advocacy and integration be done with other sectors like obstetrics, education, social welfare, child safety, politics, international, national and local - social or governmental agencies and media at large *etc*. Facilitate formation, funding, implementation, coordination and monitoring-evaluation of high quality intervention programs and public policies [4,24].
- Expert inputs are needed to finalize the preschool learning & education advises by pediatricians:
    - Awareness among caretakers of early childhood including school teachers and policy makers, about all aspects of child development, emotions and behavior at different ages, guidance on safety-security, sleep, nutrition and screen viewing.
    - Awareness in preschool teachers in age appropriate activities, pre-reading, pre-writing and attention skills, should be universal [29].
    - School / daycare crèche policies, guidelines and trainings should be developed in consultation with IAP for age, development, behavioral and emotion appropriateness. Guidelines for school entry with readiness and age appropriate activities at schools.
- Curriculum for graduate and postgraduate medical students should also include socio-emotional, speech-language, and social communication domains of development.
- Promote research in developing local and innovative methods in ECD science and delivery of care.
- Anganwadis need an additional trained worker in early stimulation and care for child development for under-3 children in addition to current practice of only pre-school education of 3-6 years.
- Pediatric facility staff needs to be trained to sensitively facilitate identification and referral for safety and security issues of children. Facilities should display/ disseminate relevant awareness material [20,22].

Recommendations in Neonatal Period

- Early identification and treatment of perinatal asphyxia in delivery room.
- Identifying high risk newborn following birth and at hospital discharge.
- Stratification of newborn based on risk factors ***(Table-I)*** [30]. Other risk factors for neuro developmental delay are preterm babies with any one or more of: PDA (patent ductus arteriosus, NEC (necrotizing enterocolitis, CLD (chronic lung disease), recurrent apnea, EUGR (extra uterine growth restriction), shock, PPHN (persistent pulmonary hypertension in newborn), complex congenital malformations, need of significant resuscitation, need for postnatal steroids, post surgery of CDH (congenital diaphragmatic hernia) and TEF (tracheo-esophageal fistula).
- Metabolic and hearing screening for all normal newborns.
- Identification of 'high risk' newborns and screening for significant hyperbilirubinemia (BIND Score and

Table I Risk Factor-based Stratification for Follow-up Care

At risk	*Risk factors*	*Care by*
Mild	>37 week, >2.5 kg, HIE stage I, Transient hypoglycemia, Suspected sepsis, Jaundice in preterm, Grade I/II IVH (intraventicular hemorrhage)	Pediatrician
Moderate	33-36 weeks, 1500-2500 gms, HIE stage II, Sepsis, jaundice with exchange transfusion, >Grade II IVH, Prolonged encephalopathy, Uncomplicated course on ventilation, Hypoglycemia >3 days, Need for some resuscitation	Neonatologist / developmental pediatrician
Severe	<1500 gms, <33 weeks, Multi organ injury, HIE stage III, >7 days ventilation, meningitis, kernicterus, abnormal neurologic exam at discharge, PVL (periventricular leucomalacia) or hydrocephalus, low Apgar at 5 min., Symptomatic hypoglycemia	Developmental Early Intervention Centre (DEIC)

Modified from reference 30; HIE: Hypoxis ischemic encephalopathy.

use of Bhutani's hour specific nomogram chart [31,32]

- Optimizing nutrition: Ensuring lactation by breastfeeding, helping maintenance of lactation in mothers of babies admitted in NICU and early detection and support for breastfeeding problems.
- Screening for hypoglycemia: Identify 'at risk' and screen all 'high risk' and sick newborns for glucose at 2 hours of age and every 4-6 hourly till first 48 hours of age and full feeds.
- Detection and management of postnatal hypoxia (for preterm newborn - Silverman Anderson Score, for full term newborn – Downes and Vidyasagar Score).
- Developmentally Supportive Care (DSC) in NICU including promotion of KMC (Kangaroo Mother Care) as comprehensive maternal care for development and nutrition.
- Follow up of NICU graduate using checklist. 'At risk' neonates may seem healthy and NICU graduates need a structured follow up, as they are at risk of significant neuro morbidity [33].

Interventions in the Neonatal Unit

The core objective of management of high risk babies is to have a 'brain protective' management strategy throughout the course of stay in NICU. Common brain protective strategies that need to be kept in mind include [34]:

- *Care during resuscitation:* Use room air / low oxygen up to 30%, for babies >32 weeks of gestation, tailoring oxygen delivery based on recommended target oxygen saturation in the first minutes after birth, labor room CPAP (Continuous Positive Airway Pressure) stabilization for preterm [10].
- *Optimizing nutrition:* EUGR is associated with poor neuro developmental outcomes [35]. Use mother's own milk (MOM), donor human milk (DHM), TPN (total parenteral nutrition), early trophic feeds. Use of MOM/DHM for its benefits in reducing late onset sepsis, NEC and ROP (retinopathy of prematurity) [12,13,15].
- *Gentle Ventilation:* Non-invasive ventilation/gentle ventilation/volume targeted ventilation to reduce incidence of BPD (broncho pulmonary dysplasia) and related morbidity [36].
- *Maintaining hemodynamic stability* to minimize post-natal ischemic brain injury [37].
- *Therapeutic hypothermia*: For babies with HIE (hypoxic ischemic encephalopathy), if facilities exist [38].
- *Neuro-protective care/Brain sensitive care/DSC* [39,40]: Protect sleep cycles, especially REM (rapid eye movement) sleep; quiet environment (<45 dB); protecting eyes from bright lighting; clustering of care; hourly 'no touch' rounds; reduction of positional deformities by maintaining infants in a midline, flexed, contained, comfortable position with nesting, hand containment, swaddling and gentle handling; and prolonged KMC [41].
- *Skin care:* Minimize use of tape, moisten adhesive skin interface before removal [42].
- *Promote self-regulation and neurodevelopmental organization:* 'cue based care giving' by identifying stress cues, stability cues and self-help cues for autonomic, motor and state stability.
- *Tactile stimulation:* Touch, gentle massage.
- *Minimizing pain:* Non-pharmacologic and pharmacologic pain relief, containment, hand holding, KMC, breastfeeding/breastmilk use, non-nutritive sucking, oral sucrose [43].

- Involvement of family members in care of baby and decision-making.

Neonatal Developmental Intervention by Family Members at Home

- *Visual stimulation*: Decoration of surroundings, with moving and brightly colored objects. Black and white contrast sends the strongest signals to newborn brain.
- *Auditory stimulation*: By talking, singing, recorded mother's voice, recorded heart beat and musical toys. Radio, television *etc* sounds should be avoided in first two years.
- *Tactile stimulation*: Non–nutritive sucking, stroking, flexing, massaging with or without oil or cream, rubbing, positioning and giving bath. Massage advices are not recommended in high risk neonates with increased muscle tone. Massage should be done very carefully in preterm babies and term babies having asymmetric reflexes or neurologic compromise.
- *Vestibular-kinesthetic stimulation*: Rocking, oscillating beds e.g., water beds.
- *Carry in arms:* Avoid use of baby pods and cots. They interfere with the proprioceptive sensory input which the baby gets when carried in the arms of the caregiver.
- Avoid overstimulation.

Recommendations in Post-neonatal Period

- Age appropriate development surveillance using red flags checklist at each routine healthy baby visits. Problems found during it should be addressed with screening test [44].
- Display of red flags and basic stimulation tips at different ages in waiting areas.
- All children should undergo developmental screening using standard tools at 9, 18, 24 and 36 months [44,45].
- Detailed assessment to be undertaken of high risk children and screening positive cases.
- Early intervention for the high risk and developmentally delayed children.
- Stimulation and parenting advices to be delivered in waiting rooms by trained health care workers. Use CDC (Centers for Disease Control and Prevention) milestone tracker app till evidence based Indian app on public domain is available.
- The international prescriptive standards designed by WHO multi-centric study are recommended for growth monitoring. Each well baby visit should incorporate nutrition monitoring and advices.
- Use Child Behavior Checklist (CBCL) for early pick up of problems like attention deficit.
- School readiness screening should be encouraged at pediatric clinics before the child is placed in preschool or kindergarten [46].
- Mapping of facilities for detailed diagnostic, therapeutic and supportive medical and nonmedical services will be done by the NDP (Neuro developmental pediatrics) and GDBP (Growth development and behavior) chapters and published in the module.

For purpose of including in routine practice, the recommended actions are arranged age-wise as a checklist **(*Table II*)**.

CONCLUSIONS

This consensus statement is envisaged to guide Indian pediatric fraternity to improve practices and advocacy in ECD as per view of experts from across the country. There is urgent need to act fast in this subject in consideration of low awareness towards combined efforts in its divergent areas. Convergence of efforts with other medical and nonmedical faculties will bring newer aspects of promoting ECD. Newer evidences are building up fast in this subject, which will lead to update of this consensus with the feedbacks from field gather.

Disclaimer: This consensus statement is prepared for assisting pediatricians in accordance with current scientific evidence and guidelines for acting in early childhood development as a whole; however, many areas are still not clearly defined. These statements cannot establish a standard of care, and decisions about treatment should be based on the judgment of the clinician on the merits of the individual cases dealt by them.

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Table II Checklist for Working in Early Childhood Development at Pediatric Clinics

	*Age**	*NBB*	*6 wk*	*10 wk*	*6 mo*	*9 mo*	*12 mo*	*18 mo*	*2 y*	*3 y*	*4 y*	*5yr*
	Date											
Health	Growth [#]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Vaccination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Anomalies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Genitals / hernia	✓	✓	✓	✓	×	×	×	×	×	×	×
	Murmur	+ SPO2	+ SPO2	✓	✓	×	×	×	×	×	×	×
	Abdomen mass	✓	✓	✓	✓	×	×	×	×	×	×	×
	Hips	✓	✓	✓	×	×	×	×	×	x	×	×
	Umbilicus	✓	✓	✓	×	×	×	×	×	×	×	×
	Teeth	×	×	×	×	×	×	✓	✓	✓	✓	✓
	Biochemistry	×	×	×	×	Hb Urine	×	Hb	Hb Urine	×	×	×
	Blood pressure	×	×	×	×	×	×	×	✓	×	×	✓
Nutrition	Nutrition	BF	BF	BF	BF + CF	BF + CF	BF + CF	BF + CF	BF + CF	Diet	Diet	Diet
	Supplementation**	D	D	D	Fe + VD + VA	Fe + VD	Fe + VD + VA	Fe + VA	Fe + VA	Fe + VA	Fe + VA	Fe + VA
	Rickets	×	×	×	✓	✓	✓	✓	✓	✓	×	×
Develop-ment	Reflexes and Tone [$]	✓	✓	✓	✓	✓	×	×	×	×	×	×
	Development	×	×	Surveillance	×	Screen	Surveillance	Screen+ M-CHAT	+ M-CHAT	Screen + ADHD + CBCL	CBCL + ADHD	CBCL + ADHD+ Pre-school Screen
Special Senses	Hearing[$$]	✓	✓	✓	×	×	×	×	×	×	✓	✓
	Eyes[##]	Red reflex	NLD	×	×	Vision Squint Optic atrophy	Squint	×	Vision Squint Optic atrophy	Refraction	✓ ✓	
	Stimulation and Caregiving advice	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Safety advice	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Early learning advice	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Maternal depression screen	×	✓	✓	✓	×	×	×	×	×	×	×

**Correction for gestational immaturity at birth should be done till 24 months age for all preterms. Use corrected age for weaning and milestone screening. Use postnatal age for vaccination; [#]At every visit check weight, height using boys/girls growth chart. Interpret head circumference with total length till 12 months of age. (HC=TL/2 + 9.5 + 2. 5 cm); [$]Amiel Tison Angles till 12 months of age; **Early iron supplementation for well preterms from 2-3 weeks of age; calcium and phosphorous for LBW <1800g, till 4 kg weight; [##]ROP Screening at 1 month age for birth at <34 weeks or birth weight <2 kg; [$$]Universal OAE screening at discharge and BERA for abnormal OAE screens and in all high risk babies, screen clinically at each visit; Checklist for preterm and high risk neonates: Use Intergrowth 21/ Fenton's chart till 40 weeks gestation for preterm. Thereafter use WHO Growth chart (2006) as for term infants.*

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ANNEXURE

Participants at the National Consultative Meeting for IAP Consensus Guidelines on ECD (in alphabetical order):

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Invited but could not attend the meeting: Dr. MKC Nair (Trivandrum), Dr. Vibha Krishnamurthy (Mumbai), Dr. Roopa Srinivasan (Mumbai), Dr. Pankaj Buch (Jamnagar), Dr. Jayashree Mondkar (Mumbai) and Dr. VP Goswami (Indore).

Integration in Medical Education

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The term integration has gained importance in Medical education over the last two decade, and is believed to facilitate knowledge, that is more meaningful to clinical practice. A move towards integration in medical education is likely to reduce fragmentation of the medical course and motivate students towards better learning, It aims to improve medical education by bridging the traditional barrier between basic and clinician sciences. Integration is one of the major changes incorporated in the new competency based curriculum for undergraduate medical program in India. There are associated changes in the assessment system too in relation to integration. However, the concept of integration/integrated curriculum lacks significant clarity as how to implement it in medical institutions with added paucity of literature on this important topic. Integrated teaching is the integration of the concepts wherein various subject-based knowledge or aspects of one theme or topic areassimilated to provide the holistic approach. Our review focusses on the need for integration with comparative analysis of the two most important models of integration (Fogarty and Harden) which are being followed, delving on their common features for simplifying this complex topic as well as for better understanding of the concept. We have also proposed six steps for implementation of integration. We conclude that the proposed change from conventional to new integrated curriculum requires robust planning and coordination amongst the various stakeholders in medical institutions.

Keywords: *Competency-based medical education, Curriculum, Multi disciplinary.*

All of us are aware of the importance of term "integration". The concept of life or even the whole universe is non-existent without integration. We cannot compartmentalize our body into various systems or organs, everything in the body has to work in coordination with each other just to stay alive. This is not only true for human lives but also holds true for all kinds of system in the universe- be it natural or man-made. We have given this example of human body just to stress upon the importance of integration in medicine as medical education is all about dealing with human body, its function, diseases and treatment.

Integration in medical education is best described by Harden as 'the organization of teaching matter to interrelate or unify subjects frequently taught in separate academic courses or departments' '(Harden et al, 1984) [1]. Shoemaker also defines an integrated curriculum as "education that is organized in such a way that it cuts across subject matter lines, bringing together various aspects of the curriculum into meaningful association to focus upon broad areas of study" [2].

Undertraditional curriculum in India, majority of the medical colleges teach subjects in isolation without much effort to integrate the basic/paraclinical with the clinical subjects. An integrated curriculum provides a platform where learning takes place in a context (contextual learning). It also promotes a holistic approach to patients and their problems. The learning theory 'constructivism' behind the integration of basic and clinical sciences states that learner needs to understand the concepts in basic sciences and make connections with its applicability in clinical sciences. There should be development of construction of understanding the relevance of learning basic sciences [3].

In this review, we will discuss, how to develop, implement and evaluate an integrated curriculum. Let us start by reviewing the importance of integrated curriculum and why it is the need of the hour.

Purpose of Integration

Knowledge is most effective when the organization of that knowledge matches the way in which the knowledge is to be used [4]. It is believed that the current system of medical education is fragmented, the subjects are taught in isolation with unnecessary repetitions and there is no structured or systematic effort to interrelate the concepts of various diseases [5,6]. For example, when students are taught about liver in different disciplines without any integration, they may develop the concept of anatomical liver, physiological liver, pathological liver and so on

without getting the holistic concept of the body and various diseases in the context of liver. As a result, it is left to the students to understand or develop the correlation between the topics taught in various disciplines.

Human body is a perfect example of integration. The knowledge learnt in isolation remains to be applied to a complex system like human body. The basic idea of integration is to develop a holistic approach to treat that particular disease affecting human body. It is true that body is divided into systems and organs but they always work in unison with highest level of coordination possible. Similarly, it is important to have coordination between subjects to understand the body and the diseases better, so that when a student sees a patient, it should all come together.

