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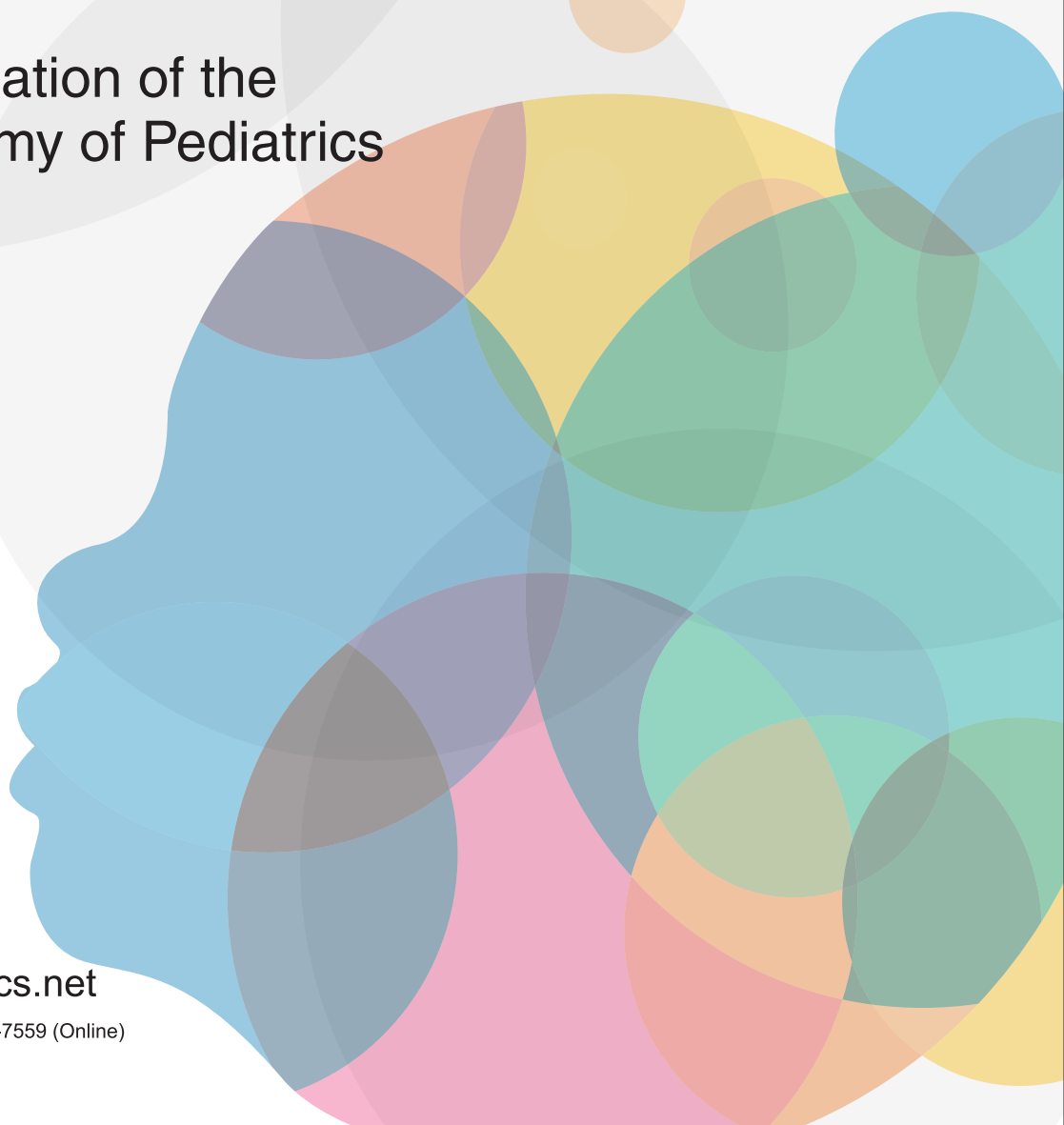

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Psychosocial Impact of COVID-19 Pandemic on Children in India

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Coronavirus disease (COVID-19) pandemic has unfolded a tsunami of challenges for mankind over the past 10 months. Despite this, it has triggered a global collaboration to control the pandemic, and transformed every individual by influencing family dynamics.

Many families are experiencing an ongoing, pervasive sense of loss *e.g*., loss of social networks, jobs, financial security and threatened loss of loved ones. This has impacted the quality of relationships among parents, children and siblings. It poses a significant risk for the adjustment of more than 37 crore children (0-14 years) in India, given their dependence on positive family processes for a host of developmental outcomes.

IMPACT OF COVID-19 ON FAMILY DYNAMICS

Social disruptions from the pandemic and changes in gender norms (moving closer to equal roles in the home) that defines, our new 'normal' have generated heightened levels of psychological distress, impacting the quality of relationships among parents and children.

In March, 2020, schools across India were shut down to curb the transmission of COVID-19. Children have been at home for longer periods of time than ever before in recent memory. Closure of schools, lack of extracurricular and outdoor activities, altered eating and sleeping habits, lack of peer-time have fostered monotony, anguish, irritation, and diverse neuro-psychiatric symptoms. Although home should be the safest place for a child, sexual, psychological and physical abuse have shown a significant rise.

This has unfolded an unparalleled global mental health problem and it presents a unique challenge to psychological resilience across the world. This may soon lead to an outbreak of a 'second pandemic' of mental health crises.

Children of single parents, including medical professionals taking care of COVID-19 patients, are likely to suffer from adjustment difficulties if their parent gets quarantined. In addition, transient or prolonged parent-child separation may lead to sifnificant psychosocial impact.

PSYCHOSOCIAL ISSUES OF COVID-19

It has been reported that the most common psychosocial and behavioral problems among children and adolescents in the pandemic were inattention, clinginess, distraction and fear of asking questions about the pandemic. This risk is greatly increased in those with pre-existing mental health conditions.

In the midst of the COVID-19 pandemic, helpline numbers for mental health counselling are seeing a huge surge in calls, with anxiety and adjustment issues topping the list. In addition, domestic violence incidence in India is at a 10-year high during the COVID-19 lockdown.

Thus, the COVID-19 disease itself, and its ripple effects of quarantine and nationwide lockdowns have and will induce acute panic, anxiety, obsessive behaviors, paranoia, and depression, and may also lead to post-traumatic stress disorder (PTSD) in the long run.

BOUNCING FORWARD FOR A NEW NORMAL

Identification of children and adolescents at risk by health care providers is especially important during clinical visits/ teleconsultation. It is important to screen for psychiatric and psychosocial effects of social distancing and quarantine on families. Asking direct questions on wellbeing and safety at home will be a critical approach to screen children at risk of or experiencing domestic abuse. Other vital interventions for families include suggesting mental health resources, contact or emergency numbers and counseling.

The current pandemic is a lingering stressor that may damage our mind and body, resulting in long-term health consequences. The impact of stress and adversity on physical and psychological wellbeing should be increasingly focused on in a pediatric clinic as the need of the hour. Proactively preventing psychosocial crisis, fostering psychosocial wellness and developing cost optimal widely accessible intervention models should be the topmost priority for the government, health care personnel and other stakeholders.

EDITORIAL COMMENTARY

Cooked Green Banana in Hospitalized Children With Acute Watery Diarrhea Without Dehydration

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Childhood diarrhea is one of the leading health problems, especially in low and middle-income countries (LMICs), and accounts for 8% of the annual 5.2 million under-five global deaths [1, 2]. Almost two-third of all under-five diarrheal deaths are reported in sub-Saharan Africa and South-East Asia [1]. Although, most of the LMICs including India failed to achieve the Millennium Development Goals (MDGs), especially the Goal-4 that aimed to reduce under-five child mortality including the deaths from diarrhea; these countries have now targeted to achieve the Sustainable Development Goals (SDGs). The SDG-3 specifically targets to reduce under-five mortality at least by 25 per 1,000 live births [3] and therefore more emphasis should be given for the reduction of diarrhea related under-five deaths. Prompt and adequate management of diarrhea is the principal factor of targeted approach for reduction of diarrheal deaths [4]. World Health Organization (WHO) recommended oral rehydration solution (ORS) and oral zinc therapy in addition to frequent breast feeding, and home available fluids are the mainstay of management of diarrhea [5]. Although, ORS is credited with saving millions of lives by correcting dehydration, it does not have any impact on the reduction of duration of diarrhea. However, zinc is already shown to have reduction of diarrheal duration and hospitalization [6].

In this issue of *Indian Pediatrics*, Gunasekaran and colleagues [7] share their findings from a randomized controlled trial (RCT) on the efficacy of green banana *(Musa paradisiaca)* for recovery in children (9 months to 5 years) with acute watery diarrhea with no dehydration. Children in the control group (n=125) received standard care, and children in the intervention group (n=125) received cooked green banana in addition to standard care. Patients were hospitalized during the initial 72 hours and thereafter continued treatment at home until diarrhea stopped or the 14th day of illness, whichever was earlier. A significantly higher proportion of children recovered in the green banana group compared to the control group (62.4% *vs.* 47.2%; P=0.002) and there was 85% lowered risk of dehydration and 70% lowered risk of developing persistent diarrhea in the green banana group compared to their counterparts. The entry criteria were a bit specific as the study included children with acute watery diarrhea (AWD) without any degree of dehydration defined by the WHO and excluded children who were undernourished (weight for age Z score <-2), and this limits the generalizability of the study. This RCT happens to be a hospital-based study although the WHO recommends that children with AWD without dehydration or under-nutrition or any co-morbidity need to be treated at home. Gunasekaran, *et al*. [7] also did not mention the number of children who were admitted with AWD during the study period and how many of them had dehydration. The reasons for the non-receipt of allocated interventions in 17 children in the green banana group were not specified in the CONSORT flow diagram. It is difficult to understand whether the supportive care at home for both the groups were similar. However, despite these limitations, this RCT revealed some valuable findings that underscored the benefit of the use of cooked green banana for the treatment of children with AWD without having any form of dehydration and under-nutrition in developing countries.

Previously, a community-based study from Bangladesh [8] evaluated the beneficial role of green banana in children not only having AWD but also with prolonged diarrhea. Gunasekaran and his colleagues conducted this trial in the hospital and reemphasized the importance of using green banana in faster recovery of childhood AWD [7]. Their data highlighted the role of cooked green banana supplemented diet as a useful adjunct to standard treat-ment (ORS, zinc, and home available fluids) in the management of AWD with no dehydration and no under-nutrition.

Overall, Gunasekaran and colleagues should be congratulated for this important work. Importantly, we need to be cautious in undertaking the problem of AWD

in developing countries, which may require an unbiased approach relating to clinical care with basic public health measures including provision of clean water, sanitation, nutrition, and immunization. In LMICs, these should be the cornerstones of any efforts to reduce the incidence of diarrhea as well as deaths from diarrhea, and this in turn may help to achieve SDG-3 by reducing under-five mortality by two-thirds till 2030.

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

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Pediatric Liver Transplantation in India: 22 Years and Counting

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Liver transplantation in India has grown exponentially in the last decade with 135 centers now performing between 1500-2000 transplants a year, 10% of which are pediatric. Survival rate surpassing 90% has been achieved, and India is now an important regional liver transplant hub in South and South-East Asia. The indications have expanded to include increasing number of liver-based metabolic disorders that may or may not cause liver disease. Recipients, who were previously considered non-transplantable such as those with pre-existing portal vein thrombosis, can be successfully managed with innovative microvascular techniques. The donor pool has grown with the use of marginal grafts and ABO incompatible organs. Financial constraints are being overcome by crowd funding and increasing philanthropic efforts.

Keywords: *Deceased donor, History, Multi-organ transplant, Outcome.*

Liver transplant is curative for acute liver failure, chronic end stage liver diseases, some liver tumors and inborn metabolic errors that may or may not cause liver disease per se. Advancements in preoperative care, surgical techniques, intensive care management along with availability of potent immunosuppressive drugs have helped attain 94% 1-year, 91% 5-year, and 88% 10-year patient survival in pediatric liver transplant recipients [1]. In India, the first successful pediatric liver transplant was performed in 1998 [2], and that boy with biliary atresia is now about to complete his graduation in medicine and is doing well on minimal immunosuppression (***Table* I**). Every year around 1500-2000 liver transplants are now performed, of which approximately 10% are pediatric. Survival rates surpassing 90% have since been attained in India [3-5]. Initial progress was slow as part of a learning curve with limitations due to scarcity of trained personnel, poor awareness amongst primary care doctors, reservations regarding donor safety and the financial implications. By 2007, only 318 liver transplants had been performed in India [6]. The growth has been exponential in the last decade; although collated data of the country is not available. This has been sustained mainly by living donor liver transplant (LDLT) though deceased donation (DDLT) is picking up, primarily in the southern part of the country where some centers report a 70/30 LDLT/DDLT overall distribution [7]. As per the Global Observatory on Donation and Transplantation, 1945 liver transplants (adult and pediatric) were performed in India in the year 2018 (1313 LDLT).

Auxiliary liver transplant (auxiliary partial orthotopic liver transplant, APOLT) with implantation of a partial graft without fully removing the native liver is technically more challenging with a higher complication rate. It is a suitable option for acute liver failure and metabolic disorders without cirrhosis as it offers a chance for immunosuppression free life in case of native liver regeneration or restoration of defective metabolic function with newer therapies. Successful APOLT for acute liver failure has been reported from India but the modality has not become popular due to the higher risks

Table I History of Pediatric Liver Transplantation in India

Event	*Year*
Pediatric living donor liver transplant (LDLT)	1998
Adult deceased donation liver transplant (DDLT)	1998
Liver transplant for acute liver failure (ALF)	1999
Adult combined liver and kidney transplant	1999
Pediatric combined liver and kidney transplant	2007
Pediatric re-transplant	2002
Pediatric DDLT	2007
Liver transplant for HIV	2008
Liver transplant for Criggler-Najjar syndrome	2008
Domino transplant	2009
LDLT for factor VII deficiency	2010
Auxillary liver transplant for ALF	2012
ABO incompatible liver transplant	2014
Domino auxillary liver transplant	2015

involved with retaining a diseased liver in acute liver failure with its attendant toxic and metabolic effects.

The establishment of a new liver transplant program requires approval from a regional health body after evaluation of infrastructure and expertise. As per the National organ and tissue transplant organisation (NOTTO) there are now about 135 centers for liver transplant in India, including second tier cities apart from the metros, with majority of the pediatric work limited to about 10 centers (***Fig.* 1**). As liver transplant is largely private sector driven and is a high cost procedure, credibility rests on preventing commercialization of the programs. This has been made feasible by the stringiest criteria laid down by the government and strict scrutiny by authorization committees in every case to ensure donation is from a relative on a wholly voluntary basis with no coercion. In camera meetings are held and all documents to establish near relationship are verified before a go ahead is attained even in cases requiring emergency transplants.

A significant proportion of pediatric patients are from overseas. Patients from about 20 countries have been transplanted at our center, and also at other Indian centers. A few are partially or wholly funded by their governments, while many others raise funds through international charities and/or social organizations. Many families have gone on to form support groups in their respective countries. The Indian Human Organ Trans-plant Act, enacted in 1994, allows foreign nationals to receive a deceased organ in India only if no suitable Indian recipient is available. As cadaveric donations are few and the waiting list is long, foreign nationals would only qualify for LDLT.

India is now an important regional center for liver transplant in South and South East Asia, more so for pediatric patients. Many of these neighboring countries have either not yet set up transplant units or are in the fledgling phase running predominantly adult programs. Pediatric liver transplant carries its own set of challenges due to the smaller diameter of vessels requiring greater surgical expertise along with need for specialized pediatric intensive care and usually a longer duration of postoperative hospital stay. Moreover, many of these countries have very few pediatric hepatologists with expertise in post-transplant care, thus necessitating a thorough coordination with the transplant unit for follow up once the families travel back to their native countries.

EXPANDING THE DONOR AND RECIPIENT POOL

Though biliary atresia remains the leading indication for liver transplant in children [8], improving outcomes have encouraged expanding indications to include liver-based metabolic defects [9]. Where these defects cause liver

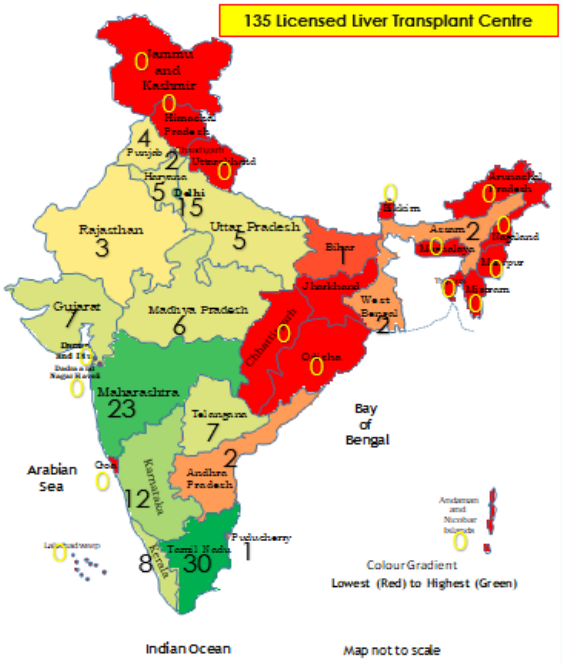

Fig. 1 *Distribution of liver transplantation centers in India, 2020.*

damage, liver transplant is curative by replacing the diseased organ as in other disorders of liver architecture leading to synthetic dysfunction and decompensation. The other group includes disorders whereby a genetically inherited enzymatic defect, wholly or partially liver based with a structurally normal liver, causes neurological/ multiorgan involvement that may be prevented by replacing the liver. Liver transplant should be performed early before irreversible damage occurs in target organs. These include Criggler Najjar syndrome, urea cycle defects and organic acidemias to achieve intact neurological status, familial hypercholesterolemia to prevent cardiac disease and/or sudden death, and primary hyperoxaluria where an early liver transplant prevents renal failure or else a combined/sequential liver kidney transplant would be required to prevent systemic oxalate overload and its multiorgan consequences. With the availability of next generation sequencing (NGS) based tests, precise and timely genetic diagnosis can now be made and timely therapy instituted.