An integrated approach in medical education captures students' attention and creates more excitement in learning, prevents repetition, enhances reinforcement of important areas or topics, and improves retention of learning [7]. The long-pending demand of students that basic and clinical sciences should be integrated can be achieved with this approach. Basic sciences' role is well documented for learning of clinical sciences [8]. The students trained with such an integrated curriculum, make more accurate diagnosis than students trained in a conventional curriculum as they learn to apply their knowledge to clinical practice as a result of more contextual learning. This promotes a holistic approach to patients and their problems. It also promotes interdepartmental collaboration and helps in rationalization of teaching resources [9,10]. It was interesting to note that in various workshops conducted at various medical colleges, few faculty members got introduced to each other for the first time; although, they had been working in the same institute for long.

Here, it is important to understand that in our body, each and every cell, every tissue, organ and system has its own importance and they need to develop fully for any kind of coordination to be successful. Similarly, each and every discipline or subject is important and should also have their identity maintained but never in isolation. It is just like a rainbow where the different colours maintain their identity but are very closely assimilated to showcase their features. The impact of a rainbow is different than the single colours. In medical curricula also there has to be a balance between integrated teaching and discipline-based teaching.

TYPES OF INTEGRATION

Integration has traditionally been divided into three types based on two basic components of curriculum as reference points that is time frame and clinical disciplines/ subjects [11].

Horizontal Integration: Integration that occurs across disciplines/subjects but within a finite period of time. For example, integration among subjects of first phase of undergraduate curriculum in India. (***Fig.* 1a**).

Vertical Integration: Integration across time – it breaks the traditional divide among the basic science and clinical subjects and brings them together. For example, integration among subjects of different phases (***Fig.* 1b**)

Spiral Integration: This is the integration across time and disciplines. It is the most complete form combining both horizontal and vertical integration. The major advantage of this model is the better reinforcement of topics through a natural progression from simple to complex using a curriculum that breaks down the barriers and boundaries between the courses and the departments [12] (***Fig.* 1c**).

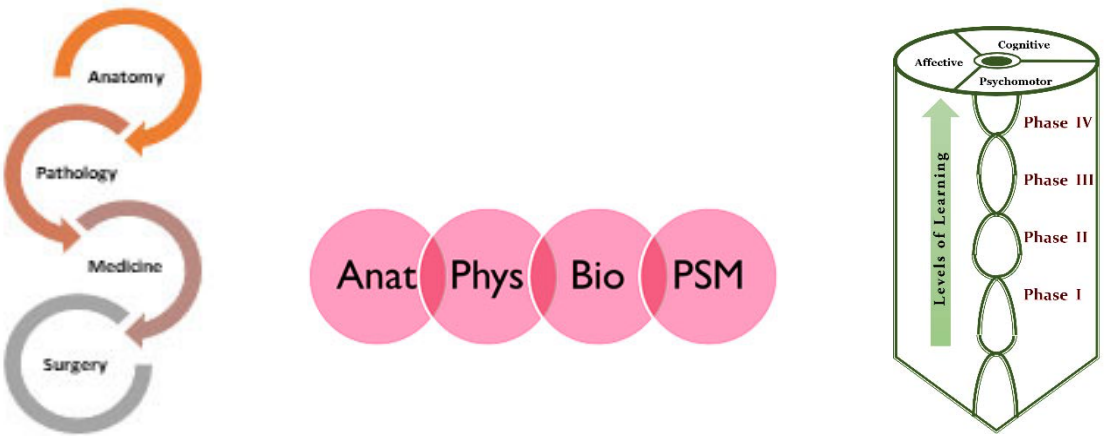

Fig. 1 *(a) Vertical Integration; (b) Horizontal Integration; (c) Spiral Integrated model*

Table I Comparison of Two Common Models of Integration

S.No.	*11 steps on the integration ladder (Harden, 2000)* [14]	*Common description*	*Ten ways to integrate curriculum (Fogarty, 1991)* [14]
1	Isolation	Various disciplines /departments organize their teaching without considering other departments or subjects	The fragmented model
2	Awareness	Teacher is made aware of what is covered in other subjects through appropriate documentation about aims and objectives of each course	
3	Harmonization	The Disciplines remain separate but the teacher may make explicit connection within the subject areas to other subjects	The connected model
4	Nesting (Infusion)	The teacher targets within a subject based course, few objectives relating to other subjects. Contents drawn from different subjects are used to enrich the teaching of a particular subject	The nested model
5	Temporal coordination	The related topics within a subject are taught separately but are sequenced / arranged/scheduled at same time in consultationwith other subjects.	The sequenced model
6	Sharing	Two disciplines may agree to plan and jointly implement a teaching program using overlapping concepts or ideas as organising elements	The shared model
7	Correlation	Within the subject based framework, integrated teaching sessions are introduced. These sessions bring together areas of common interest in each subject.	
8	Complementary programme	It has both subject based and integrated teaching. The basic difference with correlation is that the percentage of integrated sessions are increased	Webbed
9	Multidisciplinary	This step brings together a number of subject areas in a single course with themes, problems or issues as the focus of teaching. The subjects/ disciplines still preserve their identity and demonstrate how they contribute to the understanding of the theme or problem.	
10	Inter-disciplinary	The subject/discipline boundaries become blurred. There may be no reference to individual subjects or disciplines as they are not identified in the timetable. Interdisciplinary teaching implies a higher level of integration, with the content of all or most subjects combined into a new course with a new menu [15].	The integrated model
11	Trans-disciplinary	There are no subjects or discipline. There is only one subject for education, and that is Life in all its manifestations [16].The teacher provides the framework of learning opportunity and the integration takes place in the mind of the students based on situations of the real world.	Immersed

MODELS OF INTEGRATION

Over the last few decades, medical educationists have realized the importance of integration and understand that integration is a key factor in the delivery of an effective educational program [9]. The two most discussed models for the development of integrated curriculum are the ten ways to integrate Curriculum by Robin Fogarty [13], and the integration ladder by Harden [14].

We have tried to compare and correlate these two models for better understanding and simplification (***Table* I** and ***web table* I**).

Two integrated teaching models given by Fogarty which are not correlating with any of the steps of Harden ladder are the threaded model and the networked model. The threaded model of integration thread various concepts and skills throughout various disciplines. Teaching sessions are planned according to the identified skills or concepts. In the networked model, the learners themselves, knowing the intricacies and dimensions of their field, can target the necessary resources as they explore within and across their areas of specialization [13]. For example, the option of selecting electives in a course. Students chooses their own areas of interest and during the electives, he or she may come across number of experts in the field and develop the networking.

Integrated Curriculum vs Integrated Teaching

The difference between integrated curriculum and integrated teaching is almost similar to the difference between syllabus and curriculum. Integrated teaching is limited to one particular session or topic which can be achieved either by individual efforts or collectively by the concerned departments, while integrated curriculum requires effort at larger level, mostly institutional with multiple sessions of integrated teaching. Nesting, the fourth step in the Harden ladder is an example of integrated teaching while the temporal coordination, the fifth step in the ladder is not an integration in true sense as there is no connection between the subjects or the topics, they merely are aligned together. Actual curricular integration starts from the seventh step *i.e.*, Correlation. Integrated teaching is an all or none phenomenon, either it is integrated, or not integrated while integrated curriculum is a continuum from incomplete to complete.

This is usually documented during the development of curriculum whether all the teaching sessions will be integrated or a particular percentage of the curricular delivery will be integrated. Medical Council of India (MCI), in their recent revision of curriculum, have suggested that at least 20% of the curriculum should be integrated and they have also provided examples of the areas where integration can take place [17].

IMPLEMENTATION OF THE INTEGRATED CURRICULUM

Integration is represented as a continuum with full integration at one end, discipline-based teaching at the other end, and intermediate steps between the two extremes [18]. Integrated curricula can also be labelled as complete or incomplete. Horizontal and vertical integration are examples of incomplete integration while spiral integration is an example of true or complete integration.

The change from traditional subject-based curriculum to an integrated curriculum should be gradual and starts with the understanding of one's place in the integration ladder. Most of the teachers agree with the value and importance of integration but are not sure about the extent of integration required and how to go about it. The institution should take into consideration the existing curriculum, experience and training of the teachers, existing infrastructure and most importantly the aim of the curriculum, before deciding on the level of integration. The higher one moves up the integration ladder, the greater coordination and communication is required amongst different disciplines [14].

Before actually going for its implementation, it is important to understand that integrated teaching or curriculum is the integration of the concepts where various subject based knowledge or aspects of one theme or topic is assimilated to provide the holistic approach. Integration does not mean that multiple teachers from different subjects are delivering their lectures in the same session. Planning of the session is usually done before the actual teaching session by subject experts/ teachers about the content and delivery methods. It is not always necessary to actually involve the teachers of different subjects during the teaching sessions; they are mostly involved at the planning level only. However, if you think that getting a surgeon into anatomy class can encourage/motivate students to learn anatomy in context, then that can be done.

Six Steps of Integration in Curriculum-implementation

1. *Train the teaching faculty*: Implementation of integrated curriculum requires lot of dedication and coordination among faculty members of different disciplines. Still there are lot of reservations and doubts about the utility of the integrated curriculum. Faculty members should be sensitized about the importance and objectives of integrated curriculum. They should be explained about their roles and responsibilities towards the integrated curriculum. The new undergraduate medical curriculum implementation in India is being supported by MCI by training teachers in MCI affiliated medical colleges through Curriculum Implementation Support Program (CISP). The programme trains teachers in integrated teaching too. However, training requires longer sessions as well as refresher courses at all levels.
2. *Level of integration*: Integration is possible only when the components or the building blocks are ready. In medical education, basic sciences are our building blocks and that is the why most educationists feel that there is a need for both subject based as well as integrated experience in the curriculum, and it is not

advisable to have an integrated curriculum where individual disciplines completely lose their identity [1]. We should also understand that higher level of integration is difficult in basic sciences/phase I undergraduate course, so the integration level should also be different at different phases of undergraduate education. Harden ladder is a good guide to decide on the level of integration. Nesting and temporal coordination (incomplete horizontal integration) are easily possible at basic science level, while correlation, complementary program and multi-disciplinary steps are better suited for last phases of the undergraduate curriculum. Medical Council of India has given us freedom to choose between nesting, temporal coordination, sharing and correlation (Steps 4-7 of Harden ladder) at various phases of the undergraduate course [17]. The level will also depend on the topic and competencies chosen for integration.

3. *Assign the responsibilities*: The next step is to create committees or groups of faculty members across different disciplines. There should be an adequate representation from both basic sciences and concerned clinical subjects. The committee should not only be responsible for developing the integrated modules of teaching but also coordinating in its actual implementation. In the new MBBS guidelines, this responsibility has been assigned to Alignment and Integrated Topic (AITo) team.

4. *Develop integrated teaching modules or sessions*: The most crucial step in the integrated curriculum is to develop the teaching modules. A module is a set of learning opportunities with respect to a well-defined topic or problem that contains specific objectives, teaching learning activities and assessment strategies [19]. Integrated modules may include body systems like cardiovascular system, life cycles like childhood, core problem based like chest pain, thematic like organ failure [8,20,21]. The module should be developed for all phases together so that integration is pre-decided for all phases for a particular topic.

5. *Design Integrated Assessment*: Though development of a complete module includes assessment, we have decided to mention it as a separate step just to stress upon the importance of assessment in the curriculum. What is assessed and which methods are used for assessment will play an important role in what is learnt and how it is learnt [21]. The success of integrated curriculum depends on the implementation of integrated assessment [1]. Methods assessing the higher level of cognitive domain should be used. Various assessment methods suggested for integrated teaching are Reflective writing [23], Clinical Reasoning Exercises [24], Concept maps [25], Long essay questions [26], Progress tests [27], and Problem-based multiple-choice questions [28].

6. *Delivery of the integrated curriculum***:** A timetable should be prepared for all the integrated teaching sessions inclusive of theme of the integrated teaching session, teaching learning methods with duration of each methodology along with the name of the faculty member. This time table should be incorporated in the main time table of each phase for the purpose of implementation.

Challenges

There are many challenges in developing and implementing integrated teaching in a curriculum. These include lack of will, lack of good leadership support, inadequate infrastructure/resources, prefixed mindsets, and faculty resistance due to fear of more work. There are many myths associated with integrated curriculum like multiple teachers will be required for one integrated session, integrated curriculum will create more confusion, department will lose its identity and faculty will lose its importance in discipline-based compartments *etc*.

However, the challenges provide opportunities to innovate and experiment with various models of integration and evaluate their utility in the Indian context, especially in the new curriculum.

CONCLUSION

Integration in medical education is the need of the hour as we move towards holistic healthcare. The two main models of integration given by Fogarty and Harden are compared and commonalities discussed for better understanding of the concept. The various levels and models of integration provide a lead to innovate more in integrating the disciplines for better contextual learning. Integration can be implemented from the early years of the undergraduate teaching, and higher level of integration is possible as the learners progress through the course. The process of change from conventional to new integrated curriculum is difficult, yet achievable, and requires robust planning and coordination amongst the medical educationists at all the levels.

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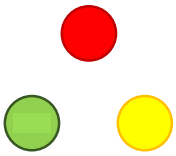
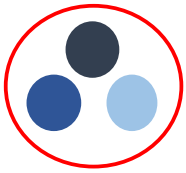
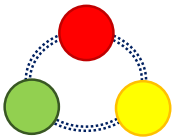
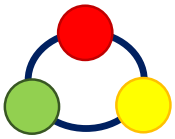
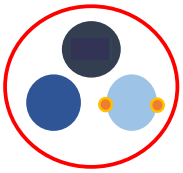
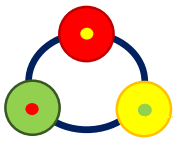
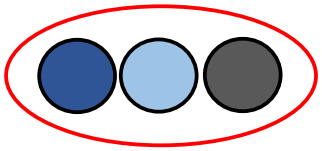
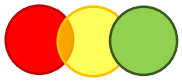
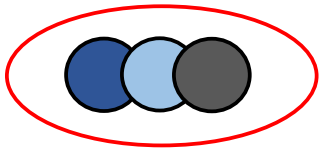
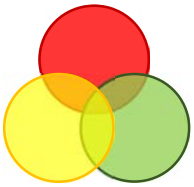
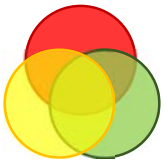
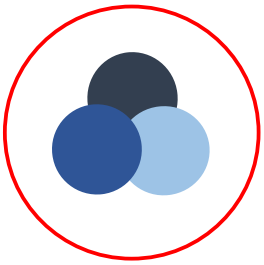
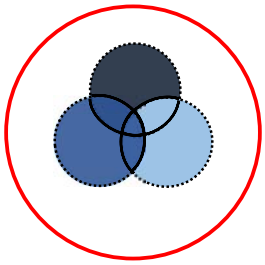
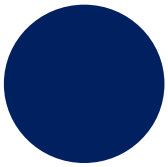
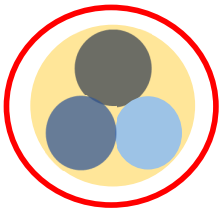
Web Table 1 Comparison of Models by Fogarty and Harden

	11 steps on the integration ladder (Harden 2000)	**Common Description**	**Ten ways to integrate curriculum (Fogarty 1991)**
1	Isolation 	Various disciplines /departments organize their teaching without considering other departments or subjects	The Fragmented Model 
2	Awareness 	Teacher is made aware of what is covered in other subjects through appropriate documentation about aims and objectives of each course	_____
3	Harmonization 	The Disciplines remain separate but the teacher may make explicit connection within the subject areas to other subjects	The Connected Model 
4	Nesting (Infusion) 	The teacher targets within a subject based course, few objectives relating to other subjects. Contents drawn from different subjects are used to enrich the teaching of a particular subject	The Nested Model 

5	Temporal Coordination 	The related topics within a subject are taught separately but are sequenced / arranged / scheduled at same time in consultation with other subjects.	The Sequenced Model 
6	Sharing 	Two disciplines may agree to plan and jointly implement a teaching program using overlapping concepts or ideas as organising elements	The Shared Model 
7	Correlation 	Within the subject based framework, integrated teaching sessions are introduced. These sessions bring together areas of common interest in each subject.	_____
8	Complementary Programme 	It has both subject based and integrated teaching. The basic difference with correlation is that the percentage of integrated sessions are increased	_____
9	Multidisciplinary 	This step brings together a number of subject areas in a single course with themes, problems or issues as the focus of teaching. The subjects/ disciplines still preserve their	Webbed 

		identity and demonstrate how they contribute to the understanding of the theme or problem.	
10	Inter-disciplinary 	The subject/ Discipline boundaries become blurred. There may be no reference to individual subjects or disciplines as they are not identified in the timetable. Interdisciplinary teaching implies a higher level of integration, with the content of all or most subjects combined into a new course with a new menu[15].	The Integrated Model 
11	Trans-disciplinary 	There are no subjects or discipline. There is only one subject for education, and that is Life in all its manifestations [16]. The teacher provides the framework of learning opportunity and the integration takes place in the mind of the students based on situations of the real world.	Immersed 

Randomized Controlled Trial Evaluating Levetiracetam as First-line Therapy for Seizures in Neonates

***Source Citation*:** Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, *et al.* Levetiracetam versus phenobarbital for neonatal seizures: A randomized controlled trial. Pediatrics. 2020;145(6): e20193182.