Livers from patients with Maple syrup urine disease (MSUD) and familial hypercholesterolemia may be donated to cirrhotic patients as they are structurally and functionally normal apart from an enzyme deficiency, which may be compensated by other body tissues to sustain function. Such transplants, known as domino transplants, have been successfully reported from India [10]. As our programs are primarily living-related, the majority of the donors are parents who are carriers of the

recipients' metabolic or genetic disorders with autosomal recessive inheritance. Use of such heterozygous donors has been debated. Data from the Japanese multicenter registry [11] has reported that outcome after employing heterozygous donors was excellent with better long-term survival rate. Portal vein thrombosis (PVT), a known sequelae of cirrhosis, especially more frequently seen in infants with biliary atresia due to portal vein hypoplasia, is no longer a contraindication to liver transplant despite the technical difficulty and higher risks of post-transplant vascular thrombosis endangering the graft [12].

Pediatric liver transplant has now progressed beyond the ABO blood group barrier. ABO incompatible (ABOi) transplants are being increasingly performed when blood group compatible donor from the family is not available. Despite concerns about liver graft regeneration, antibody mediated rejection (AMR), higher incidence of biliary strictures and sepsis, both pediatric and adult ABOi liver transplant survival has improved markedly and has become comparable to ABO-compatible liver transplant with the introduction of rituximab prophylaxis before transplant [13]. Rituximab and/or other B cell desensitization strategies including plasmapheresis and IVIg are used to bring down isoagglutinin titers to less than 1/8 pre liver transplant. Children younger than 2 years of age may not require these desensitization therapies as blood group isoagglutinins titers are low and complement system activation is not robust, thus minimizing the risks of AMR [14]. ABOi liver transplant grafts in acute liver failure in infants have thus been used more often as lack of time window for desensitization strategies may limit use of this modality in older children and adults with acute liver failure [15]. Most busy centers in India have successfully performed ABOi transplants since the initial reports of success in 2014 [16].

Size-matching determined by the graft-to-recipient weight ratio (GRWR) is a crucial determinant for graft suitability and ideal ratios of 0.8-1 have been advocated. Many centers now have experience with small for size grafts and it is acceptable for the GRWR to be as low as 0.5-0.6 if there are accompanying factors of portal vein pressure ≤15 mmHg, middle hepatic vein reconstruction, or young donor age [17]. On the other hand, large for size grafts are problematic in small infants due to compromised portal venous flow and small abdominal cavity. Use of reduced mono/bi-segment grafts and delayed abdominal closure using mesh/skin closure help circumvent abdominal compartment syndrome [16]. Thus, babies as small as 4-5 kg are now being routinely transplanted at select centers in India.

Other marginal grafts are increasingly being accepted. These include older donors in the absence of size mismatch and severe steatosis, moderately steatotic liver grafts if predominant pattern is of microsteatosis instead of macrosteatosis, donors with a BMI ≥30 kg/m^2 and HBsAg-negative/HBcAb-positive liver grafts in HBsAg negative recipients with active immunization and post-transplant antiviral prophylaxis to prevent *de novo* HBV infection [17]. These strategies have considerably increased the donor pool for liver transplant in scenarios hitherto found unsuitable.

PERSISTING CONCERNS

Studies on long term morbidities, effects of immunosuppression and quality of life post liver transplant are lacking from our country. LT requires lower immunosuppression compared to other organs. Indian patients have been shown to do well on lower immunosuppression as infections are more common in our scenario [4,5]. Regimens vary across different programs but corticosteroids remain the induction agents of choice with dual agent regimens including calcineurin inhibitors and renal sparing mycophenolate for the first year, with the aim to come down to a single agent by the second year. The desired ideal outcome is attainment of prope tolerance, *i.e.*, almost immune tolerant state where the recipient is alive with first allograft with no ongoing rejection episode on tacrolimus therapy with trough levels less than 3 ng/mL, three years post LT. Studies indicate that almost 20% pediatric patients may attain such immune tolerance with maximal chances for those transplanted in infancy [18]. However, the SPLIT database analysis has revealed that the ideal triad of normal growth, stable allograft function on single-agent immunosuppression, and an absence of immunosuppression-related complications is achieved in only about a third of recipients 10 years after LT [1]. Steroid free protocols using antibody induction (ATG/basiliximab) along with tacrolimus are not yet in vogue but steroid-free tacrolimus-based immunosuppression may result in an enhancement of graft acceptance in the long term as well as in a higher proportion of children becoming prope tolerant [19,20].

Lack of a database greatly inhibits accurate analysis of trends, outcomes and long term results. Non-availability of long term followup from many recipients from overseas is another disadvantage. With the formation of the Liver Transplant Society of India, efforts are on for a national registry, hopefully more data should be available in the coming years. Low numbers for DDLT, especially in Northern India, is amongst the foremost immediate concern that requires intense campaigning and education to change the social mindset. Encouraging organ donation is the need of the hour.

CHANGING SOCIAL SCENARIO

Perhaps, the most crucial limiting factor in our country has been the cost of liver transplant. The programs are largely driven through the private sector, and health care insurance is still not widely prevalent in our country. Moreover, most insurance companies do not provide cover for diseases of perinatal onset or genetic etiology. The advent of crowd funding platforms where strangers come together on the internet to fund a medical catastrophe for an unknown person is heart-warming and provides an insight into the social responsibility the community is prompt to take up when transparency is assured. These campaigns run on social media with tight timelines ranging from a week to a month, and at times funds have been raised in a day or two for emergency transplants. Crowd funding with the support of few philantrophic organizations and individuals dedicated to funding liver transplants has thus made transplantation attainable for those with limited resources. Crowd funding works best for children awaiting transplants, perhaps due to the emotive pull of images and videos of innocent children struggling to wade off certain death that a transplant could prevent. The predicament of the parents, one of whom is the organ donor most of the time, also touches a cord. With this active support of the community in facilitating transplants for children, liver transplant seems to have finally come of age in our country.

FUTURE DIRECTIONS

High-resolution sequence mapping of DNA variation is now feasible and liver tissue transcriptional signatures are being studied to identify candidates likely to achieve tolerance and withdrawal of immune suppression. Genome wide association studies or NGS for cytokine genotyping to detect single nucleotide polymorphisms in cytokine gene promotor regions may help identify recipients at low risk for rejection.

Meanwhile, expansion of this facility in the public sector is needed as liver transplant is still not available routinely to those with limited resources. We wait to realize the dream of DDLT becoming the primary modality, as it is in the Western countries, by concerted efforts to promote organ donation.

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RESEARCH PAPER

Effect of Green Banana *(Musa paradisiaca)* on Recovery in Children With Acute Watery Diarrhea With No Dehydration : *A Randomized Controlled Trial*

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Background: Cooked green banana (*Musa paradisiaca*) has been observed to be useful in reducing the duration of diarrheal illness in children.

Objective: To evaluate whether supplementation of cooked green banana shortens the duration of diarrhea in children with acute watery diarrhea with no dehydration.

Study design: Open label randomized controlled trial.

Participants: Consecutive children aged 9 months to 5 years who presented with acute watery diarrhea within 48 hours of onset of illness with no dehydration.

Intervention: Children in the control group received standard care, while those in the intervention group received cooked green banana in addition to standard care under supervision in the hospital for 72 hours, and then continued at home until diarrhea stopped or 14th day of illness, whichever is earlier.

Outcome measures: Proportion of children who improved at 72 hours of intervention (passing formed stools with normal frequency) was considered as the primary outcome and the incidence of complications such as dehydration, persistent diarrhea and secondary lactose intolerance were evaluated as the secondary outcomes.

Results: The proportion of children who recovered within 72 hours was significantly higher (62.4%) in the green banana group compared to the control group (47.2%) [RR 1.3 (95% CI 1.05-1.7), NNT=7].The number of children with complications such as dehydration and persistent diarrhea was also signi-ficantly less in the intervention group.

Conclusion: Supplementation of cooked green banana in the diet of children with acute watery diarrhea with no dehydration hastens their recovery.

Key words: *Duration, Management, Outcomes*.

Trial registration: CTRI/2017/05/008623

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Diarrhea is an important determinant of childhood mortality and also predisposes the child to under-nutrition [1,2]. Supportive measures such as adequate hydration (by frequent breast feeding, home available fluids and oral rehydration solution) and oral zinc therapy are the mainstay of management as per World Health Organization (WHO) [3].

Cooked green banana (*Musa paradisiaca*) is shown to have a beneficial effect in lessening the duration of diarrhea and dysentery [4,5]. The short chain fatty acids released from the resistant starch, a major constituent of green banana, has been demonstrated to increase the absorption of water and electrolytes from the large intestine and prevent complications such as dehydration [6]. Literature on green banana in diarrheal illness is sparse and is limited to resource-constrained countries like Bangladesh. Given the paucity of data from India, our objective was to evaluate whether supplementation of cooked green banana shortened the duration of diarrhea in children with acute watery diarrhea with no dehydration.

Accompanying Editorial: Pages 1108-1109

METHODS

This open label randomized controlled trial was conducted from June, 2017 to June, 2018, in the department of pediatrics of a tertiary care teaching hospital in India. Children aged 9 months to 5 years, presenting within 48 hours of onset of acute watery diarrhea (AWD) with no dehydration (based on WHO criteria) [3] and whose parents were willing to admit their children in the hospital for three days were considered for the study. It was ensured that the parents did not have any financial

burden due to the hospital stay. From among these, children who could not be fed orally, who were under-nourished (weight for age *Z* score <-2) [7], those having any concurrent or pre-existing severe illness, and those who had received any antibiotic or anti-motility agents in the last seven days were excluded. Children with blood in stool were also excluded. After getting written informed consent from the parents, one of the investigators randomized the eligible children into two groups based on block randomization with variable block size using computer-generated randomization sequence. Allocation conceal-ment was done using sequentially numbered, opaque, and sealed envelopes. All the investigators enrolled and assigned the participants to interventions. Blinding could not be done in view of the logistics involved. Assuming the proportion of children with formed stools at 72 hours (primary outcome) to be 60% in the control arm [4] and 80% in the intervention arm (absolute difference of 20%), the sample size estimated with a power of 90% and alpha error of 5% was 105 in each group. Considering a dropout rate of 20%, it was decided to recruit 125 children in each group.

Children in the Control group, received standard care for acute diarrhea (zinc sulphate 20 mg orally once daily for 14 days, plus frequent breast milk, if on breast feeding, plenty of home available fluids, such as rice *kanji*, butter milk or tender coconut water, ORS 10 mL/kg/loose stool, and regular diet). Children in Green banana supplemented diet (GB) group received standard care, as above, and cooked green banana, in addition. The raw green banana was boiled for ten minutes following which the skin was peeled and the pulp was mashed to semi-solid consis-tency using a spoon. The cooked green banana was offered either alone (with little salt for taste) or mixed with any other food of their choice; the dose of green banana was 50 g twice daily for children younger than 1 year, 100 g twice daily for those aged 1-3 years, and 100g thrice daily for those aged 3-5 years [4]. The green banana supplemented diet was continued until diarrhea stopped or till the 14th day of illness, whichever was earlier. Children who developed dehydration were managed as per WHO protocol [3]; other complications were treated uniformly as per the institutional protocol. Children who persisted to have diarrhea beyond 72 hours from the beginning of intervention were advised to continue the standard treatment at home. The parents of the GB group were also advised to give cooked green banana daily until cessation of diarrhea – the cooking method was explained to the parents prior to discharge. Compliance for home available fluids, ORS and zinc for both the groups and in addition cooked green banana for

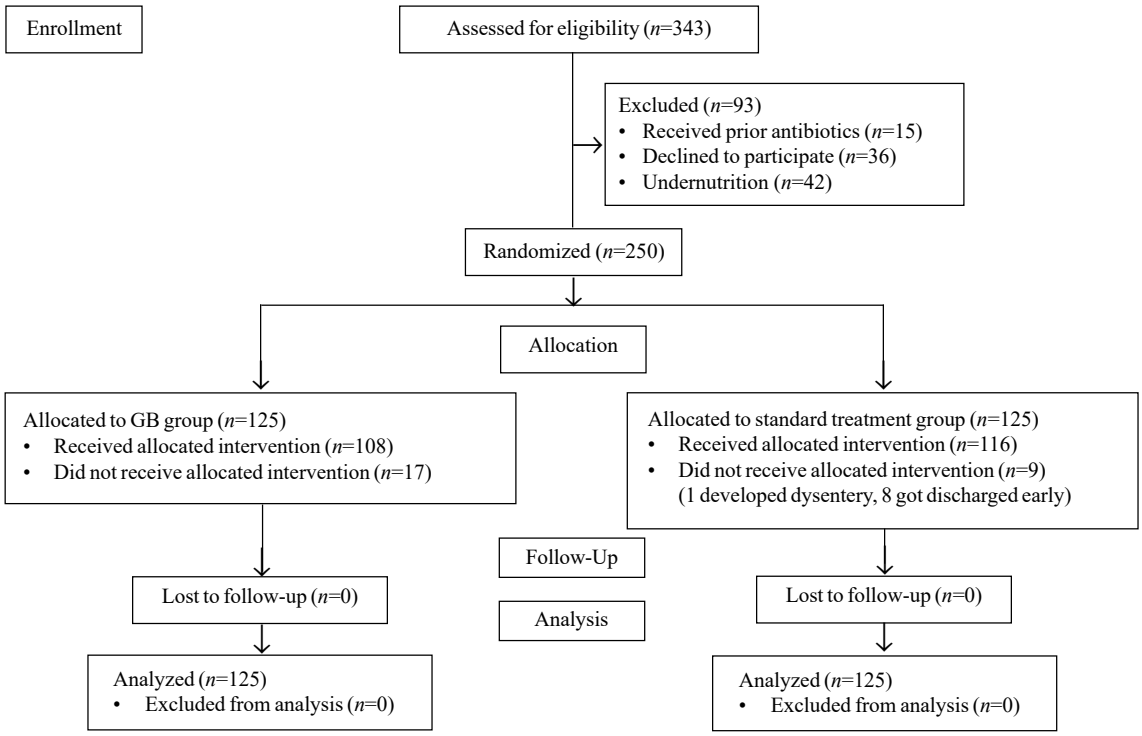


Fig. 1 *Consort flow diagram depicting study methodology.*

the intervention group was ensured by daily telephonic contact until the 14th day of illness and the details were collected. The parents were asked to bring the child for review if there were any concerns on telephonic discussion. Children with diarrhea persisting for more than 14 days were also reviewed again in the hospital.

The primary outcome assessed was the proportion of children who improved at 72 hours of intervention (passing formed stools with the usual frequency), as observed by the mother and verified by one of the investigators. The incidence of dehydration, persistent diarrhea (diarrhea persisting beyond 14 days), lactose intolerance (as evidenced by perianal excoriation and positive stool reducing substances test) and any other complications were evaluated as the secondary outcomes. The study was approved by the Institutional ethics committee, and the trial was prospectively registered in Clinical Trials Registry of India.

Statistical analyses: Data collection was done with the help of a semi-structured pretested proforma and was transcribed into Microsoft Excel spread sheet. Data analysis was done using the software STATA version 12. The baseline socio-demographic variables were compared between groups using chisquare test. An intention to treat analysis was performed. The proportion of children recovering within 72 hours, and the development of complications in both the groups were compared using the chisquare test. In addition, time to event analysis was carried out for recovery using Kaplan Meier survival graphs and the recovery time between the groups was compared using log rank test. All statistical testing was carried out at 5% level of significance.

Table I Baseline Characteristics of Children With Acute Diarrhea Enrolled in the Study (*N*=250)

Characteristics	*Green banana group (n=125)*	*Control group (n=125)*
Age, mo	23 (13.7)	22.8 (13)
Weight for Age		
-2 to -1 Z	72 (57.6)	67 (53.6)
1 to 0 Z	44 (35.2)	52 (41.6)
>0 Z	9 (7.2)	6 (4.8)
Current breastfed		
09-12 mo of age	25 (20)	20 (16)
13-24 mo of age	13 (10.4)	16 (12.8)
25-36 mo of age	1 (0.8)	0
Duration of illness[*]		
0-12 h	13 (10.4)	16 (12.8)
13-24 h	42 (33.6)	38 (30.4)
25-36 h	37 (29.6)	42 (33.6)
37-48 h	33 (26.4)	29 (23.2)
Fever[*]	46 (36.8)	42 (33.6)
Vomiting (1-3 times/d)[*]	32 (25.6)	37 (29.6)

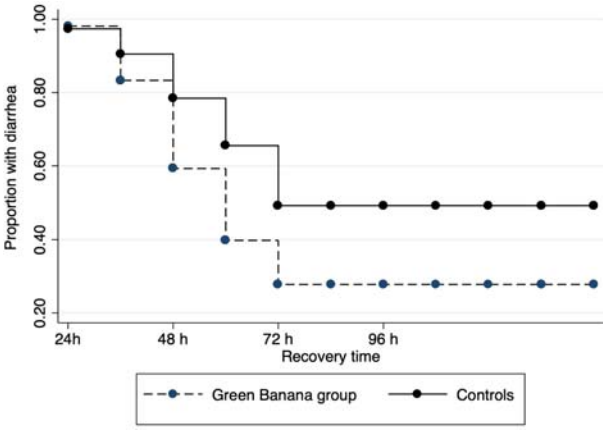
[*]*at presentation; All values in no. (%) except age in mean (SD); P>0.05 for all comparisons.*

RESULTS

Of the 250 children recruited, 108 children in the green banana group and 116 children in the control group completed the study (***Fig.* 1**). There was no significant difference between the groups with respect to the baseline demographic characteristics, socioeconomic status, duration of the illness (between the onset of illness and reporting for treatment), fever, vomiting and the prevalence of breastfeeding (***Table* I**). Children in the intervention group received GB diet for a median (IQR) duration of 3 (2) days (range, 2-14 day of illness). depending on the duration of diarrhea. The proportion of children recovering within 72 hours was significantly higher (62.4%) in the GB group as compared to the Control group (47.2%) [RR (95% CI) 1.3 (1.05-1.7), NNT=7; *P*=0.002] (***Table* II**). Moreover, on comparing the time to recovery using Kaplan Meier graph, the proportion of children with diarrhea at 72 hours was significantly less in the green banana group (***Fig.* 2**).