SUMMARY

This multicenter, randomized, blinded, controlled, trial investigated the efficacy and safety of levetiracetam compared with phenobarbital as a preferred treatment for neonatal seizures of any cause. The primary outcome variable was complete seizure freedom for 24 hours, assessed by independent review of the EEGs by 2 experts. Eighty percent of patients randomly assigned to phenobarbital remained seizure free for 24 hours, compared with 28% of patients randomly assigned to levetiracetam (P, .001; relative risk 0.35 [95% confidence interval: 0.22-0.56]; modified intention-to-treat population). A 7.5% improvement in efficacy was achieved with a dose escalation of levetiracetam from 40 to 60 mg/kg. More adverse effects were seen in subjects randomly assigned to phenobarbital (not statistically significant). The authors concluded that phenobarbital was more effective than levetiracetam for the treatment of neonatal seizures and higher rates of adverse effects were seen with phenobarbital treatment.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: A group of investigators undertook a multi-centre randomized controlled trial (RCT), designated NEOLEV2, to study the efficacy and safety of using levetiracetam as first-line therapy for seizures in neonates [1]. ***Box* I** presents an outline of the trial [1] and ***Web Table* I** presents a summary of the results.

Critical Appraisal

Randomization: The method of preparing the randomization sequence was not described, however it was done by an independent team. The sequence was generated so as to allocate 60% participants to levetiracetam. The reason for this should have been specified considering that trial efficiency is maximal with a 1:1 allocation ratio. Block randomization was used, though block sizes were not described. Randomization was stratified by site.

Allocation concealment: The random sequence was communicated to pharmacies of the participating institutions, who prepared identical appearing levetiracetam and phenobarbital injections (such that the same volume would be injected, whichever drug was used). However, it is not clear whether sequentially numbered injections were provided to treating physicians, or they had to use other means such as opening sealed envelopes to identify the allocation.

Blinding: The pharmacies prepared both medications so that identical volume would be injected in both treatment arms. However, the method of ensuring similar appearance of the medication was not specified. The investigators mentioned that all investigators, clinical personnel, neurophysiologists interpreting the EEG, and parents of enrolled neonates, were blinded.

Strengths and Limitations: A major strength of this study is that the occurrence of seizures was defined by cEEG, rather than identifying convulsions clinically or indirectly through changes in vital sign parameters detected electronically. An elaborate protocol was developed for real-time reading and interpreting of cEEG recordings by trained technicians. Additional inputs by automated software were also used. This ensured high sensitivity for seizure detection (so that no seizure episode was missed). This is perhaps one of very few clinical trials wherein elaborate measures were taken to define and document seizures. However, it is unclear whether heightened sensitivity could compromise specificity or trigger administration of medications for episodes that would have been otherwise missed or ignored. The investigators also have acknowledged the latter point.

Another important strength is that the EEG recordings were also reviewed by at least two expert neurophysiologists working independently. Although this was done retrospectively, it is as near as the gold-

Box I Summary of the Trial [1]

Clinical question

The research question of this RCT could be expressed as follows: "In term-infants with neonatal seizures (*P=Population*), what is the effect of levetiracetam as first-line therapy (*I=Intervention*), compared to phenobarbital (*C=Comparison*), on seizure control and development of adverse effects (O=Outcomes), within 48 hours of treatment (*T=Time frame*)?"

Study design: Multi-centre, blinded RCT with allocation of individual participants to the trial arms.

Study setting: Six neonatal units; five located in California (USA) and one in Auckland (New Zealand).

Study duration: March 2013 to October 2017 (55 months)

Inclusion criteria

Neonates having seizures or at risk for having seizures, were eligible if they were <2 weeks old, born at term with corrected gestation ranging from 36 to 44 weeks, and weighed ≥2200g. Such neonates underwent continuous EEG (cEEG) recording to determine the occurrence of seizures. This was defined as "abrupt electrical activity for ≥10 seconds with change in 2 or more of the following EEG characteristics: frequency, amplitude and spatial distribution". The cEEG recordings were read by trained personnel in real-time and also processed using automated software. In addition, retrospective review by specialist neurophysiologists was used for confirmation.

Exclusion criteria

Neonates were ineligible if they had already received anti-convulsant medication, had serum creatinine >1.6 mg/dL, seizures were related to hypocalcemia or hypoglycaemia, and if EEG recording could not be started before treatment. Neonates in whom mortality was imminent were also excluded.

Recruitment procedure

Neonates fulfilling the eligibility criteria underwent cEEG recording and were enrolled if seizures occurred.

Intervention and Comparison groups

Neonates with seizures (defined by cEEG recording) received loading with either 40 mg/kg levetiracetam, or 20 mg/kg phenobarbital, infused over 15 minutes. This was followed by maintenance dose of levetiracetam 10 mg/kg TDS for 5 days; or phenobarbital 1.5 mg/kg TDS for 5 days. If seizures persisted after an observation period of 15 minutes after the loading dose (or recurred within 24 hours), additional loading was done with 20 mg/kg levetiracetam, or 20 mg/kg phenobarbital, infused over 15 minutes. If seizures persisted after another 15 minutes of observation (or recurred within 24 hours), those who had received 60 mg/kg levetiracetam were given 20 mg/kg phenobarbital, whereas those who had received 40 mg/kg phenobarbital were given 40 mg/kg levetiracetam. These were infused over 15 minutes, followed by an observation period of another 15 minutes. If seizures persisted or recurred within 24 hours, the groups received additional 20 mg/kg phenobarbital, or 20 mg/g levetiracetam, respectively. Thus each neonate could potentially receive a maximum total loading dose of 40 mg/kg phenobarbital plus 60 mg/kg levetiracetam. Persistence of seizures despite this was managed as per individual institution protocols (not described by the authors).

Follow-up protocol

EEG recordings were analysed for the first 24 hours after starting therapy, in real-time by technicians based at a remote site as well as by using commercial computerized algorithms designed to detect neonatal seizures. In addition to these protocols to detect seizures (and trigger administration of medications), seizure cessation/control was retrospectively confirmed by at least two neurophysiologists. Where available, cEEG recordings were analysed at the end of 48 hours of treatment. Adverse events were identified by observing recognized events, and also monitoring vital signs including heart rate, blood pressure, respiratory abnormality, sedation, inability to feed, oxygen therapy, vasopressor therapy, and need for respiratory support. Complete blood cell count and metabolic profile were evaluated at 48 hours after treatment.

Outcomes

Primary outcome:

- Seizure control for 24 hours.

Secondary outcomes:

- Seizure control for 48 hours
- Seizure control for one hour
- Seizure control for 24 hours in neonates receiving therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE).
- Proportion of neonates with seizure control for 24 hours after receiving an additional loading dose (of the originally used medication).
- Adverse events
- Serious adverse events
- Death
- Discontinuation from the study
- Complete blood cell count at 48 hours

- Panel of metabolic parameters at 48 hours

Sample size

The investigators reported that a sample size of 60 (randomized to levetiracetam group) and 40 (randomized to phenobarbital group) would have 80% power to detect an absolute increase of seizure control by ≥28% from the assumed 50% control in those receiving phenobarbital, taking alpha error 0.05. Presumably this calculation was done *a priori* and not *post hoc*.

Data analysis

Modified intention-to-treat (mITT) analysis was performed (for efficacy parameters) wherein only those neonates were included in the denominator, who had seizures confirmed by neurophysiologist, and seizure control evaluation at 24 hours. *Post hoc* analyses included sensitivity analyses (using two scenarios to handle missing data), primary outcome assessed by a neurologist at the bedside, and a covariate-adjusted model based on severity of seizure, therapeutic hypothermia and etiology of HIE. Safety analysis was done by a routine intention-to-treat (ITT) model wherein all randomized participants were included in the denominator of the arm they were randomized to Additional per protocol analyses were performed.

Comparison of groups at baseline

The groups were comparable at baseline in terms of gestational age, birth weight, gender, proportion with HIE as the cause for seizures, proportion receiving therapeutic hypothermia, Apgar score at 5 minutes, cord blood pH and pre-treatment severity (although the method of calculating severity was not specified).

Box I Summary of Results (Levetiracetam *vs* Phenobarbital Groups)

Primary outcome

- Seizure control for 24 hours: 15/53 *vs* 24/30 (RR 0.35, CI: 0.22, 0.56)

Secondary outcomes

- Seizure control for 48 hours: 8/47 *vs* 18/28 (RR 0.26, CI: 0.13, 0.53)
- Seizure control for one hour: 26/53 *vs* 28/30 (RR 0.53, CI: 0.39, 0.70)
- Seizure control for 24 hours in neonates receiving therapeutic hypothermia for HIE: 6/17 vs 9/10 (RR 0.39, CI: 0.20, 0.77).
- Proportion of neonates with seizure control for 24 hours after receiving a second loading dose: 4/53 vs 3/30 (RR 0.75, CI: 0.18, 3.15).
- Proportion of neonates who had to be given two loading doses of the medication used in the other arm: 37/53 vs 6/30. Among the 37 in the levetiracetam arm (who received two loading doses of phenobarbital), 20 (54%) were seizure free for 24 hours. Among 6 in the phenobarbital arm (who received two loading doses of levetiracetam), 1 (17%) became seizure free for 24 hours.
- Death within 5 days : 2/64 *vs* 1/42 (RR 1.31, CI: 0.12, 14.02 (RR 4.63, CI: 0.24. 87.43))
- Death beyond five days and any time during the neonatal period: 3/64 vs 0/42
- Serious adverse events (SAE): Not shown separately
- Grade 4 or 5 SAE or AE: 4/64 *vs* 5/42 (RR 0.53, CI: 0.15, 1.84)
- Hypotension: 3/64 *vs* 7/42 (RR 0.28, CI: 0.08, 1.03)
- Abnormal heart rate: 3/64 *vs* 1/42 (RR 1.97, CI: 0.22, 18.30)
- Abnormal respiration: 8/64 *vs* 11/42 (RR 0.48, CI: 0.21, 1.09)
- Sedation: 7/64 *vs* 8/42 (RR 0.57, CI: 0.23, 1.47)
- Inability to feed: 6/64 *vs* 7/42 (RR 0.56, CI: 0.20, 1.56)
- Infection: 2/64 *vs* 3/42 (RR 0.44, CI: 0.08, 2.51)
- Oxygen supplementation: 38/64 vs 24/42 (RR 1.04, CI: 0.75, 1.45)
- Ventilation: 24/64 *vs* 19/42 (RR 0.83, CI: 0.52, 1.31)
- Vasopressor support: 10/64 *vs* 13/42 (RR 0.50, CI 0.24, 1.04)
- Discontinuation from the study: Data not shown
- Complete blood cell count at 48 hours: Data not shown
- Panel of metabolic parameters at 48 hours: Data not shown

Post hoc analysis of primary outcome

- Efficacy defined by assessment of neurologist at the bedside: 23/64 *vs* 35/42 (RR 0.43, CI: 0.30, 0.61)
- Best-worst scenario (*i.e* among those with missing data, those in intervention group were assumed to have seizure control and those in the comparison arm were assumed to have no seizure control): 26/64 *vs* 33/42 (RR 0.52, CI: 0.37, 0.72).
- Worst-best scenario (*i.e* among those with missing data, those in intervention group were assumed to have no seizure control and those in the comparison arm were assumed to have seizure control): 18/64 *vs* 36/42 (RR 0.33, CI: 0.22, 0.50)

standard for reading EEG. However, it is important to note that there were differences in interpretation by the paired experts in 22 cases, necessitating arbitration by a third expert. This raises a concern about the validity of the elaborate arrangements for defining and recording seizures. It is also unclear whether the 22 cases pertain to 22 enrolled neonates, or 22 episodes (among an unknown number of neonates).

The investigators chose the dose of levetiracetam on the basis of pharmacokinetic profile of the drug in the target age group. The dose was chosen so that levels higher than the maximum trough concentration could be achieved.

A total of 23 (of 106 randomized) neonates *i.e.* 22% were excluded from the analysis of the primary outcome. Thus, the intended sample size was not achieved, compromising power. A total of 11/64 (17%) were excluded in the levetiracetam arm, and 12/42 (29%) in the phenobarbital arm. These exclusions were because 8 and 3 neonates respectively did not have the data for the primary outcome. These were handled statistically using methods to impute data. Neurophysiologist cEEG review did not confirm seizures at the start of treatment in 3 and 9 neonates respectively. In a sense, excluding these 12 infants is justified because the distribution between the groups was uneven (5% *vs* 21%). Inclusion of a greater proportion of neonates without seizures at the start of treatment, into the phenobarbital arm would have falsely improved the efficacy and safety profile of the drug. On the other hand, it raises the concern that the sophisticated methods used in this study (to detect seizures), labelled it incorrectly in 12/106 (11%) of the randomized neonates.

The original plan was to measure seizure control at 48 hours as the primary outcome; however, this had to be revised to 24 hours because cEEG recordings were discontinued before 48 hours in many neonates (for various reasons). However, the change in primary outcome was duly approved by the United States Food and Drug Administration (US FDA). The investigators acknowledged that some clinically relevant and patient-centric outcomes, notably neuro-developmental outcome (short-term and long-term) were not measured in this study.

Conclusion: This RCT (1) showed that levetiracetam first-line therapy was inferior to phenobarbital for seizure control. There was no statistically significant difference in the safety profile either. A second loading dose of the original medication resulted in a modest beneficial effect in both arms. In children who were not seizure free despite two loading doses of levetiracetam, more than half became seizure free with two additional loading doses of phenobarbital.

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Pediatric Neurologist's Viewpoint

Neonatal seizures are altogether different from pediatric seizures. The risk for neonatal seizures is highest in the first week of life and especially in the first 48 hours of life. The immature neonatal brain has the highest propensity for seizure development because of excessive neuronal excitation and less inhibition. Neonatal seizures are subtle and have electroclinical dissociation, making them difficult to recognize and intervene. While managing neonatal seizure, not only short-term seizure control is desirable, but also protection of long term cognitive outcome is of paramount importance. Several of the anti-epileptic drugs (AEDs) in neonates are known to cause neuronal apoptosis and brain atrophy.

Levetiracetam is an efficacious AED with a favorable safety profile in pediatric status epilepticus [1]. It has been increasingly used to treat neonatal seizures with variable efficacy, despite limited safety and efficacy data [2,3]. Thus, this study [4] on efficacy and safety of levetiracetam in comparison to phenobarbitone for management of neonatal seizures is a welcome addition to the literature on the topic. It has several strengths such as use of continuous video electroencephalography (VEEG) monitoring for seizure identification and cessation, verification of VEEG findings by neurophysiologist, documentation of baseline seizure severity in both the arms (mean 11 min electrographic seizures/h), and levetiracetam drug level monitoring and maintenance of trough levels >20µg/mL for 3 days.