During the three days of stay in the hospital, none of the children in the two groups developed severe dehydration. Significantly higher number of children in the control group developed some dehydration (*P*=0.006) and persistent diarrhea (*P*=0.01) (***Table* II**). None of the children in either group developed any other complications, including acute kidney injury.

None of the children had any side effects to the cooked green banana (excessive vomiting or abdominal



GB: green banana.

Fig. 2 *Kaplan Meier graph showing recovery time in the two groups.*

Table II Recovery From Acute Diarrhea and Complications in the Study Population (*N*=250)

Parameter	*Green banana group (n=125)*	*Control group (n=125)*	*Risk ratio (95% CI)*	*P value*
Recovery within 72 h	78 (62.4)	59 (47.2)	1.3 (1.05-1.7)	0.02
Dehydration within 72 h	2 (1.6)	13 (10.4)	0.15 (0.03-0.7)	0.006
Persistent diarrhea	4 (3.2)	15 (12)	0.3 (0.1-0.8)	0.01
Secondary lactose intolerance	1 (0.8)	5 (4)	0.2 (0.02-1.7)	0.2

Values in no. (%).

pain). Fifteen children (12%) in the green banana group refused to eat the specified amount of green banana despite trying multiple times. The green bananas were purchased daily from the local market and the approximate cost was three rupees (INR) per child per day.

DISCUSSION

This open label randomized control trial documented faster recovery following supplementation of green banana in the diet of under-five children with acute watery diarrhea with no dehydration. Our findings are in agreement with the pioneering work from Bangladesh [4], documenting recovery both on day 3 and day 7 after supplementation with green banana among 2968 children with acute diarrhea in a cluster randomized field trial. The serial assessment over 72 hours of all the recruited children in the hospital by physicians is one of the strength of the current study. The present study also demonstrates the lesser number of children developing dehydration in the intervention group highlighting stool volume reduction, as also shown previously [5]. Moore, *et al*. [8] noted a six-fold higher incidence of persistent diarrhea in children with diarrhea lasting for more than seven days. We noticed only 30% children receiving intervention to develop persistent diarrhea. Hence, early initiation of green banana supplemented diet, as in our study, may limit the number of diarrhea days and may lower the progression to persistent diarrhea.

The exact mechanism of action of green banana in acute watery diarrhea remains elusive. The widely recognized hypothesis involves the role of resistant starch in diarrhea. Resistant starch, constituting 83.7% of green banana [9], is refractory to enzyme hydrolysis in the small intestine, and passes unaltered to the colon where it is acted upon by the normal commensals to produce short chain fatty acids (SCFA), which are the primary mediators of the beneficial activity [10]. The cytoprotective properties of SCFAs play an active role in the maintenance of the tight junction integrity through increased claudin expression [11], regeneration of infected epithelium by stimulation of the mucosal transglutaminase activity [12] and positive jejunotrophic effects through autonomic nervous system [13]. All these mechanisms assist in the absorption of sodium and water. Moreover, an exclusive Butyrate-HCO_3^- transporter mechanism in absorption of sodium and water is also demonstrated [14]. Also, by promoting the growth of the commensals [10] and by producing antimicrobial peptides at the epithelium [15], SCFAs also exert non-specific antimicrobial activity. This has been demonstrated by *in vitro* studies [16] and in animal studies [17].

Our study has few limitations. The cooked green banana was mixed with salt for better palatability. This could have altered the electrolyte intake and might have had a potential effect on the outcome as well. As post-discharge compliance was assessed by daily telephonic conversations, objective measurement was not possible during that period. Despite mothers' efforts, acceptability of green banana was a major problem (12%) in our study. Introduction of green banana as a complementary food in infancy, addition of flavors of infant's choice to the green banana diet [18], or use of palatable preparations of green banana such as papads are suggested [19].

Although oral rehydration solution is the mainstay of treatment in children with acute watery diarrhea, we feel that green banana diet with its above-mentioned properties has a promising role, especially in developing countries. In conclusion, this open label randomized controlled trial highlights the role of cooked green banana supplemented diet as a useful adjunct to standard treatment (ORS, home available fluids and zinc) in the management of acute watery diarrhea with no dehydration.

Ethical clearance: Institutional ethics committee of MGMCRI, Puducherry; ECR/451/Inst/PO/2013/RR-16 dated 08/06/2016.
Contributors: DG, AC: conceptualized, designed the study and finalized the manuscript; KK, BB, PJ, PS: collected, compiled the data and helped in analyzing and drafting the manuscript. All have approved the final draft.
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WHAT IS ALREADY KNOWN?

- Addition of cooked green banana in the diet is beneficial in diarrheal illness.

WHAT THIS STUDY ADDS?

- Cooked green banana diet in addition to standard treatment reduces the duration of illness and lessens the chances of complications in under-five children with acute watery diarrhea without dehydration.

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RESEARCH PAPER

Effect of Umbilical Cord Milking *vs* Delayed Cord Clamping on Venous Hematocrit at 48 Hours in Late Preterm and Term Neonates: *A Randomized Controlled Trial*

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Objective: To compare the effect of intact umbilical cord milking (MUC) and delayed cord clamping (DCC) on venous hematocrit at 48 (±6) hours in late preterm and term neonates ($35^{0/7}$- $42^{6/7}$ wk).

Study Design: Randomized trial.

Setting and participants: All late preterm and term neonates ($35^{0/7}$ - $42^{6/7}$ wk) neonates born in the labor room and maternity operation theatre of tertiary care unit were included.

Intervention: We randomly allocated enrolled neonates to MUC group (cord milked four times towards the baby while being attached to the placenta; *n*=72) or DCC group (cord clamped after 60 seconds; *n*=72).

Outcome: Primary outcome was venous hematocrit at 48 (±6) hours of life. Additional outcomes were venous hematocrit at 48 (±6) hours in newborns delivered through lower segment caesarean section (LSCS), incidence of polycythemia requiring partial exchange transfusion, incidence of hyperbilirubinemia requiring phototherapy, and venous hematocrit and serum ferritin levels at 6 (±1) weeks of age.

Results: The mean (SD) hematocrit at 48 (±6) hours in the MUC group was higher than in DCC group [57.7 (4.3) *vs.* 55.9 (4.4); *P*=0.002]. Venous hematocrit at 6 (±1) weeks was higher in MUC than in DCC group [mean (SD), 37.7 (4.3) *vs.* 36 (3.4); mean difference 1.75 (95% CI 0.53 to 2.9); *P*=0.005]. Other parameters were similar in the two groups.

Conclusion: MUC leads to a higher venous hematocrit at 48 (±6) hours in late preterm and term neonates when compared with DCC.

Keywords: *Anemia, Infant, Placental redistribution, Transfusion,*

Trial Registration: CTRI/2016/11/007470

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Placental transfusion provides sufficient iron reserves for the first 3 to 6 months of life; thus, preventing or delaying the development of iron deficiency until the use of iron-fortified foods is implemented [4]. Delayed cord clamping (defined variably as clamping till cessation of pulsations or up to 60-180 seconds) leads to improvement in levels of hemoglobin and hematocrit at two months of age [5]. However, universal application is limited in particular due to obstetrician concerns for the risk of hypothermia, and delay in initiation of resuscitation, when indicated [6,7].

Umbilical cord milking, on the other hand, involves milking the entire contents of the umbilical cord towards the baby. Cut umbilical cord milking (umbilical cord detached from placenta) limits the refilling of cord from placenta, so less blood is likely to be transfused when compared to intact umbilical cord milking (pushing the blood toward the infant at least four times before clamping the umbilical cord) [8-12].

Till date, two studies [13,14] have evaluated the effect of delayed cord clamping and umbilical cord milking in term neonates. In both studies, cut umbilical cord milking was performed. Hence, we planned the present study to evaluate the effect of intact umbilical cord milking on venous hematocrit at 48 hours of age in late preterm and term neonates when compared with delayed cord clamping.

METHODS

This open labelled randomized trial was conducted in the department of obstetrics and gynecology, All India Institute of Medical Sciences, New Delhi from May to September, 2016. All late preterm and term neonates ($35^{0/7}$ - $42^{6/7}$ week) were included in the study. Neonates with fetal hydrops, major congenital malformation, Rh isoimmunization (Rh positive neonate born to Rh negative mother with indirect Coombs test (ICT) positive) [15], newborns born through meconium stained

liquor who were non-vigorous at birth (defined by poor/no respiratory efforts, weak/no muscle tone and heart rate less than 100 beats per minute, limp or apneic or poor tone at birth) [16], forceps or vacuum assisted delivery, and newborns born to HIV positive mother (on enzyme-linked immunosorbent assay (ELISA) followed by Western blot test for HIV) and maternal eclampsia (defined as generalized seizure in pregnant females with preeclampsia) [17] were excluded from the study. The study was approved by the institutional ethics committee.

All eligible mothers admitted in the labor room were screened for eligibility and enrolled, after informed written consent. We allocated mothers using computer generated random sequence to intact umbilical cord milking group and delayed cord clamping group. Opaque envelopes containing allocation group were serially numbered, and sealed to conceal the identity. The sealed envelope was opened by the nursing staff when the expectant mother was wheeled inside the labor room. The intervention written on slip was carried out by the obstetrics and gynecology resident and pediatric resident team posted in the labor room. Blinding of the clinicians was not possible due to the obvious nature of intervention.

Intact umbilical cord milking (MUC) group: The intact umbilical cord for its remaining accessible length (nearly half of the total length) was milked four times towards the baby by the residents on duty in the obstetrics department, and then clamped. All the health care providers (postgraduate residents of pediatrics and obstetrics) were trained in a structured manner for intact umbilical cord milking.

Delayed cord clamping (DCC) group: Umbilical cord was clamped at least 60 seconds from the time of delivery.

Time of all interventions was recorded by a stopwatch and noted in the study form. In both the groups, the baby was held at introitus after vaginal delivery, and over mother's thigh in caesarean delivery. After delivery, the babies were kept with mothers unless they required admission in the neonatal intensive care unit (NICU) for standard indications. Gestational age was assigned based on the last menstrual period. The appropriateness of birthweight for gestational age was assigned by stan-dard intrauterine growth chart [18]; weight less than 10th centile and weight more than 90th centile being adjudged as small for gestational age (SGA) and large for gestational age (LGA), respectively [18]. Early breastfeeding was encouraged in all babies as per standard guidelines. The infants were evaluated at birth, and at the age of 24 hours and then at 48 hours.

The primary outcome was venous hematocrit evaluated at 48 (±6) hours. Additional outcomes were venous hematocrit at 48 (±6) hours in newborns delivered by lower segment caesarean section (LSCS), incidence of polycythemia (defined as venous hematocrit greater than 65% at 48 (±6) hours of life) [19] requiring partial exchange (PET), incidence of hyperbilirubinemia requiring phototherapy (as per American Academy of Pediatrics (AAP) charts) [20], venous hematocrit at 6 (±1) weeks, and levels of serum ferritin at 6 (±1) weeks.

Venous sample was collected in micro- capillaries for measurement of hematocrit, and an additional 1 mL sample was separately collected for serum ferritin levels. Micro-capillaries were micro-centrifuged at a speed of 9000 rpm for 5 minutes and analyzed with card reader for hematocrit measurement. Serum bilirubin was assessed in babies with clinical icterus by spectrophotometer (Apel BR 5100, APEL). Calibration of the spectrophotometer was done at defined intervals, as recommended by the manufacturer and phototherapy was instituted, if required. Serum ferritin levels were evaluated with ELISA orgentech kit (analytical sensitivity, 5 ng/mL; range of evaluated concentrations 5-1000 ng/mL).

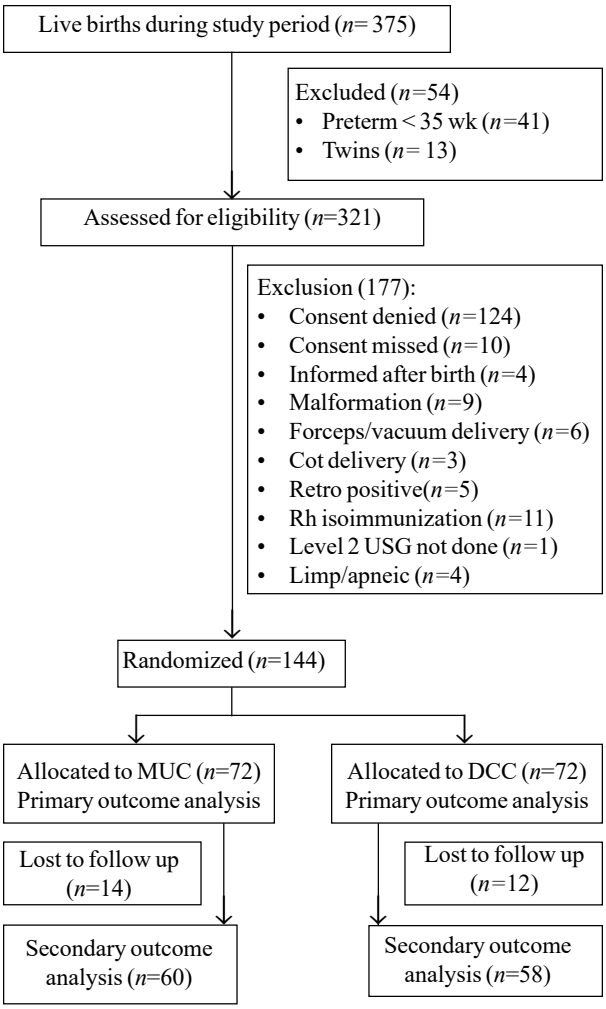
Attendants were counseled by the principal investigator to follow up at 6 (±1) weeks, which coincided with their immunization visit. Hematocrit evaluation and serum ferritin levels were evaluated at this time point. On follow up, parents were asked about any intercurrent illnesses since birth, and type and mode of feeding (top fed, exclusively breastfed or predominantly breastfed.

Venous hematocrit at 48 (±6) hours in a previous study was 50% [10]. Anticipating that intact umbilical cord milking will lead to at least a 5% absolute increase in the hematocrit and assuming a standard deviation (SD) of 7 in each group with power of 90% and alpha of 0.05, we needed to enroll at least 42 neonates in each arm. Considering an attrition rate of 40% on follow up, total sample size was increased to 72 in each group.

Statistical analyses: Statistical analyses were performed with Stata 11 (Stata Corp LP). Baseline categorical variables were compared using Chi-square or Fisher exact test, as appropriate, and whereas continuous variables were compared using Student t-test. A P-value of less than 0.05 was considered as significant. The analysis was by the intention to treat.

RESULTS

A total of 375 babies were delivered during the enrolment period, of which 144 babies fulfilled the inclusion criteria and were enrolled (***Fig.* 1**). Baseline characteristics including maternal pregnancy induced hypertension,



MUC: Milking of umbilical cord, DCC: Delayed cord clamping.

Fig. 1 *Study flow chart.*

gestational diabetes, gestational age and birthweight were comparable between the two groups (***Table* I**). 72 neonates were enrolled to DCC and 72 neonates to MUC group. Out of the 144 neonates, 118 (82%) completed the trial at 6 (±1) weeks. There were no adverse events in either group during the study period.

The mean (SD) hematocrit at 48 (±6) hours in the MUC group [57.7 (4.3)] was significantly higher than the DCC group [55.9 (4.4)] [mean difference (MD) 1.7 (95% CI 0.21 to 3.1); *P*=0.002] (***Table* II**). Venous hematocrit in newborn delivered by caesarean section at 48 (±6) hours was similar in the two groups. Incidence of polycythemia was also similar in the two groups. One neonate in each group required phototherapy. Mean (SD) Venous hematocrit at 6 (±1) weeks was higher in MUC than in DCC group [MD (95% CI) 1.75 (0.53 to 2.9); *P*= 0.005] (***Table* II**). The levels of serum ferritin were similar in the two groups (***Table* II** and ***Fig.* 2**).

Table I Baseline Maternal and Neonatal Characteristics of the Two Groups

	Umbilical cord milking group (n=72)	*Delayed cord clamping group (n=72)*
Maternal characteristics		
Booked pregnancy	72 (100)	71 (99)
Maternal age (y)*	29.1 (4.2)	28.3 (3.3)
Lower segment caesarean section	31 (43)	36 (50)
Hemoglobin (g/dL)*	11.7 (1.2)	11.4 (1.1)
Chronic hypertension	7 (9.7)	4 (5.5)
Pregnancy induced hypertension	3 (4.1)	3 (4.1)
Meconium stained liquor	2 (2.7)	6 (8.3)
Intra uterine growth retardation	1 (1.4)	3 (4.1)
Gestational diabetes mellitus	13 (18.1)	11 (15.2)
Neonatal characteristics		
Gestation age (wk)*	37.9 (1.0)	37.8 (1.6)
Male sex	36 (50)	36 (50)
Small for date	1 (1.4)	0
Large for date	10 (13.9)	9 (12.5)
Weight (g)*	3038 (436)	2909 (435)
Use of any respiratory support	3 (4.1)	3 (4.1)
Admission in NICU	1 (1.4)	2 (2.8)
Time since cord clamp (s)*#	12.9 (0.8)	60 (0)

*Data depicted as n (%) or *mean (SD); All P<0.05 except #P<0.01.*

DISCUSSION

This randomized trial compared intact umbilical cord milking (MUC) with delayed cord clamping (DCC) on venous hematocrit at 48 (±6) hours of life in late preterm and term neonates. The hematocrit at 48 (±6) hours and at 6 (±1) week was higher in the intact MUC group. However, it was similar in the two groups in infants delivered by LSCS. Other parameters including incidence of polycythemia, incidence of hyperbilirubinemia requiring phototherapy and ferritin were similar in the two groups.