The primary efficacy endpoint of this study was seizure freedom for first 24 hours following the therapeutic intervention, 28% neonates in the levetiracetam group and 80% neonates in the phenobarbitone group remained seizure-free for 24 hours. Response to levetiracetam was not sustained, only 17% neonates remained seizure-free for 48 hours, while 64% neonate remained seizure-free for 48 hours in pheno-barbitone group. Among 53 neonates in the

levetiracetam group, 69% required phenobarbitone for seizure control. Secondary efficacy of phenobarbitone was 54%, while only 12% neonates who did not respond to 40 mg/kg phenobarbitone responded to 60 mg/kg levetiracetam.

The other important observation in this study was the effect of delay in achieving seizure cessation. It is well known that delay in achieving seizure cessation increases neuronal damage, and seizures become less responsive to subsequent AEDs. Hence it is vital to have quick seizure cessation. It was observed in this study that 30% neonates in the levetiracetam group remained unresponsive to all study drugs in comparison to 16% in the phenobarbitone group. It suggests that delayed seizure cessation reduces the likelihood of response to subsequent AEDs.

The primary etiology for neonatal seizures in this study were hypoxic ischemic encephalopathy (HIE), intraventricular haemorrhage and infracts. Neonatal seizures in HIE persist for a longer duration, hence sustained remission is desirable to prevent late recurrences. In this regard also pheno-barbitone worked better with sustained seizure remission in 64% neonates.

Authors have used 40mg/kg followed by additional 20mg/kg levetiracetam if no response. Among 53 neonates, 28% responded to 40 mg/kg, and 7.5% more neonates responded to 60mg/kg dose levetiracetam. It suggests that neonates may benefit from a higher dosage of levetiracetam. The authors should have reported whether trough levels of >20 µg/mL was achieved with 60 mg/kg levetiracetam.

Seizures are often subtle and difficult to recognize in neonates, and many of these neonates are sick requiring sedation and neuromuscular paralysis. Bedside seizure evaluation and seizure cessation assessment remain difficult. Though VEEG monitoring is the ideal method for neonatal seizure monitoring, however, it reduces the generalizability of the study. In the post hoc analysis of the study, neurologist at the bedside could determine seizure termination in 83% neonates in phenobarbitone group and 36% in the levetiracetam group suggesting marked electroclinical dissociation in the levetiracetam arm.

Gowda, *et al.* [2] from India in a randomized controlled trial reported 83% cases of neonatal seizures responded to levetiracetam and 62% responded to phenobarbitone. This dramatic difference in response rate to levetiracetam (83% *vs* 28%) in these two studies could be related to the differences in the methodology. Continuous VEEG monitoring allowed better seizure quantification, and electrographic seizures might persist even after clinical cessation. Neonates in the levetiracetam arm were sicker (cord PH 7.07, APGAR score 0-10) and had higher pre-treatment seizures frequency [4]. It might be possible that acute symptomatic seizures in the neonates due to HIE, infract, hemorrhage are less responsive to levetiracetam.

Thus, this study provides class 1 evidence for first-line AED for treatment of neonatal seizures. Phenobarbitone has superior efficacy for seizure control in comparison to levetiracetam. Further studies with a higher dosage of levetiracetam with drug level monitoring are required for neonatal seizure. Till then, phenobarbitone remains the gold standard for neonatal seizure.

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Neonatologist's Viewpoint

Immature brain is hyper-excitable, and it is no surprise that seizures are more common in neonates than in other age groups. Unlike older children and adults, there is a limited choice to treat seizures in this age group, as newer antiepileptic drugs have not been adequately tested on this unique population. Although phenobarbital is used as first line agent in neonatal seizures, it is effective in fewer than half of the neonates [1], and there are concerns of its short- and long-term toxicity, particularly on developing brain [2,3]. Despite these shortcomings, phenobarbital is still in vogue due to its availability in parenteral and oral formulations and lack of better alternative anticonvulsants to treat neonatal seizures.

In recent years, levetiracetam has emerged as an alternative to phenobarbital to treat neonatal seizures due to its reported effectiveness in retrospective studies [4] and favorable safety profile [5]. However, there is no high-quality evidence to support its use in neonates. The study under review [6], a phase IIb randomized controlled trial compared levetiracetam with phenobarbital for neonatal seizures. Authors used continuous electroencephalographic (cEEG) monitoring rather than clinical impression to assess primary outcome – cessation of seizures for 24 hours after medication use. cEEG monitoring, the gold standard for detecting seizures, is an important tool to avoid both under- and over-diagnosis of neonatal seizures. The study found that phenobarbital was more effective but also more toxic than levetiracetam for the treatment of neonatal seizures. This well designed randomized controlled trial has established the superiority of phenobarbital over levetiracetam in terminating neonatal seizures acutely. Although levetiracetam appeared safe, the study was not powered to compare adverse events. There is no information on neurodevelopmental outcomes, a major limitation of this study.

This study presents a difficult choice to the treating physician and parents: to use more effective but toxic drug versus less effective but safer drug for controlling neonatal seizures. Only long-term neurodevelopmental outcome of study cohort can settle this issue. The primary efficacy of phenobarbital was better (80%) than secondary efficacy (54%), suggesting that early use of phenobarbital is better in controlling seizures. The requirement of cEEG monitoring and trained neurophysiologists to interpret the records is a challenging task for most neonatal units in India. In the absence of these facilities we continue relying on our imperfect clinical acumen to diagnose and treat neonatal seizures.

In the light of present study, phenobarbital has re-established itself as a first line anti-seizure medication in newborns, notwithstanding its adverse safety profile. However, the story of levetiracetam is not yet over. High dose levetiracetam has been found to be effective in children with intractable epilepsy when standard dosages have failed [7]. Studies are needed to confirm the efficacy and safety of this approach in neonates. Further, the search continues for a better and a safer alternative anticonvulsant available in parenteral and oral formulations to control neonatal seizures.

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Immune Thrombocytopenia: American Society of Hematology Guidelines, 2019

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Immune Thrombocytopenia is the commonest cause of thrombocytopenia in young children. A thorough history, examination and peripheral smear evaluation is central to diagnosis. The recent American Society of Hematology guidelines 2019, has shed light on diagnosis and management based on latest available literature. We, herein, delineate the important aspects of these guidelines.

Keywords: *Bleeding, Diagnosis, Intravenous immunoglobulin, Guidelines, Management.*

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a low platelet count (<100,000/mm^3) due to 'antibody mediated' destruction of platelets and impaired mega-karyopoiesis with peak incidence in 2-5 years old [1]. Despite being the commonest cause of thrombocytopenia in children, there have been more controversies than consensus in its diagnosis and management. The American Society of Hematology first published guidelines on ITP in 1996 with updates published in 2011 and now in December, 2019 to answer the relevant questions in wake of new available evidence. The highlights of the latest update are listed in ***Table* I**. The definitions of 'grades of recommendation' may be referred to in the respective guidelines [1,2]

ITP is termed acute/newly diagnosed, if lasting less than 3 months; persistent, if lasting 3-12 months, and chronic, if persisting beyond 12 months. Majority of children (60-75%) have acute ITP that resolves within 2-3 months of diagnosis, regardless of therapy. ITP may be primary (where no cause is found) or secondary to other conditions like infections (HIV, Hepatitis C, *H. pylori*), autoimmune syndromes (SLE, APLA syndrome), primary immunodeficiency (common variable immune-deficiency i.e. CVID) and drugs (valproate, heparin). As per the latest ASH 2019 guidelines, routine testing for bone marrow aspirate/bone marrow biopsy (Grade 1B), anti-nuclear antibody (grade 2C) and *H. pylori* (grade 2C) is not recommended unless there are clinical pointers. The utility of screening all ITP patients for CVID, hepatitis C, HIV and Hepatitis B is still unclear [1]. Thrombocytopenic syndromes (like Wiskott–Aldrich syndrome) and CVID are important masqueraders of immune thrombocytopenia. While a detailed family history and a meticulous examination may diagnose these mimickers at outset, at times these syndromes are recognized later in cases mislabelled as ITP, who fail to respond to all therapy [3].

Clinically, ITP is characterized by bleeding events that show no linear correlation with the severity of thrombocytopenia [4]. Most of children (62-74%) with ITP spontaneously remit within a year [5]. Therefore, the decision regarding use of platelet enhancing therapy should be based on multiple factors (access to care, patient and provider preferences, risk of bleeding, duration of disease, co-morbidities and age at presentation). In newly diagnosed ITP with no/mild bleeding, the ASH 2019 guidelines recommend observation over treatment irrespective of the platelet count. Moreover, they suggest observation at home is preferable to hospital admission. However, they add that if a decision to observe on outpatient basis is made, it is desirable for the patient to be seen by a pediatrician within 24-72 hours [2]. In those set-ups, where patient follow-up is uncertain due to social/ financial concerns or residence is in remote areas which are far from hospitals, admission to the hospital and treatment is preferable. Similar recommendations have been stated by the Joint working group (JWG) of several European hematology societies (Germany, Austria, and Switzerland) published in 2018, wherein special emphasis has been placed on the patient's choice of therapy [6].

Minimizing the risk of hemorrhage and decreasing the long-term side effects of treatment are the goals of therapy. Treatment is guided by the severity of bleeding rather than on the platelet count. The ASH 2019 guidelines have defined major bleeding as any one of the following (*i*) WHO grade 3 or 4 bleeding, (*ii*) Buchanan severe grade, (*iii*) Bolton-Maggs and Moon major bleeding, (*iv*) IBLS grade 2

or higher, or (*v*) life-threatening bleeding or intracerebral hemorrhage. Minor bleeding is any bleeding not meeting the criteria for major bleeding. Adolescents with ITP are treated as per pediatric guidelines [1].

Acute/newly diagnosed ITP: In a child with newly diagnosed ITP with no/mild bleeding, ASH continues to recommend observation over pharmacotherapy irrespective of the platelet count. However, in a child with moderate to severe bleeding and/or a diminished health related quality of life, a short course of corticosteroids (<7 days) is preferred over intravenous immunoglobulin (IVIG) or anti-D immunoglobulin (anti-D Ig) therapy [2]. A short prednisolone course (2-4 mg/kg/day; maximum 120 mg/day) of 5-7 days is preferable to dexamethasone (0.6 mg/kg/day; maximum 40 mg/day) for 4 days. The European joint working group (JWG) has also endorsed a shorter course of steroids less than 2 weeks, without specifying the preferred type of steroid [6]. ASH 2019 states that as per limited available data IVIG and anti-D Ig have similar benefits, and both are associated with rare but potential black box warnings. Thus, either of them may be used. In practice, the choice between the three available treatments is usually guided by cost, availability and adverse effects [7].

Persistent ITP: If treatment with steroids, IVIG or anti-D Ig has been successful, these options may be used to prevent bleeding as needed, especially in the first 12 months of diagnosis when the possibility of spontaneous remission is high [1].

Chronic ITP: In children with "newly diagnosed" ITP or persistent ITP with non-response to first line pharmacotherapy or those with chronic ITP, second line pharmacotherapy is suggested wherein thrombopoietin receptor agonists (TPO-RAs) (romiplostim, eltrombopag *etc*.) are preferred over rituximab. This is premised on acceptable response to TPO-RA with low side effects and avoidance of immunosuppression. Similar views were given by the European JWG [6]. Other treatment options include high dose dexamethasone (0.6 mg/kg/d for 4 days every 4 weeks for 6 cycles) [1]. Use of alternate immunosuppressive agents (dapsone, azathioprine, danazol, mycophenolate mofetil, cyclosporine, cyclophosphamide, anti-CD52 monoclonal antibody, vinca alkaloids) and combination of different agents has been tried but data are sparse and hence ASH 2019 categorically mentions that recommendations were not feasible. Splenectomy should be deferred, if possible, to

Table I Highlights of Updates From the Previous ASH, 2011 and Current ASH, 2019 ITP Guidelines

	ASH, 2011guidelines	*ASH, 2019 guidelines*
Outpatient *vs* Inpatient management	No recommendation	A child with newly diagnosed ITP with no/mild bleeding may be managed at home irrespective of the platelet count.*
		However, if the diagnosis is uncertain or follow up is difficult, admission is preferable.
Treatment *vs* observation	A child with newly diagnosed ITP with no/mild bleeding may be managed with observation alone, irrespective of platelet count	In a child with newly diagnosed ITP with no/mild bleeding, observation is preferable to pharmacotherapy (steroids,***** IVIG,# anti-D Ig#) irrespective of platelet count
First line pharmacotherapy	Single dose IVIG (0.8-1g/kg) or a short course of corticosteroids can be used. IVIG can be used if a more rapid rise in platelets is required.	Short course of steroids (<7 d) is preferred over IVIG or anti D therapy*****
Steroid type and duration as first line pharmacotherapy	No steroid type or dose is preferred over the other	A short prednisolone course (2-4 mg/kg/d; max. 120 mg/d) of 5-7 d is preferable to dexamethasone (0.6 mg/kg/d; max. 40 mg/d) for 4 d*****
IVIG *vs* anti D as first line pharmacotherapy	Grade of recommendation for use of IVIG as first line (grade 1B) is stronger than Anti-D Ig (grade 2C)	Either IVIG or anti-D Ig may be used*
Newly diagnosed ITP who are treatment non-responders (*i.e.* non responsive to first line therapy)/Persistent ITP/ Chronic ITP	Rituximab or high dose dexamethasone may be used for treatment both of which are preferred over splenectomy.	In children with non-response to first line therapy, TPO receptor agonists are preferred over rituximab which is preferred over splenectomy.

*ITP: Immune thrombocytopenic purpura; *Conditional recommendation based on low certainty of the evidence of effects; #strong recommendation based on moderate certainty in the evidence of effects.*

Table II Treatment of Immune Thrombocytopenic Purpura

Category	*Symptoms/treatment options*	
Newly diagnosed ITP or Persistent ITP*	No/mild bleeding: Close observation (grade 1B) Moderate bleeding: Short course steroids/IVIG/anti-D Ig* Severe bleeding: Short course Steroids/IVIG/anti-D Ig (along with platelet transfusion in life threatening bleeds)	
Chronic ITP	No/mild bleeding	Observation
	Moderate to severe bleeding	Available therapies include: • TPO receptor agonists (Romiplostim, Eltrompobag)# • High dose dexamethasone$ • Rituximab^ • Other immunosuppressive agents • Splenectomy (along with platelet transfusion in life threatening bleeds)

**The doses of drugs used are as follows: Prednisolone 2-4 g/kg/d for 5-7 d; Dexamethasone 0.6 mg/kg/d for 4 d; IVIG 1 g/kg/d for 1-2 d; Anti-D Ig 50-75 mg/kg; #Romiplostim 1-10 µg/kg SC wkly; Eltrombopag>6-y-old 50 mg/d oral, 1-6 y: 25 mg/d oral; $High dose dexamethasone: 0.6 mg/kg/d for 4 d every 4 wks for 6 cycles;^Rituximab (anti CD20 monoclonal antibody) is given at dose of 375 mg/m^2/wk for 4 doses.*

beyond 12 months from disease onset. It may be the last resort in situations where ITP is unresponsive to all other therapy, the child shows intolerance to other drugs and quality of life is impaired. These recommendations are in concurrence with those of the European JWG [6].

In the Indian scenario, the cost and availability of TPO-RAs is prohibitive which makes them unsuitable as a frontline therapy [7]. Rituximab is promising with a median response duration of 12.8 months, relative ease of availability and tolerable side effects [8]. In cases where there is non-response to rituximab or availability is an issue, high dose dexamethasone and dapsone have been used as alternatives. Although high dose steroids have a good efficacy, their long-term use is associated with significant adverse effects. Dapsone is an easily available low-cost drug with response rates of around 50%; hemolysis and methemoglobinemia being important side effects and to be avoided in G6PD deficient individuals [9].

Secondary ITP: Treatment is directed towards the underlying cause [1]. Withdrawal of the causative drug results in remission of drug-induced ITP. ASH 2019 reiterates that children with ITP should receive first MMR vaccine per routine schedule (grade1B). Those who have already received MMR previously can get a vaccine titre done to assess need for booster dose [1]. A summary of available treatment options is given in ***Table* II**.

Assessment of response to treatment: The International working group provides specific recommendations for assessing the response to ITP treatments [10]. Although not based on evidence, these thresholds provide a useful standardization that will allow better comparison of responses between studies and the ASH 2019 endorses the same.

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Non-Contact Infrared Thermometry in Febrile Infants

This cross-sectional study was done to find the agreement between non-contact infrared thermometry and mercury-in-glass thermometer. Two hundred and fifty febrile infants were recruited over a period of two months and axillary temperature was measured by both techniques. The mean (SD) temperature recordings of infrared and mercury thermometer were 37.6 (0.91)°C and 37.6 (2.49)°C, respectively; mean difference – 0.016 (96% CI – 0.32, 0.29). There was moderate agreement between both methods (kappa=0.602). Non-contact infrared thermometry can be used with good accuracy in febrile infants for temperature measurements.

Keywords: *Diagnosis, Mercury thermometer, Measurement, Temperature*.

Axillary thermometry is a non-invasive method for temperature measurement in sick febrile infants but may disturb the sleep of the infants and may contribute to infections by frequent direct contact. Non-contact infrared thermometry (NCIT) avoids these risks preserving the clinical accuracy of conventional methods [1-3]. It is a rapid non-invasive method for temperature measurement in febrile infants; however, with discordant results reported earlier [3,4]. The objective of this study was to study the agreement between NCIT and mercury-in-glass thermometer.

This was a cross-sectional study conducted in the pediatric department of a tertiary healthcare facility after approval from institute research and ethics committee. Written informed consent was obtained from the parents/legal representative. Infants from 1st day of life to 12 mo of age attending the pediatric outpatient department between 1st September to 31st October, 2018 were included in the study population. Sick and unstable infants were excluded. Axillary temperature was measured using mercury-in-glass thermometer (Enbee; Wuxi Moxibei Clinical Thermometer Co. Ltd.) after the axilla was wiped with a dry towel. The thermometer probe tip was placed under the axilla so that the tip was touching the skin and the temperature was measured after 5 min. Forehead temperature was recorded for NCIT with infrared thermometer Equinox EQ-IF-02 (Equinox Meditech Private Limited, New Delhi). Accuracy Range-10°C to 40°C) at approximately 0.5-1 cm distance from the glabella [5]. Measurements were taken by a trained nurse and the duty doctor from both the devices within 6 minutes.

The degree of agreement between the two methods was studied using the Bland and Altman method and the mean difference with 95% confidence limits noted for clinical consideration. SPSS 18.0 software was used to analyze the results.

Among 250 infants approached for the study, 7 (2.8%) were aged less than 28 days and 243 (97.2%) were aged from one month to one year. The mean (SD) infrared thermometer and temperature recordings of mercury-in-glass thermometer were 37.6 (0.91)°C and 37.6 (2.49) °C, respectively; mean difference -0.016 (95% CI: -0.32, 0.29). There was a significant correlation between NCIT and axillary thermometry measurements (r=0.22; P<0.001). Number of observed agreement was for 80.8% of observations, indicating moderate agreement (kappa=0.602) between both instruments (***Fig***. **1**).

The mean (SD) temperature recordings of infrared thermometer and mercury-in-glass thermometer were 37.6 (0.91)°C and 37.6 (2.49)°C, respectively; mean difference. The present study established a good correlation between NCIT and axillary thermometry. Few earlier studies revealed conflicting results about the validity and accuracy of NCIT [4,6]. However, other studies have proven the clinical accuracy of NCIT compared to digital axillary thermometry [7-9]. The accuracy and reproducibility of NCIT in different body sites in comparison to conventional thermometers was demonstrated by Osio, *et al*. [8]. Digital thermometer is safer but its clinical accuracy is considered inferior to mercury-in-glass thermometer. Thus, we compared the clinical accuracy of NCIT with that of mercury-in-glass thermometer as also conducted by Chiappini, *et al*. [10] who reported significant correlation between the two methods (P<0·0001), similar to our study.

In our study, moderate agreement between NCIT and mercury thermometry reading was demonstrated. The cost effectiveness of NCIT in resource poor settings needs to be determined. Further studies comparing NCIT with rectal thermometry which is the gold standard would support the use of NCIT in clinical settings.

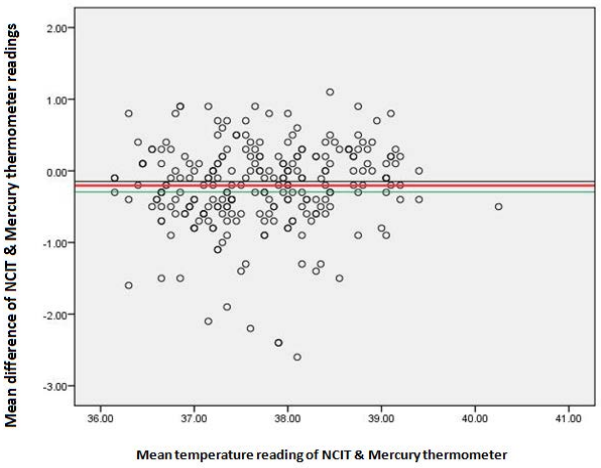

Fig. 1 *Bland altman plot showing the comparison of now-contact infrared thermometer (NCIT) and mercury thermometer readings.*

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Ultrasound Guided Confirmation of Tip of Peripherally Inserted Central Catheter in Neonates

The neonatal peripherally inserted central catheter (PICC) is commonly inserted in the neonatal intensive care unit (NICU) for long-duration intravascular access and the tip of PICC is normally placed at the junction of the right atrium and either superior or inferior vena cava [1]. Often the catheter tip is not in the correct place and requires manipulation and frequent radiographs [2,3]. In this study, we sought to determine the time taken-up by bedside ultrasound (as compared to *X*-ray) and its accuracy for PICC placement and tip confirmation.

A cross-sectional study was conducted at the neonatal intensive care unit, Manipal hospital, Bangalore from August, 2017 to September, 2018, among neonates requiring PICC line insertion as a part of their intensive care management. The study protocol was cleared by the Ethics Committee of Manipal Hospital. Data were collected in a pre-designed proforma after taking consent from parents. Neonates with major congenital anomalies involving thorax and abdomen were excluded from the study.

Objectively, the time taken during the confirmation of the tip of PICC by using bedside ultrasound and digital *X*-ray in each patient was determined, and also the number of attempts was documented. PICC line was placed by the neonatal fellow under the guidance of the consultant neonatologist. Ultrasound was performed by Philips CX50 by using an S 12-4 frequency footprint probe in the subcostal sagittal view to identifying the inferior vena cava and high parasternal view to identify superior vena cava. After the insertion of predetermined length, the tip was visualized and manipulated by using real-time ultrasound for optimal position. A small volume (1 mL) of sterile normal saline was injected to confirm the location of the catheter tip. Bedside digital *X*-ray was ordered at the same time. Time taken to confirm the position of the tip of PICC was recorded by using bedside ultrasound and *X*-ray. The start time was defined as the time of ordering *X*-ray after inserting the predetermined length of the PICC catheter. The starting time was the same for ultrasound and *X*-ray, whereas the completion time was defined as the time when ultrasound confirmed the tip of the PICC catheter and for the *X*-ray method when the *X*-ray was read by the neonatologist on-site. A single attempt was counted after the determination of tip by ultrasound and catheter fixed. The repositioning of the catheter was done if the position was not correct as confirmed by *X*-ray.

Forty neonates out of a total of 300 neonates admitted to neonatal intensive care unit during the study period which required PICC insertion; consent could not be obtained for seven neonates. For these 33 neonates (72% males, 72% appropriate for gestational age), the mean (SD) gestational age and birthweight were 29 (3) weeks and 1087 (561) g.

The mean (SD) time taken in tip confirmation by using bedside ultrasound was 5.1(1.2) minutes, *X*-ray it was 28 (8.1) minutes (P<0.001). The catheter tip was in an optimal position in the first attempt in 30 (91%) neonates after the ultrasound and confirmed by *X*-ray. In these three cases (9%) the tip of the PICC catheter was in the right atrium after first attempt confirmation. There was no inter-observer variation in the interpretation of the result.

Previous studies [4-8] have also shown that the mean time taken in confirmation of tip by using ultrasound is significantly less than standard care. The accuracy of ultrasound was also comparable with radiography. By using ultrasound, we can reduce radiation exposure, and ensure lesser handling of babies.

Bedside ultrasound is an accurate and time-efficient modality to guide the insertion and confirmation of the tip of the PICC line. However, training of neonatologists in ultrasound may be required before routine use of this modality.

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Infantile Cardiac Beriberi in Rural North East India

Twenty eight exclusively breastfed infants presented between 1 July, 2017 and 30 June, 2018 with acute heart failure syndrome, with 23 (92%) showing dramatic clinical resolution of shock within 24 hours of receiving intravenous thiamine (100 mg) bolus. Our findings raise awareness for addressing this neglected nutritional disease in North East India.

Keywords: *Heart Failure, Infantile Beriberi, Thiamine*.

The cardiac form of infantile beriberi is a fulminant disease, affecting exclusively breastfed infants of mothers with thiamine deficiency. The classical description is a well thriving infant presenting in acute cardiac failure succumbing to the illness within four hours, if left untreated [1]. Laos has documented widespread thiamine deficiency in communities, causing a peak in infant mortality in the third month of life [2]. The overall infant mortality rates in the Karen refugee camp in Thailand reduced from 183 to 78 per 1000 live births after early diagnosis and management of infantile beriberi [3]. We report on infantile beriberi as a preventable cause of death among infants from rural North East India.

The study was conducted in a charitable hospital in Karimganj district of Assam, which has an infant mortality rate of 69 per 1000 live births in 2012-13 (National average, 42/1000 live births). A retrospective review of medical records was conducted for all infants who were discharged between 1 July, 2017 and 30 June, 2018 with a diagnosis of infantile beriberi. Infantile beri beri was diagnosed when an otherwise well, exclusively breastfed infant presented with a thiamine responsive acute cardiac failure syndrome [1].

A total of 28 infants with a mean (SD) age 69 (29.1) days and weight 3.84 (1.26) kg from rural Assam and Tripura were diagnosed with infantile beriberi during the study duration. The commonest complaints were short history of vomiting, breathlessness and poor feeding. All infants presented in a critically ill state with prolonged capillary refill time (93%), tachycardia (93%), seizures (36%) and severe respiratory distress (92%). The capillary blood gas of all infants showed severe high anion-gap metabolic acidosis (***Table* I**).

Table I Laboratory Abnormalities in Infants With Cardiac Beriberi (*N*=28)

Variable	*Value, median (IQR)*
Hemoglobin (g/dL)	8.2 (7.7-9.9)
Leukocyte count (per mm^3)	20510 (15410-27030)
Platelet count (per mm^3)	297000 (15410-27030)
Blood sugar (mg/dL)	115 (70-206)
pH	6.9 (6.7-7.1)
HCO3 (mmol/L)	5.2 (4.8-7.8)
Base excess	-26.6 (-23.05 to -29.0)
Anion gap	42.25 (30.9-43.0)

Of these, 25 (89%) received 100 mg of intravenous thiamine bolus within one hour of admission, followed by 100 mg intravenously for a minimum of seven days till discharge. Infants also received other treatment modalities as per the pediatric protocol for treatment of shock in the hospital. 20 infants (71%) required inotropes. Twenty three infants (92%) showed dramatic recovery, with features of shock resolving within 24 hours, and were initiated on breast feeds within two days. All 14 infants (50%) requiring invasive ventilation could be weaned within 60 hours, with 12 infants (86%) being extubated in the first 24 hours. There was a rapid improvement in the capillary blood gas measurements within 4-8 hours of bolus thiamine, with mean (SD) pH improving from 6.9 (0.22) to 7.35 (0.11) and mean (SD) base excess from –24.3 (6.69) to –3.8 (5.69).

The three infants who did not receive parenteral thiamine died within half an hour of admission while of those who received parenteral thiamine, two infants died. One of these due to a ventilator-associated adverse event. All infants who survived were discharged after a mean (SD) in-patient stay of 7 (2.81) days. They were prescribed 10 mg per day of thiamine supplements; 17 babies (74%) were subsequently reviewed and found to be well.

The presentation of infants in this case series corroborates with the classical description of infantile cardiac beriberi in literature, including a cohort from Kashmir [5]. Moreover, we have previously documented peripheral neuropathy with or without cardiomyopathy among peripartum women [6]. Since the clinical manifestation of beriberi in infants reflects poor maternal stores, communities in North East India are at risk populations, explaining the prevalence of this nutritional disease.

All infants presented in an acute critically ill state and none had documented fever or history of fluid loss to account for shock. The dramatic therapeutic response to parenteral thiamine administration in 92% of infants along with the rapid clinical deterioration of the three infants who did not receive it, favors the diagnosis of cardiac beriberi. *X*-ray done on five babies revealed cardiomegaly at admission, which disappeared after five days of thiamine. The diagnosis could have been strengthened using echocardiography, and determining RBC transketolase activity, which were not available at our institute. Subsequent to the study, echocardiography in other such infants has demonstrated features of pulmonary hypertension, which responded after thiamine administration.

Although infantile beriberi was believed to have been eliminated from India [7], there is emerging evidence to suggest that beriberi still continues to be a cause of preventable infant mortality among Indian children [4,8]. In places with high infant mortality and peak age of deaths at three months of age, beriberi needs to be considered in the differential diagnoses of infants presenting with unexplained shock.

Being a fatal but preventable and easily treatable disease, these observations on infantile beriberi require a strong public health response. Education campaigns and thiamine supplementation in pregnant and post partum women are possible strategies. Prospective studies using data from population surveys and nutritional assessments to identify the factors contributing to the epidemic in these high-risk populations are being planned with the National Institute of Nutrition, Government of India.

Ethical Clearance: Local research committee of MCL General Hospital; 27 June, 2017.
Contributions: ST: RMK conceptualized and designed the study, developed protocol; ST: collected and analyzed data, reviewed literature and prepared initial manuscript; RMK & VAI: Manuscript review; VAI: performed echocardiogram on some babies included in study. All the authors approved the final version of the manuscript.
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Pulsatile Swelling of Umbilicus in a Cyanotic Neonate

Cantrell syndrome is a rare, usually lethal, congenital malformation [1]. In the complete form, five anomalies exist, namely a midline supra-umbilical abdominal wall defect, a sternal defect, an anterior diaphragmatic defect, a diaphragmatic pericardial defect and a congenital heart defect. However, the extent of individual defects and their combination varies considerably; broad spectrum of associated cardiac abnormalities have been reported in most cases. We describe a neonate presenting with a pulsatile umbilical swelling and cyanosis since birth, later confirmed to be due to Cantrell syndrome.

A full term male neonate with uneventful antenatal and perinatal course, born to a primigravida mother by normal vaginal delivery, was noted to have a pulsatile umbilical mass immediately after birth. Antenatal second trimester sonographic scans were reported normal, but detailed anomaly scan was not done. Baby was seen at our institute on day seven of life. He was feeding well, had a capillary filling time <3 second and normal urine output. Examination revealed tachycardia with a heart rate of 200 beats per minute, and central cyanosis (oxygen saturation 85% in room air). A peculiar mass arising from just above the umbilical stump, measuring 5×2×2 cm was noted. The mass enlarged with each cardiac systole (***Fig.* 1a**). It was covered with skin on its dorsal aspect but its ventral aspect was devoid of skin. On palpation, the structure had a forceful impulse and auscultation revealed a loud to-and-fro murmur over the mass. Cardiovascular examination revealed no evidence of heart failure, wide split second heart sound with a soft pulmonic component and a grade 3/6 ejection systolic murmur at left upper sternal border. A midline defect was palpable in the anterior abdominal wall.

Electrocardiogram revealed atrial flutter with ventricular rate of 200/min. Chest radiograph showed situs solitus, levocardia, normal sized heart and pulmonary oligemia. Ultrasound and Doppler evaluation of the mass revealed normal umbilical arteries, with a connection between umbilical vein and left ventricle through falciform ligament, suggestive of left ventricular diverticulum. Echocardiogram showed double outlet right ventricle with infundibular pulmonary stenosis. There was a tubular structure arising from apex of left ventricle which had a to-and-fro Doppler flow through it (***Fig.* 1b**). Computed tomography (CT) angiography revealed a dilated vascular channel beginning from the umbilical outpouching and travelling cranially within the anterior abdominal wall and along the falciform ligament to drain into the left ventricular apex through a 2 mm opening. There were multiple stenosis throughout its course, confirming the diagnosis of left ventricular diverticulum (***Fig.* 1c**). Defect in anterior diaphragm was present, but there was no associated sternal defect.