There are very few studies in late preterm and term infants comparing MUC with DCC. Jaiswal, *et al*. [13] evaluated the effect of MUC and DCC on hematological parameters (serum ferritin and hemoglobin) at 6 (±1) weeks of life in term neonates. The packed cell volume (PCV) at 48 (±6) hours and hemoglobin level at 6 (±1) weeks postnatal age was similar in the two groups in contrast to the results of the present study. Studies in preterm infants comparing DCC suggest mixed results [8,9,11,12]. The cord vein contains nearly 20 mL of placental blood and one-time umbilical cord milking (of

Table II Primary and Secondary Outcome Variables in Late Preterm and Term Neonates in the Study

Parameter	*MUC group (n=72)*	*DCC group (n=72)*	*Mean difference (95% CI)*
Hematocrit at 48 (±6) h	57.7 (4.3)	55.9 (4.4)	1.68 (0.21, 3.1)
Secondary outcomes	(*n* = 58)	(*n* = 60)	
Hematocrit[#]	37.7 (3.3)	36 9 (3.4)	1.7 (0.53, 2.9)
Serum ferritin (ng/mL)[#]	363.1	295.8	67.2 (-24.0, 158.5)
Hyperbilirubinemia*	1 (1.4)	1 (1.4)	-
Polycythemia^	0	2 (2.8)	-
Hematocrit at 48 (±6) h[‡]	57.4 (4.4)	56.4 (4.8)	1.02 (-1.2, 3.2)

**Requiring phototherapy; [#]at 6 (±1) wk; ^requiring partial exchange transfusion; [‡]Newborns delivered by lower segment caesarean section, n=31 in UCC and 36 in DCC group.*

cut segment of about 30 cm) can transfer nearly 18 mL/kg of blood to the newborn [9,21,22]. The newborn is likely to get more blood if the cord segment is intact, since this allows subsequent refilling of cord from placenta explaining the higher hematocrit at 48 (±6) hours and higher hemoglobin at 6 (±1) weeks seen in the present study.

We observed no difference in the hematocrit in MUC and DCC group in neonates delivered by LSCS. A recent study by Katheria, *et al*. [11] in preterm neonates delivered by cesarean delivery suggested a higher hemoglobin (within the first 24 hours) in MUC group. Infants delivered by cesarean section have a lower

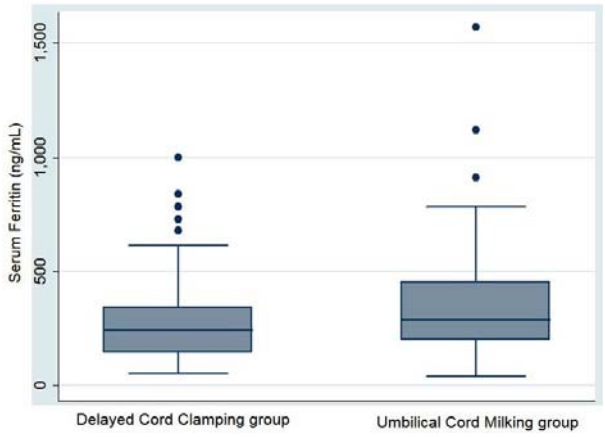


Fig. 2 *Box-and-whisker plot for serum ferritin at 6 (±1) weeks in neonates in the delayed cord clamping and umbilical cords milking groups.*

circulating red cell volume due to the anesthetic and surgical interventions which interfere with active uterine contraction, thus leading to more blood volume remaining in placenta and hence a lower hematocrit [22]. However, we did not evaluate the hematocrit at birth or within 24 hours.

We did not observe any difference in the incidence of hyperbilirubinemia requiring phototherapy or the incidence of polycythemia at 48 (±6) or any difference in serum ferritin at 6 (±1) weeks. These findings have been previously reported [8,9,12,16].

Our study is the first study in late preterm and term neonates where intact umbilical cord milking (milking done with umbilical cord attached to placenta) was compared to delayed cord clamping for evaluation of hematological parameters. This trial ensured appropriate allocation concealment. The outcome assessors and laboratory team were blinded to the intervention arm. We had a follow up rate of 82%. Our study had some limitations too. A longer follow-up till at least 6 to 12 months is desirable to establish whether the initial advantage in hematocrit also translates into gains in infancy and early childhood, which we did not plan.

Umbilical cord milking leads to higher venous hematocrit at 48 (±6) hours when compared with delayed cord clamping in late preterm and term neonates, however long-term effects of milking need to be further evaluated.

Ethics clearance: Institute Ethics Committee, AIIMS; No. IECPG/197/24.02.2016, RT-10, dated March 30, 2016.
Contributors: MKM: protocol development, study implementation, data management and writing the manuscript; AT, MJS: development of the protocol and supervised implementation of the study and contributed to writing of the manuscript and did data analysis; VKP, AKD, RA: protocol development, and provided critical inputs in manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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WHAT IS ALREADY KNOWN?

- Delayed cord clamping leads to improvement in levels of hemoglobin and hematocrit at two months of age.

WHAT THIS STUDY ADDS?

- Umbilical cord milking leads to higher venous hematocrit at 48 (±6) hours when compared with delayed cord clamping in late preterm and term neonates
- Intact cord milking does not result in neonatal hyperbilirubinemia or symptomatic polycythemia as compared to delayed cord clamping.

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RESEARCH PAPER

Pediatric Psychiatric Emergencies at a Tertiary Care Center in India

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Objective: To describe the clinical profile and pattern of pediatric psychiatric emergency referrals at a tertiary-care center in India. **Methods**: Retrospective chart review of emergency psychiatry records over a 13-month period (January, 2015-January, 2016). **Results**: Pediatric psychiatric emergencies (*n*=65) (mean (SD) age, 14.2 (2.39) y) constituted 10% of all-age psychiatric emergencies. Risk of harm to self and/or others was seen in a third of patients (aggression, 18.5%; self-harm, 16.9%). Common psychiatric diagnoses were dissociative disorder (27.7%), mood disorders (9.3%) and psychotic disorders (7.7%). Compared to adult emergencies attended during same time period, pediatric group had more females (63.1% *vs* 47.4%; *P*=0.02), more patients with dissociative disorders (28.7% *vs* 8.2%; *P*<0.01) and absence of psychotropic medication prescriptions (36.9% *vs* 20.6%; *P*=0.003), while frequency of self-harm and aggression as a reason for presentation was similar to adults. **Conclusion**: The report helps to understand the service needs of younger age group presenting with psychiatric emergencies.

Keywords: *Adolescents, Aggression, Dissociation, Self-harm.*

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Western reports indicate a steady increase in the number of emergency visits for pediatric mental health conditions, constituting 5% of all pediatric emergency visits [1]. Systematic data on emergencies is not available from India, but community-based studies reveal 10-12.5% of those below 16 years of age have a diagnosable psychiatric disorder [2]. Less than 1% of children suffering from mental disorders receive any treatment, reflecting a huge treatment gap. The emergency department (ED) is often the first contact for children and adolescents with a mental health crisis. The recent Indo-US joint working group white paper [3] highlighted the need of academic training for pediatric emergency physicians, including in psychiatric emergencies.

In the Indian context, available studies on psychiatric emergencies [4-6] or pediatric emergencies [7-9] have not focussed on younger age groups or psychiatric emergencies. Other than ED setting, few studies are available from out-patient or ward settings [10,11]. We studied clinical profile and pattern of referrals sought for pediatric psychiatric emergencies presenting to ED of a tertiary-care hospital in India.

METHODS

This paper is based on a descriptive, quantitative analysis through retrospective review of psychiatric emergency records between the months of January, 2015 and January, 2016 (13-month period). The emergency psychiatry services are provided on a round-the-clock basis for all referrals ('calls') made from Department of Emergency Medicine, All India Institute of Medical Sciences, Delhi for known or suspected mental health issues on the discretion of chief medical officer. Psychiatric emergency services are provided in ED by the psychiatric emergency team comprising of a senior resident (psychiatrist) accompanied by a trainee resident and, by consultant on call, if required.

The evaluation is conducted by the psychiatric team with reliance on various informants (child, parents, relatives, police), behavioral observations, and mental state examination. A provisional, consensus psychiatric diagnosis as per the ICD-10 (International Classification of Diseases, tenth revision) is made after rounds and academic discussions between the team (occasionally after evaluating more than once during ED stay), and recorded in a register in a predesigned semi-structured format.The completion of data entries is supervised by one designated faculty member.