In view of atrial flutter, patient was started on propranolol and digoxin, and good heart rate control was achieved. After discussion with the cardiac surgical team, it was decided to close the left ventricular diverticulum, the cardiac lesion to be addressed later, since the oxygen saturation of the baby stayed above 85%. Left anterolateral thoracotomy was done and the fistulous tract arising from anterior most part of the left ventricular apex was identified. It was double clamped and divided and both ends were sutured. Defect in diaphragm was closed. The umbilical swelling was excised and the skin repaired. Patient had a smooth post-operative course and recovered well. The cardiac rhythm reverted to sinus rhythm on postoperative day 6. He was discharged on ninth post-operative day. Digoxin was stopped at six-week follow-up. Currently, at one-year follow up, baby is doing well, his oxygen saturation is 80% and he is in sinus rhythm. He is planned for Glenn surgery in view of non-committed muscular VSD, and is awaiting the same.

Only 250 cases of Cantrell syndrome have been reported in the literature [2]. It has high morbidity and mortality, with more than half of patients dying, many despite surgery [3]. Abnormal migration of the splanchnic and somatic mesoderm (which affects the development of the heart and the major vessels) with premature breakage of the chorion or vitelline sac at about day 14 to 18 of gestation, may lead to a mid-line defect [4] Congenital cardiac malformations are associated in majority,

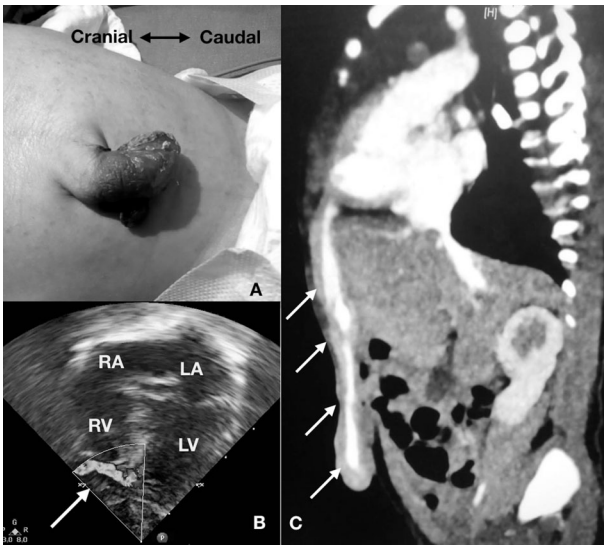

Fig. 1 *(a) Clinical photograph of umbilical swelling; (b) echocardiogram in four chamber view showing a vascular channel (white arrow) arising from left ventricle apex; (c) CT angiographic section in sagittal view showing the abnormal vascular channel (white arrows) arising from left ventricle apex.*

ventricular septal defect is the commonest abnormality. Association with double outlet right ventricle has also been previously reported [5].

Over 70% of patients with left ventricular diverticulum have Cantrell syndrome. The diverticulum originates from the left ventricular apex in these cases and may be associated with umbilical hernia and complex cardiac abnormalities. Ventricular aneurysm must be differentiated from diverticulum. A narrow mouth and synchronous contractility characterize a diverticulum. On the other hand, aneurysms show akinesia or paradoxic contractility of the outpouching, which is asynchronous with the rest of heart.

Early surgical repair is indicated in cases of left ventricular diverticulum, as it may rupture spontaneously, thrombose or produce arrhythmias. It is generally recommended that the midline thoraco-abdominal defect is treated first and heart defects be corrected later [6]. We present this case in view of the interesting presentation in a neonate with a pulsatile umbilical swelling and cyanosis, and a good outcome after surgery.

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Mechanical Thrombectomy for Cerebral Venous Sinus Thrombosis in a Neonate

Cerebral venous sinus thrombosis has a reported incidence of 0.35-0.67 per 100000 children per year, and about 40% of cases occur during the neonatal period [1]. In the pediatric population, standard choice of treatment is the use of low molecular weight heparin (LMWH). The indication criteria and the role of mechanical thrombectomy and other interventional procedures in infants with cerebral venous thrombosis is unknown [2,5]. Even in neonates treated with LMWH, the incidence of neurological disability is unfavorably high,especially in those with multi-sinus thrombosis [1]. We report a neonate with this disorder managed with mechanical thrombectomy.

A 10-day-old term male neonate presented to the pediatric emergency department with partial seizure of the upper extremities. The infant was born after an uncomplicated pregnancy followed by a normal spontaneous vaginal delivery and was discharged home from neonatal nursery after 72 hours, with no need of intervention and medication. At presentation, the infant was afebrile, apathetic, with feeding difficulties, and had mild tachycardia and delayed capillary refill time. A weight loss of 15% compared to the discharge weight was noted. The clinical state was evaluated as dehydration, and intravenous rehydration was started. Two hours after admission, myoclonic seizures of upper extremities occurred, along with multiple apneic spells reappeared. Anticonvulsant treatment with intravenous phenobarbital was started. Laboratory examinations (blood count, plasma minerals and serum biochemistry, C-reactive protein, procalcitonin, coagulation profile) and lumbar puncture results were unremarkable, except for lactate concentration (4.75 mmol/L), hematocrit level (61%) and hemoglobin concentration (20 g/dL). Magnetic resonance imaging (MRI) with consecutive time-of-flight (TOF) venography and contrast enhanced T1WI revealed cerebral venous thrombosis. Superior sagittal sinus, right transverse sinus, straight sinus, vein of Galen and internal cerebral veins thrombosed, along with hemorrhage from right choroid plexus, and bilateral thalamic vasogenic edema. After multi-specialty consultation, mechanical thrombectomy was planned, in view of the presence of multi-sinus thrombosis with thalamic edema and signs of neurologic deterioration with acute repetitive seizures.

After obtaining informed consent from the baby's mother, the procedure was performed under general anesthesia with ultrasound control. The right internal jugular vein was punctured and a 3F introducer (IVA, BALT) was placed by the Seldinger technique. The microcatheter (Orion, Medtronic) was navigated *via* micro-guide wires Hybrid .008" and Hybrid.1214DA (BALT) into the straight sinus as well as into the superior sagittal sinus directly without the use of a guide catheter. Mechanical thrombectomy was performed *via* a Solitaire platinum 6ã40 (Medtronic) three times per sinus. Hemostasis in the puncture site was achieved by compression with usage of HemCon Patch.

After the interventional procedure, the infant was monitored in the neonatal intensive care unit for 18 days. The newborn was extubated and could breathe spontaneously with no apneic spells 24 hours after the procedure. Neurological examination confirmed normal findings without clinical seizures, and no abnormal electrical brain activity on electroencephalography, thus anticonvulsant medication were discontinued. After the procedure, LMWH was prescribed prophylactically. Further workup after the procedure revealed low antithrombin III plasma concentrations with the need for parenteral substitution the following month, with normalization of the value. During the hospital stay and follow-up period, MRI scans confirmed a full recanalization of cerebral venous system. Neurodevelopmental outcomes at 3, 6, and 8 months assessed by general pediatrician have been favorable with normal psychomotor development. Bayley III assessment at age of 21 months was done. The composite cognitive and motor score was age appropriate.

Cerebral venous sinus thrombosis in neonates is usually multifactorial, with one risk factors identified in up to 95% of patients [6]. In the index case, the infant had dehydration with elevated hematocrit level. Antithrombin III deficiency was considered to be due to dehydration with normalization of plasma concentration before discharge.

The main pathophysiological mechanism of brain damage in cerebral sinus thrombosis is related to outflow obstruction with venous congestion producing edema and the formation of hemorrhagic infarction in most cases [6]. The presence of collateral flow and the time of recanalization is crucial for the development of parenchymal injuries. In neonates, there is an association between intraventricular hemorrhage and cerebral venous sinus thrombosis [1,2]. Thalamic and basal ganglia lesions in newborns are associated with poor neurodevelopmental outcome including dyskinetic-spastic cerebral palsy with cognitive delay, visual impairment, and the risk of post-neonatal epilepsy [2].

The ideal treatment of cerebral venous sinus thrombosis in newborns is unclear, particularly in case of coincident intracranial hemorrhage. In most guidelines, the standard treatment of cerebral venous sinus thrombosis is LMWH or unfractionated heparin. Anticoagulation therapy in the case of intracranial bleeding is not recommended during first 5-7 days [3]. The indication criteria for endovascular treatment of cerebral venous sinus thrombosis are under study. In adults, mechanical thrombectomy is reserved for patients with deep cerebral vein thrombosis, worsening clinical conditions, and failure of anticoagulation treatment [3,4]. In the pediatric population the role of endovascular intervention in presence of cerebral sinus thrombosis is not documented. The youngest child yet reported to have undergone mechanical thrombectomy was aged two years, and had an improved neurological outcome [5].

To the best of our knowledge, this is the first documented mechanical thrombectomy procedure during the neonatal period. This case report raises the question if endovascular interventions should not be reserved for newborns with multi-sinus thrombosis, especially when a deep cerebral veins are involved. This is particularly relevant if recent advances in endovascular techniques can render previously published data obsolete [4].

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Rescue Treatment with Terlipressin for Persistent Pulmonary Hypertension and Refractory Shock in a Preterm Infant

Persistent pulmonary hypertension of the newborn (PPHN) affects about 2/1000 newborn. The mainstay of therapy is supportive high frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (NO), which have decreased the need for Extracorporeal membrane oxygenation (ECMO) in these patients [1].However, still there is significant mortality and affected infants are at risk of long-term neurological impairment. We present the case of a preterm infant with severe PPHN and shock that failed all available therapies and was successfully rescued with the administration of terlipressin.

A 33-week male preterm baby (birthweight 2010 g) was admitted to our neonatal intensive care unit. Soon after birth he developed respiratory distress and hypoxemia. He was intubated and a surfactant dose was administered but without significant improvement. An echocardiogram showed a structurally normal heart and a near-systemic pulmonary artery systolic pressure (PASP) of 55-60 mmHg. HFOV and inhaled NO (20 ppm) were then initiated. The infant was hypotensive (Mean arterial pressure, MAP <5th percentile) requiring inotropic support with dopamine and dobutamine. At 36 hours of life, the infant remained hypotensive and with oxygenation failure (oxygenation index 31). Sequential echocardiograms showed supra-systemic PASP (80-100mmHg), right heart failure and pure right-to-left shunts. Sildenafil was added and continuous prostaglandin E1 infusion was started to keep the ductus open and support cardiac output. Adequate MAP could not be maintained despite escalating inotropic support: norepinephrine (up to 0.8 µg/kg/min), epinephrine (up to 0.8 µg/kg/min) and hydrocortisone (1mg/kg/6h). In this context, bosentan (2mg/kg/12h) was added but neither improvement in pulmonary hypertension nor oxygenation was observed. Continuous epoprostenol infusion was initiated at 40 hours of life because of persistent right heart failure and shock. Pulmonary hypertension partially responded to this therapy with improved oxygenation (OI change from 40 to 24) but it was impossible to maintain systemic MAP at maximal inotropic support (vasoactive-inotropic score: 131). A contact with two ECMO transport teams was made at 2nd day of life but ECMO was considered not indicated because of prematurity and a poor expected survival. At 4th day of life, the child was in profound shock and it was decided, in agreement with parents, to use compassionate rescue treatment with terlipressin. A 5 µg/kg bolus dose was administered followed by 10 µg/kg/h continuous infusion. Terlipressin rapidly raised MAP to 60 mmHg, allowing escalation of epoprostenol up to 60 ng/kg/min. PASP decreased from 85 to 40 mmHg with improvement in oxygenation (OI from 38 to 15). In the next 24 hours, he developed left to right ductal shunt and he was progressively weaned from pulmonary vasodilators. Terlipressin was maintained for 48 hours and then tapered gradually (1 µg/kg/h) allowing the infant to be weaned from catecholamines (7th day of life) and finally extubated at 12th day of life. The child was discharged home without any clinically significant sequelae. At 2 years follow up, the child has age-appropriate developmental status.

With terlipressin we observed a rapid raise in MAP with a marked improvement in pulmonary hypertension and oxygenation, allowing tapering of catecholamines. Terlipressin has been used to treat catecholamine-resistant vasodilatory shock in adults, showing restoration of arterial blood pressure. Terlipressin has also been used in pediatric and neonatal refractory shock with unclear clinical benefits [2,3]. Unlike adults, pure vasodilatory shock is uncommon in the pediatric and neonatal population and in consequence excessive vasoconstriction can induce tissue ischemia and worsen heart function and is not generally recommended.

Terlipressin is a vasopressin analogue with long half-life that exerts effects via V1 and V2 receptors.The main clinical effect is mediated by V1-receptor that causes smooth muscle contraction and induces a potent increase in systemic vascular resistance (SVR) and blood pressure.Terlipressin is reported to increase SVR without a concomitant increase in pulmonary vascular resistance (PVR) [4]. In fact terlipressin may induce direct pulmonary vasodilatation via NO-release and lower pulmonary arterial pressure. Terlipressin-induced increase in SVR also improves coronary perfusion and right heart function contributing to increased pulmonary blood flow and oxygenation; which is newborn infants may be further facilitated by reversal of right to left intra-cardiac shunts as a consequence of increased MAP/PAP ratio [5].

Successful use of terlipressin in term infants with different causes of PPHN such as congenital diaphragmatic hernia has been reported [6]. However, its use has not been reported in preterm infants, in whom refractory PPHN is uncommon. In our patient, given the potentially reversible nature of idiopathic PPHN we decided to exhaust all therapeutic measures and try rescue treatment with terlipressin. We observed improved blood pressure, heart function, and oxygenation. During the infusion, cardio-respiratory monitoring, NIRS, ion control, echocardiography, troponin and serial clinical evaluations were used to monitor side effects. We only observed transient skin vasoconstriction and discoloration without development of skin necrosis or evidence of new-organ failure.

In conclusion we believe that terlipressin may be considered as a salvage therapy in severe PPHN and refractory hypotension when ECMO is not available or it is considered contraindicated.

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Bartter Syndrome Masquerading as Acute Kidney Injury in a Neonate

Infants and children with Bartter syndrome present with polyuria and polydipsia, whereas older children present with constipation, salt craving and muscle cramps. The symptomatology is mainly due to renal concentrating defect [1]. This disorder is characterized by hypokalemia, hypochloremia, hypercalciuria, salt wasting with metabolic alkalosis.

A 10-day-old male child born out of third degree consanguineous marriage presented with severe respiratory distress.The antenatal history was uneventful. The neonate was suspected as late-onset sepsis and appropriate management was started. The investigations showed normal counts, C-reactive protein (CRP) levels and urine examination.The condition deteriorated further and required mechanical ventilation. The baby was started on intravenous piperacillin-tazobactam and amikacin, but antibiotics were stopped after 7 days as blood culture sensitivity was negative.

The baby's condition gradually improved and was weaned from the ventilator after 8 days. Renal parameters, urine output and leucocyte counts were monitored regularly and remained normal. The blood gases were all normal. The child was started on breast feeds on day 32 of life and was under observation for proper feed establishment and weight gain. On day 48, the infant developed decreased urine output along with respiratory distress for second time. Investigations showed normal leucocyte counts and normal CRP levels but renal parameters were suggestive of intrinsic renal failure. Peritoneal dialysis and non-invasive ventilation were started. The condition of the child improved and he was weaned from ventilator after 4 days. The renal parameters normalized after 20 cycles of dialysis.Blood and urine cultures were negative.Post-dialysis the child developed polyuria with a daily urine output >8 mL/kg/day. The infant continued to have polyuria inspite of measures to decrease urine output. The infant developed metabolic alkalosis despite acute kidney injury and polyuria. The blood pressures were in normal range. The urine examination showed, red blood cells, granular casts and proteinuria. Urinary electrolytes values showed urine osmolality – 133.2 mOsm/kg (normal 500 – 850 mOsm/kg), urinary chloride–66 mEq/L (normal <10 mEq/L), and spot calcium creatinine ratio - 2.96:1.0 (normal <0.86:1). Serum calcium,vitamin D and parathyroid hormone levels were within normal range. Ultrasonography of kidney and bladder showed calcifications in apex of medullary pyramids suggesting bilateral medullary nephrocalcinosis. We diagnosed our case as type 2 Bartter syndrome.

The classical Bartter syndrome (type 3) is perinatal in onset and presents with polyhydramnios, neonatal salt wasting and recurrent episodes of dehydration. Antenatal Bartter syndrome (type 1,2 and 4) typically manifests in infancy with severe phenotype compared to the classical syndrome [2]. The biochemical features reflect defect in sodium, chloride and potassium transporter on ascending limb of loop of Henle [3].

Various genes are associated with Bartter syndrome [4]; *MAGED2* mutation described recently is associated with transient Bartter syndrome which starts antenatally with severe phenotype and usually resolves by six weeks of age. Our case presented at around six weeks with acute kidney injury without hypomagnesemia [5]. The diagnosis of Bartter syndrome in neonate or infant is suggested by severe hypokalemia, hypochloremia and metabolic alkalosis. Hypercalciuria is typical and nephrocalcinosis is seen resulting from hyper-

calciuria in type 1 and 2. Hypomagnesemia is seen in minority. Urinary levels of chloride are also very much elevated which helps in differentiating this picture from chronic vomiting and cystic fibrosis. The tubular defect in Bartter or Gittlemann syndrome cannot be corrected [6], but with careful fluid and electrolyte management, long term prognosis is good. We treated the child with proper fluid and electrolyte correction following which hyperkalemia improved. The potassium levels normalised after a period of eight days without any therapy for potassium corrections except for restriction. Urinary electrolytes continued to remain elevated. The child was discharged in a stable condition after establishing oral feeds.

The child followed-up with us two weeks after the discharge which was uneventful. Our case focuses light on the rare presentation of Bartter syndrome with acute kidney injury probably due to nephrocalcinosis which might have started in utero.

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Fetal Ovarian Cyst Managed Laparoscopically in the Neonatal Period

Most antenatally diagnosed fetal cystic lesions are of renal or ovarian origin, and timely postnatal diagnosis facilitates early and appropriate management. We report early diagnosis of a fetal abdominal cyst with successful laparoscopic management.

A 1900 gram female baby was born vaginally at 38 weeks to a 24-year-old second gravid mother who had conceived spontaneously. Antenatal period was uneventful. Sonography at 30 weeks of gestation revealed a large well defined intra-abdominal fetal cystic lesion extending from pelvis to sub-hepatic region measuring, 4.8 cm × 4.2 cm × 4.8 cm with evident septations, with maximum wall thickness of 3.5mm. No subsequent antenatal scans were available. Baby did not need any resuscitation after birth but was detected with a palpable lower abdominal lump that was cystic in consistency. Rest of the examination including vitals was normal. A postnatal abdominal sonography showed a large cystic mass located in the right flank extending from sub-hepatic region to the pelvis measuring approximately 6.1 cm × 4 cm × 4.6 cm in size with internal solid areas (possibly fibrinous products) with no obvious vascularity or fluid debris level. Right ovary was not visualized, right kidney was seen distinctly separate from the cyst, and uterus, left ovary and left kidney were normal. Plain *X*-ray abdomen revealed displacement of bowel loops to left side. These findings were consistent with the diagnosis of ovarian cyst with internal hemorrhage (complicated). A thyroid scan performed later was normal. Laparoscopic excision of cyst with preservation of rest of the ovary was performed using three ports and a maximum of 10mm pneumo-peritoneum on day 8 of life. The cyst was seen to originate from right ovary, had a short pedicle and had undergone torsion on its own axis. Dark brown color fluid was aspirated from cyst, which was excised with Harmonic as energy source. Histopathological examination of excised cyst revealed complicated ovarian cyst with necrosed wall. Left ovary was normal. Intraoperative and postoperative course was uncomplicated. Breastfeeding was started on first postoperative day. The baby is currently on follow-up, is feeding and growing normally.

Fetal cystic masses in females are mostly benign and ovarian in origin. In a case series of 41 fetal abdominal cysts, 21 were ovarian cysts whereas 11, 6 and 3 cases were found to be bile duct cyst, intestinal duplication and mesenteric cysts respectively [1]. An antenatally detected isolated, non-lethal lesion should be monitored with repeated ultrasound examination, as the evolution of such a lesion *in utero* is extremely variable [2]. Serial antenatal ultrasounds help to determine the location and nature of the cyst and plan management. Accurate delineation of the mass may require fetal MRI.

Ovarian cysts are the commonest ovarian tumors in newborn period. Simple ovarian cysts are characteristically

round, anechoic, uni-locular, and usually thin walled. Complex cysts are characterized by presence of multiple septations, fluid levels, or mobile internal echoes [3]. Management options include expectant management, antenatal or neonatal cyst aspiration, laparoscopic cystectomy, and laparotomy. About 25-50% of small ovarian cysts (<4 cm in diameter) regress spontaneously often beginning at the end of pregnancy or within first few postnatal days with complete resolution within 6 months as hormonal stimulation decreases [4]. Only symptomatic cysts or cysts with diameter >4 cm, which do not regress or enlarge, should be surgically treated [5,6]. One in two cysts may undergo torsion, as in our case, occurring mostly in the antenatal period. In cases of torsion, the aim of treatment is to avoid complications associated with its rupture and preserve as much as ovarian parenchyma as possible. Open or laparoscopic excision with total oophorectomy or an ovary preserving procedure can be done. Laparoscopy provides for excellent visualization of the contralateral ovary, rapid postoperative recovery, and excellent cosmesis.

To conclude, fetal cystic lesions are mostly benign and ovarian in origin in females. Sonography helps localize the organ of origin and decide appropriate management.

Contributors: SP: responsible for managing the case and review of literature; PK: drafted the manuscript; SKS: investigated and operated on the case; AJ: responsible for final approval of manuscript.

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Pediatric Inflammatory Multisystem Syndrome Temporally Associated With COVID-19

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We read with interest the recent systematic review written by Meena, *et al*. [1], wherein the authors have highlighted the clinical features and outcome of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children. The review covers several aspects related to SARS-CoV-2 infection in children. However, recent emergence of a new clinical syndrome in children in association with SARS-CoV-2 infection also needs a special mention. This pediatric inflammatory multisystem syndrome (PIMS) is characterized by an unusual febrile illness with associated features suggestive of Kawasaki disease, toxic shock syndrome, myocardial dysfunction, or multi-organ failure [2-4]. The diagnostic criteria proposed by the Centre for Disease Control (CDC); World Health Organization (WHO) and Royal College of Paediatrics and Child Health are also not uniform [2-4], signifying a possible geographical difference in the spectrum of clinical manifestations.

A large proportion of children with coronavirus disease 2019 (COVID-19) fall in mild disease category [1]. On the contrary, cases of PIMS-TS reported so far have shown a rather severe course of illness with five deaths out of approximately 300 cases that have been reported [5]. Only up to 70% of PIMS individuals reported so far were either RT-PCR and/or serology positive [6]. This signifies that a positive PCR is not mandatory [3] for diagnosis of PIMS as even contact with a confirmed or suspected case of COVID-19 is enough to make the diagnosis [2,4].

Balasubramanian, *et al*. [7] recently reported one case of PIMS from India, who was successfully managed with intravenous immunoglobulin (IVIg) and additional immuno-suppressants, and also had positive nasopharyngeal RT- PCR.

We wish to highlight that PIMS is a severe spectrum of SARS-CoV-2 infection in children. This syndrome needs early recognition and aggressive management.

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Medical Education During the COVID-19 Pandemic: Experience From a Newly Established Medical School

We read with interest the recent article in the journal addressing medical education issues amid the COVID-19 pandemic [1]. We appreciate the authors for addressing the area of medical education during the COVID-19 pandemic. We would like to report our experience with undergraduate education at a newly established medical school, during the lockdown ensuing from this pandemic.

After the detection of the first COVID-19 case in Turkey on March 11, 2020, all universities were closed. Our institution had opened a year ago, and we have 48 undergraduate students. Our first year integrated curriculum was based on face-to-face interaction and laboratory sessions. Though, the past epidemics/ pandemics were one of the topics in the group discussions [2], yet we discovered that we ourselves were unprepared for providing medical education in this situation.

This disruption of education forced us to make a rapid transition to online teaching systems [3]. We discussed with the faculty members about adapting our program to distance education; and trained them for internet-based distance learning. After informing the students, we started providing our theoretical lectures online, as per a fixed schedule. Initially, the students' participation in the lectures was low. We tried to reach the non-participants to learn about their problems, and made an effort to keep them in the training system, which lead to increasing participation by students.

Before conducting the phase-end summative examination, we provided mock tests for the students, so as to get their feedback. In the end, we completed the program but had to postpone some laboratory sessions until the beginning of Phase 2.

We learned an important lesson that maintaining online programs successfully in medical education would need to be done through close communication with students. Moreover, despite the ever-present possibility of a pandemic arising at any time, medical schools were not ready for continuing their teaching. While face-to-face learning is the cornerstone of medical education, some distance-based educational activities might be incorporated as a routine in medical education, so as to ensure trained faculty and well-aware students.

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Pediatric Coronavirus Disease-19 (COVID-19): Meta-analyzing Literature Versus Natural History

We read with interest the recent systematic review on clinical features and outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children [1]. However, a major deficiency in the strategy seems to be the omission of Pediatric multisystem inflammatory syndrome (PMIS) [2]. Thus, the natural history of coronavirus disease 19 (COVID-19) in children seems innocuous. An early narrative review in the journal [3] observed that the mortality due to COVID-19 in children is rare, with majority being asymptomatic or having mild respiratory and gastrointestinal manifestations. The present systematic review [1] also substantiates that most children with COVID-19 were asymptomatic; amongst symptomatic children, only 0.7% required mechanical ventilation. The unique delayed cardiovascular manifestations in children have been omitted altogether from the suggested screening strategy for SARS-CoV-2 infection.

In these circumstances, the elucidation of clinical features and outcome using a strategy of systematic review and meta-analysis is premature. The average time for the process of a systematic review is about 17 months [4]. On the other hand, a living systematic review methodology allows minimal loss to methodological rigor. It preserves and improves the currency, relevance, and usefulness of a systematic review. Technology is often applied for arduous data extraction processes. These facilitate efficient extraction of relevant data, and fast and maintained synthesis of evidence. The benefit for researchers and policy makers is also immense [4].

The included studies in this review [1] were small and retrospective, with lot of heterogeneity and publication bias, the overall evidence generated is very low quality. Meta-analysis should be conducted with a group of homogeneous studies in terms of interventions involved and outcomes so as, to provide a meaningful summary [5].

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AUTHORS' REPLY

We appreciate the interest of the reader in our article [1]. The search of literature was performed till May 10, 2020, till when there were no published studies with ten or more patients describing the pediatric multisystem inflammatory syndrome (PMIS). It might be possible that there were a few case reports, but as mentioned in the methods, we did not include case reports and case series with less than ten cases. Therefore, this syndrome did not appear in our review.

We do not agree with the author's suggestion of including PMIS in the screening strategy for COVID-19 in children. As of now, PMIS is a rare and poorly understood presentation of COVID-19 in children [2]. The preliminary case definition itself is too complex to assess in the screening area [3]. Therefore, it might not be feasible to use it for the screening of COVID-19.

Living systematic review (LSR) is an emerging approach in which the review is updated frequently (classically at monthly intervals) and usually published online-only. Thought LSR seems a reasonable approach in COVID-19, it is very time consuming, requires lots of funding, and a dedicated team with long-term commitment. Moreover, agreement on methods to manage the data synthesis in LSR is still lacking, and the frequent statistical analyses can lead to an inflated false-positive rate. Moreover, such a review can be published online only, therefore requiring a major change in the existing publication norms [4]. Therefore, at present, rather than considering it as a replacement, LSR should be considered as supplementary to the conventional review.

Ideally, meta-analysis should not have significant heterogeneity and the confidence interval should be very narrow. However, both of these conditions are extremely difficult to meet in observational studies, that too in the early stages of a pandemic. We explored heterogeneity using subgroup and sensitivity analysis using standard methods, but did not find any significant difference in the pooled estimates of any of the clinical or laboratory parameters. For a clinician, the knowledge of the pooled estimates for various clinical and laboratory conditions is indispensable, and it did not involve any intervention, therefore the meta-analysis was warranted. The limitations pointed out were already mentioned in our review [1].

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Profile of Vitamin B12 and Vitamin D in Rural Schoolchildren in Raigad, India

Deficiency of vitamin B12 and vitamin D is reported to be common in India [1,2]. Vitamin B12 deficiency is especially common in vegetarian families [3]. The prevalence of ferritin, folate and vitamin B12 deficiency was reported to be 54.5%, 42.5% and 67.2%, respectively in Delhi [4]. In rural India, serum vitamin B12 and Vitamin D profile of children may be different due to differences in dietary practices. We herein share our data on serum vitamin B12 and vitamin D levels among children in selected schools of Raigad district.

Two hundred children between the ages of 5 and 15 years (42.9% females) from the five selected schools had 5 mL of blood collected for hemoglobin, vitamin B12 and vitamin D measurement. Written informed consent was obtained from parents prior to the data collection, and all procedures were as per the Helsinki Declaration, as revised in 2013. Samples were transported to the study laboratory in Mumbai by maintaining a continuous cold chain. Children were classified as per the socio-economic status of their parents (Kuppuswamy classification) and their routine dietary habits (24-hour dietary recall).

Vitamin B12 deficiency was observed in 26%, 32%, and 16% in the upper, middle, and lower socioeconomic groups, respectively, but was not seen in any child in the below poverty line group (***Table* I**). Vitamin D levels were low in categories A1, B, C and D.

Irrespective of a non-vegetarian or vegetarian diet, vitamin B12 may be lost during cooking under high pressure. The non-pathogenic B12 synthesizing bacteria grow on green leaves of vegetables. Due to the routine use of pesticide sprays and extensive washing of green vegetables before cooking, majority of these B12 synthesizing bacteria are killed or washed out. On the other hand, the meat of black crabs is a rich source of vitamin B12, and half-cooked crab and fish is a staple food for people of the tribal community in the region of school D.

In the present report, we found that contrary to the previous reports that vitamin B12 deficiency is rare in children, it is in fact not that uncommon [1,3]. However, fortification of food with folic acid solely, in a patient of unrecognized vitamin B12 deficiency, has the potential for causing harmful effects in the patient [5]. Low vitamin D levels could possibly be due to a lack of exposure to sunlight. It is interesting to note that 66% of school children in school A, had supra-normal vitamin D. One of the possible factors could be that this school is situated at a hilltop and has sufficient direct sunlight exposure throughout the year, contrary to the situation in other schools in this study.

We conclude that vitamin B12 and vitamin D levels in various communities may differ due to local conditions, which need to be identified and addressed for a lasting solution.

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Table I Vitamin D and Vitamin B12 Levels in Schoolchildren of Five Different Schools, Raigad, Maharashtra

School, No.	*Socioeconomic status*	*Routine diet*	*Vitamin D, ng/mL*				*Vitamin B12, ng/mL*	
			<10	*11-15*	*16-30*	*> 30*	*< 200*	> 200
A, 50	High SES, upper class	Green vegetables, fruits, daily eggs and milk, fish and meat twice/wk	2 (4)	5 (10)	10 (20)	33 (66)	12 (24)	38 (76)
A1, 50	High SES, Upper	Fruits, green vegetables, daily eggs and milk, fish and meat twice/wk	9 (18)	4 (8)	25 (50)	12 (24)	1 (2)	49 (98)
B, 25	Middle SES	Green vegetables, rice, bread, Fish and meat once/wk	3 (12)	12 (48)	10 (40)	0	8 (32)	17 (68)
C, 50	Lower SES	Curry, bread, rice, green fresh vegetables and dry fish	5 (10)	17 (34)	27 (54)	1 (2)	8 (16)	42 (84)
D, 25	BPL	Rice, fresh crab and fish	0	2 (4)	22 (88)	1 (4)	0	25 (100)

Values in no. (%); School classification: A-English school; A1-Urdu school; B-school at village; C-municipal school at Mahad; D-tribal school; BPL-below poverty line.

Serotonin Syndrome: A Real Risk of Anti-migraine Therapy

A 13-year-old girl, diagnosed as migraine without aura was under our follow-up for last one year. She was doing well on flunarizine and rarely required nonsteroidal anti-inflammatory drugs (NSAIDs) or rizatriptan for acute attacks. However, following the poor academic performance in the terminal examination, she developed depressive features including poor sleep, anorexia, decreased interest in the study, withdrawal from leisure activities and other daily routine work, decreased interaction with parents, emotional lability and inconsolable crying even on the minimal conversation regarding resumption of academic activities. She also developed an increased frequency of acute attacks of migraine, especially after prolonged periods of insomnia and hunger. Given the above features, she was prescribed amitriptyline 25 mg/day by a local practitioner. However, after consuming amitriptyline and rizatriptan daily for five days, she developed worsening of symptoms along with excessive anxiety, agitation, dizziness, palpitation, sweating and tremors of hands. She was then referred to our center with a diagnosis of conversion disorder.

On evaluation, she was found to have temperature of 38.7°C, diarrhea, vomiting and generalized hyperreflexia. Hematological and biochemical parameters, thyroid profile and MRI brain studies were within normal limits. Urine drug screen was negative for metabolites of any addictive drug. Serotonin syndrome scale score was 11, suggestive of serotonin toxicity. Both rizatriptan and amitriptyline were discontinued and she was started on oral lorazepam for anxiety and agitation. Within 48 hours, the symptoms dramatically improved and the serotonin syndrome scale score reduced to 2. She was advised flunarizine and naproxen for migraine and low dose olanzapine for depressive symptoms, apart from cognitive behavioral therapy.

Serotonin syndrome, caused by increased serotonin levels in the body, may occur as an adverse drug reaction after using some serotonergic medications in combination or overdose of such medications [1,2]. While rizatriptan is a 5-$HT_{1B/1D}$ receptor agonist, amitriptyline is a tricyclic antidepressant. Both the drugs increase serotonergic activity in the body by inhibition of the uptake of serotonin and norepinephrine in adrenergic and serotonergic neurons by acting on the membrane pump mechanism [3]. An alert was issued by Food and Drug Administration (FDA) in 2006 on the possibility of life-threatening serotonin syndrome when triptans are combined with selective serotonin receptor inhibitors (SSRIs) and selective norepinephrine receptor inhibitors (SNRIs) [4]. Although this combination is less commonly prescribed in children, pediatricians still need to be aware of this entity for timely diagnosis and prompt treatment.

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NOTES AND NEWS

NEWS IN BRIEF

Definition of pain amended after four decades

The International Association for the Study of Pain (IASP) Council earlier in 1979 defined pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*" This definition had long been condemned for disregarding the heterogeneity of mind-body interactions, ignoring 'the ethical dimensions of pain', inadequately addressing pain in disempowered and neglected populations (neonates and elderly), belittling severe pain, and suffering associated with many diseases and excluding cognitive and social aspects inherent to the experience of pain.

The IASP felt the need for an unambiguous and concise definition to provide those dealing with pain with a shared understanding of the term to apply to health policy, research, and clinical care. A 14-member, multinational multidisciplinary Task Force updated the definition which was unanimously accepted by the IASP Council early in 2020. The revised definition is: *"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."* The definition also includes the "etymology of the word pain" and "six notes" that highlight the need to assess the untoward effects of pain on an individual's function, social and psychological well-being to help personalize their management.

The goal was to redefine pain in broad terms, in tune with the latest understanding of various factors that possibly contribute to the experience of pain, in hope that a better understanding of the nuances and the complexity of pain could result in better assessment and management of those with pain. A key amendment is replacing the terminology that relied upon a patient's capacity to describe the experience to qualify as pain. The revised definition gives more room and respect for self-report by underscoring that tissue damage is not required.
(Pain July 2020)

Support breastfeeding for a healthier planet

Since 1992, the first week of August has been celebrated globally as the *World Breastfeeding Week*. The theme this year is 'Support breastfeeding for a healthier planet.' The main objectives as per the Breastfeeding Promotion Network of India are to generate awareness and action on the deleterious effects of breast milk substitutes (BMS) and the protective role of breastfeeding on the environment and to involve groups for advocacy in different states to improve protection, promotion, and support of breastfeeding.

Breastfeeding safeguards the environment and is a climate-friendly and environmentally sustainable method of feeding. On the other hand, the use of BMS generates greenhouse gases in the production process and waste in the form of bottles, teats, tin containers, and promotional material, imposing further burden on the planet. The sale of BMS is increasing rapidly despite the myriad advantages of breastfeeding. The total sale of BMS in India was 26,900 tons in 2016 with an estimated sale of 30,700 tons in 2021 (a 14% cumulative increase). Herculean efforts are needed to reduce its consumption and augment breastfeeding rates through good support systems for mothers.

WHO and UNICEF have called on governments to protect and foster mothers' access to skilled breastfeeding counseling that can empower women to overcome obstacles and prevent practices interfering with optimal breastfeeding, such as the provision of BMS. Amidst the COVID-19 pandemic, it is necessary to ensure that mothers obtain the breastfeeding counselling they need.
(www.bpni.org July 2020, www.who.int 31 July 2020)

A game changer in COVID-19 testing

Testing for SARS-CoV-2 has been a major deterrent in our battle against COVID-19, with protracted delays and dearth of kits and reagents. In what could be a ground-breaking diagnostic innovation, the US FDA authorized the emergency use of a rapid, inexpensive, non-invasive saliva-based test, called Saliva Direct on August 15, 2020.

Developed at Yale's School of Public Health, SalivaDirect uses saliva instead of nasopharyngeal samples, permitting non-invasive frequent sampling. Saliva can be self-collected in any sterile container, mitigating the need for special swabs, collection devices and trained healthcare professionals. This dualplex quantitative reverse transcription PCR assay does not require a preservative or the time-consuming and expensive nucleic acid extraction process. The ability to perform the test without these kits intensifies the capacity for increased testing, while making it less resource dependent. Another key component is its validation with reagents and instruments from multiple vendors, thereby minimizing risk for supply chain issues. It is highly sensitive (88-94%) with a limit of detection of 6-12 copies/μL. Yale envisages providing theSalivaDirect protocol open source to interested laboratories. As widespread testing is the key to containment of the virus, this flexible and inexpensive test (about $10/sample) is a viable and accessible option to help alleviate COVID-19 testing demands.

This test, coming at a time of intense pressure on supplies and resources, could prove to be a turning point in our fight against the virus.
(The Hindu 17 August 2020, MedRxiv preprint 4 August 2020)

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Theme: Pediatric Gastroenterology

Very early-onset inflammatory bowel disease– NASPGHAN position paper
(*J Pediat Gastroent Nutr. 2020;70:389-403*)

In view of the increasing rate of pediatric inflammatory bowel disease (IBD) and increasing knowledge and experience with this condition, the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) has come out with a position paper on very early onset (VEO) IBD. It describes the epidemiology classification, genetic etiologies, phenotypes and treatment modalities for VEO-IBD. IBD diag-nosed in the first 2 years of life is called infantile-onset IBD while that diagnosed between 2 to 6 years is known as VEO-IBD. Monogenic defects can be detected in 15-20% of children with VEO-IBD. The genes involved are those of the intestinal epithelial barrier function and immunological disorders. Detailed phenotypic characterization including clinical evaluation, endoscopy and biopsies can help narrow down the plausible genetic defects, which can further be identified by targeted or whole exome sequencing. The current data on VEO-IBD is limited to case reports and small case series. The available treatment modalities include immunomodulators such as methotrexate and azathioprine, biologi-cals such as infliximab and abatacept. The child may also require surgical interventions or hematopoietic stem cell transplant. It is important to have a collaborative multidisciplinary team to manage these patients.

Monogenic pediatric inflammatory bowel disease
(*Gastroenterology. 2020;158:2208-20*)

It is estimated that more than a quarter of the cases of inflammatory bowel disease (IBD) develop during childhood or adolescence. The younger the age of onset of an illness, the more is the role of host genetics. The role of monogenic variants in IBD across the entire pediatric age range is unknown. This study was conducted at the Sick Kids IBD centre Toronto, Canada to evaluate the same. Whole exome sequencing of 1005 children with IBD was done. The authors identified 40 rare variants associated with 21 monogenic genes among 31 of the 1005 patients. The variants were identified in 7.8% of children younger than 6 years and 2.3% of the children between 6 to 18 years. Monogenic IBD was more likely to be seen if the age of onset was younger than 2 years or there was a family history of an autoimmune disease or if there were extraintestinal manifestations or surgery.

Chronic vomiting in children: Rumination syndrome an underdiagnosed and untreated etiology
(*Indian J Gastroenterol. 2020;39:196–203*)

This was a prospective study that enrolled 50 children aged 5-18 years presenting with chronic or recurrent vomiting of a minimum of two months duration. Clinical evaluation was done by a single investigator using a structured questionnaire. The first line of investigation included routine urine and blood tests, ultrasound abdomen, a fundus examination, an ultrasound and barium meal follow through. The second line investigations involved endoscopy with esophageal biopsies and gastric emptying scan. A diagnosis of rumination syndrome was made in 30 children followed by cyclical and functional vomiting in 8 and 6 children, respectively. Intestinal tuberculosis was diagnosed in 4 children. Children with rumination syndrome had a relapsing and remitting course in 40% and a chronically symptomatic course in 60% of the cases. It was seen that a diagnosis of rumination syndrome was often missed or delayed. The authors concluded that the diagnosis can often be made clinically, and diaphragmatic breathing is an effective treatment.

Ursodeoxycholic acid in infants with cholestasis – Increased morbidity and mortality
(*Medicine (Baltimore). 2020;99:e18730*)

Ursodeoxycholic acid is often used in the management of infants with cholestasis. This is an off label use. In this study from Egypt, a retrospective review was done of the data of 779 neonates and infants with cholestasis over a period of 10 years. The etiology was surgical in 19.5% cases, neonatal hepatitis in 67.2%, and paucity of intrahepatic bile ducts in 13.3%. Out of all the infants, 54.4% received UDCA (15-30 mg/kg/d), 45.6% did not. Both groups were matched with regards to the etiology and severity. Seventy three percent achieved a cure without UDCA as against only 45% of those on UDCA. Those on UDCA had significantly worse outcomes and more complications. The authors concluded that the use of UDCA was associated with serious morbidity and death which was preventable. They suggested that off-label use of UDCA in neonates and children should be utterly prohibited.

Predictors of non-alcoholic fatty liver disease (NAFLD) among children with obesity
(*J Pediatr Endocrinol Metab*. 2020;33:247-53)

The prevalence of childhood obesity is increasing all over the world. Non-alcoholic fatty liver disease (NAFLD) is a known complication of obesity at all ages. This study was done to determine the prevalence and predictors of NAFLD in obese children. Clinical and biochemical parameters were studied in the NAFLD and non-NAFLD group. Out of 33 obese children, 63.6% were found to have NAFLD. Mean values of anthropometric parameters such as BMI and waist circumference were higher in the NAFLD group, so were the, triglycerides and the alanine aminotransferase levels. Multivariate regression analysis revealed that triglycerides were an independent predictor of NAFLD.

Identification of risk factors must now lead to screening strategies for high-risk children, so that morbidity related to this chronic problem can be reduced.

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IMAGE

Pitted Keratolysis

A 12-year-old girl presented with malodorous pits over both soles associated with hyperhidrosis for the past three months. On cutaneous examination, multiple yellowish-brown circular crateriform pits (2-5 mm) with punched out appearance were seen over the ventral aspect of the great toe, the ball, and heel of both feet; the pits coalesced into large, shallow macerated furrows with focal erosion (***Fig.* 1**). A characteristic sparing of the non-pressure bearing areas was noted. Potassium hydroxide mount of skin scrapings showed no fungal elements. Based on the characteristic history and cutaneous findings, a diagnosis of pitted keratolysis was made. She was treated with topical clindamycin and advised to avoid occlusive footwear; the lesions resolved in 3 weeks.

Pitted keratolysis is a bacterial infection of the plantar stratum corneum, predominating the weight-bearing areas of the soles, commonly caused by gram-positive *Kytococcus sedentarius*. Although a straight forward diagnosis clinically, differential diagnosis include plantar warts (absense of skin markings), tinea pedis (erythema, scaling with fungal elements on KOH mount), and punctate keratoderma (tiny hard rounded bumps). Topical antibiotics and adequate preventive measures are recommended.

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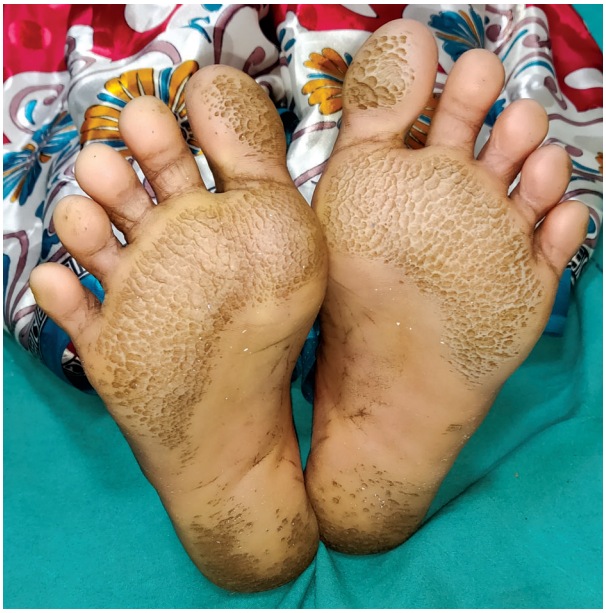
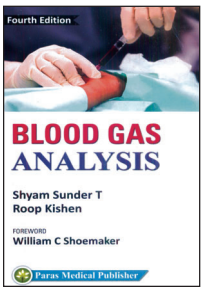


Fig. 1 *Pitted keratolysis characterized by multiple crateriform pits with punched out appearance over the pressure-bearing areas of both feet.*

BOOK REVIEW



Blood Gas Analysis

Shyam Sunder T and Roop Kishen
M/s. Paras Medical Publisher, Andhra Pradesh, India.
Pages: 425; Price: Rs. 625/-.

This book very clearly explains the basics of acid base equilibrium, abnormalities of acid base in the body and compensatory mechanisms for these abnormalities. Topics are well classified with an index in the beginning, and most aspects of blood gas analysis are covered.

Print quality is good and language is simple to understand. The case studies at the end of the book improve understanding of application of knowledge of acid-base analysis in clinical scenarios.

Overall, it is a valuable addition to books for physicians, pediatricians and intensivists and particularly, residents in these branches.

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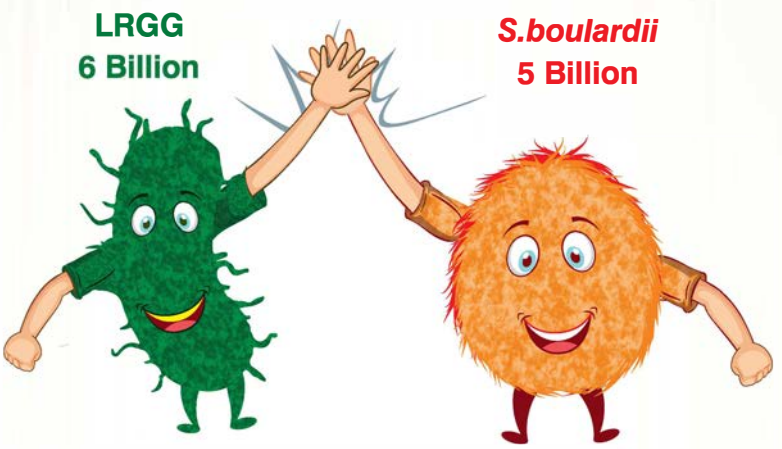

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