Statistical analyses: For the study period, the variables of interest were extracted manually by the study authors. Relevant data was entered into Microsoft excel (version 2013) spreadsheet for building-up the initial dataset. Subsequently, standardized response codes were defined for all variables to arrive at final data-set used for

statistical analysis using SPSS version 23.0 (IBM, USA). Patient confidentiality was maintained by using anonymized data with unique identifiers and by password protected dataset with restricted access.

RESULTS

Of 666 psychiatric emergency referrals attended in total, age data was missing for 19, and pediatric psychiatric emergencies represented 10% (65/647) of remaining referrals.

***Table* I** shows the socio-demographic and clinical profile of 65 pediatric psychiatric patients (63.1% female). Mean age of the pediatric sample was 14.12 (2.39) years, with 38.4% and 53.8% in 11-14 and 15-17 year age-groups, respectively. A medicolegal issue was recorded in 14 (21.5%) cases. Of 14 cases with medico-legal issues, 11 were suicide/self-harm attempts, 2 patients were found wandering and brought by police, and one patient had alleged physical assault and was brought for medical examination.

Table I Pediatric Psychiatric Emergencies (*N*=65)

Characteristic	*No. (%)*
Medicolegal case	14 (21.5)
Known psychiatric illness	18 (27.7)
Comorbid medical illness	10 (15.4)
Reason for referral	
Dissociation	18 (27.7)
Aggression/agitation	12 (18.5)
Self-harm attempt	11 (16.9)
*ICD-10 psychiatric diagnoses**	
Dissociative disorder	18 (27.7)
Schizophrenia and other psychotic disorders	5 (7.7)
Mood (affective) disorders	6 (9.3)
Mental and behavioral disorders due to use of psychoactive substance	1 (1.5)
Anxiety disorders	3 (4.6)
Delirium	3 (4.6)
Mental retardation	2 (3.1)
Others/miscellaneous	8 (12.3)
No psychiatric diagnosis	5 (7.7)
Diagnosis deferred[#]	11 (16.9)
Psychotropic medications prescribed	
Benzodiazepines	25 (38.4)
Antipsychotics	10 (15.4)
Antidepressants	6 (9.2)
None advised	24 (36.9)

**Acute stress reaction and Attention-deficit hyperactivity disorders in 1 child each; [#]pending further evaluation/investigations.*

As compared to adult psychiatric emergency patients seen during the same period [4], this pediatric group had more females (63.1% *vs.* 47.4%; *P*-0.02), higher frequency of dissociative disorders (27.7% *vs.* 8.2%, *P*<0.001), lesser frequency of disorders due to psychoactive substance (1.5% *vs* 13.6%, *P*=0.002), and were more likely not to be prescribed any psychotropic medication (36.9% *vs* 20.6%, *P*=0.03). Antipsychotic medications were prescribed to 10 (15.4%) children.

Further in-patient care/admission was advised in four children (6.2%), of which three (4.6%) were admitted in the psychiatric ward (imminent suicidal risk in one, and inability to manage at home in other two patients) and one in pediatric ward (for organic catatonia).

DISCUSSION

About one-third of the pediatric psychiatric presentations to the ED were due to risk of harm to self/others and only 27.7% had a prior psychiatric diagnosis; 4.6% required psychiatric admission. The presentation for dissociation (27.7%) was also quite common. Often dissociation mimics neurological symptom/s (*e.g.,* pseudo-seizures, dissociative stupor or aphonia), warranting an immediate visit to ED.

In available literature, toxic ingestions/self-harm, aggression or dissociation have been similarly reported as common presentations to pediatric EDs [12,13]. Williams, *et al*. [14] reported 27-month data from regional EDs across Detroit (*n*=225, aged 5-18 years). Thirty-eight percent had severe depression, and 52% were judged to be at acute risk of suicide, 16% had psychotic features, and 34% had potential risk of harming others [14]. In another study from US [15], 21.4% presentations were related to mood disorders, 32.5% to anxiety disorders and 41.3% had substance misuse (41.3%) over the four year review period.

Substance use related emergencies were not much represented in this pediatric sample, in contrast to available literature [13], and in contrast to an adult sample during the same period [4]. Adolescent users are non-dependent with no substantial withdrawals, though they may present with road traffic accidents and fights under influence. It is possible that such cases are not being identified as problematic users, emphasizing the need for screening and brief interventions for early users in EDs. No case of child abuse was encountered in the study period. The child sexual abuse with injuries might have been admitted by surgical specialities, with psychological evaluation at later date. A high index of suspicion is required as child abuse may go unrecognized.

Majority (over 70%) had new-onset symptoms, with no psychiatric diagnosis assigned in past. Such cases pose a diagnostic dilemma especially as diverse medical etio-

WHAT THIS STUDY ADDS?

Majority of the pediatric psychiatric presentations to the emergency department had new onset behavioral symptoms at the time of presentation, and around one-third had a risk of harm to self or for others.

logies may also lead to mental or behavioral symptoms. The pediatricians must take a systematic approach to diagnosis and consider need to involve a psychiatrist for an opinion. A formal psychiatric assessment is warranted for behavioral changes such as irritability, withdrawn behavior, self-harm ideation, aggression, muttering/gesturing to self, especially in absence of 'red flag' signs (*e.g* disorientation, tactile or visual hallucinations, fever *etc*) [12]. The deferred psychiatric diagnosis in nearly 17% patients highlights the diagnostic difficulties, more so in children and adolescents, often requiring multiple, longitudinal assessments.

Limitations of the study include retrospective design, limited generalizability to other settings, and lack of information on subsequent follow-up status. The diagnosis may be provisional in view of need for subsequent evaluations and longitudinal observations. Certain investigations and diagnostic tests may take several days, for which diagnosis was deferred in a few. Further, the study sample is restricted to patients for whom psychiatric team was consulted in ED. Nonetheless, in spite of these limitations, the report provide a large data set of pediatric patients presenting to ED with mental or behavioral symptoms and ICD-10 diagnosis by trained psychiatrists.

The study findings have implications for service delivery aspects. There is a need to train pediatric residents to identify, provide initial management, stabilization and subsequent referral for common psychiatric presentations in ED, especially imminent suicidal risk or violence among children or adolescents in mental health crisis. Additionally, a close liaison is needed between pediatricians and mental health professionals for providing lateral entry points from ED to mental health-care systems.

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Contributors: SS, SK: extracted the data, performed the data analysis and contributed to initial manuscript draft; SS, SK, RD: conceptualised the study, interpreted the findings and finalized the manuscript. All authors approved the final version.
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RESEARCH PAPER

Arrhythmia in Children and Adolescents and Outcome of Radiofrequency Ablation for Tachyarrhythmias - A Single Center Experience Over 16 Years

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Objectives: Radiofrequency (RF) ablation for tachycardia in children poses challenges in view of slender veins and delicate cardiac structures in close proximity. **Methods**: We reviewed hospital records for patients below 18 years,who underwent RF ablation from August, 2001 to February, 2017 at a single hospital. **Results**: Among 214 patients (134 males, age12.5 (4.6) years), there were 221 tachycardia substrates: accessory pathways in 85 patients (39%), AV nodal re-entrant tachycardia in 79 patients (36%), ventricular tachycardia in 28 patients (13%) and atrial tachycardia in 21 patients (9.6%).The overall success rate of RF ablation was 95% (204/214). Success rate in those younger than 6 years was similar to those in older age groups.There were no major complication. **Conclusion**: RF ablation below 18 years of age has a high success rates and low complications.

Keywords: *Catheter ablation, Management, Outcome, Supraventricular tachycardia*.

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Catheter ablation in children using radiofrequency (RF) energy has been in vogue since 1989 [1]. Radiofrequency ablation ensures a permanent cure of arrhythmias and hence, is the preferred treatment in the vast majority. Previous registries have demonstrated that RF ablation can safely and effectively be performed in children [2,3]. However, patients weighing less than 15 kg have been identified as being at greater risk for complications [2,3]. Though medical therapy is an alternative option, it has its own limitations [5]. The experience from India on RF ablation is also limited [4], due to a lack of widespread availability, lack of expertise, and fear of complications in children, though rare [6].

We have been using conventional RF ablation techniques in the pediatric age group since the last two decades. We conducted a retrospective study of patients aged up to 18 years and analyzed them for the tachycardia substrates, success and complications.

METHODS

The patients were categorized into three groups according to age: Groups A (younger than six year), B (aged 6-12 years) and C (older than 12 years). General anesthesia was required for the procedure for majority of children in Groups A and B; midazolam, propofol, fentanyl and sevoflurane were the drugs used. For Group C, local anesthesia and sedation were used.

All anti-arrhythmic drugs were suspended for a duration of at least four half-lives before the procedure. For AVNRT (Atrioventricular nodal re-entrant tachycardia) and right-sided accessory pathways (APs), three venous punctures were sufficient – for coronary sinus (CS), His bundle and a roving catheter. For left sided APs, two femoral venous accesses and one femoral arterial route were employed. The sheaths used ranged from 4F to 7F caliber. Unfractionated heparin was used for all cases (50 units/ kg for venous route and 100 units/kg for arterial route).

When the arrhythmia was not induced at baseline, intravenous isoprenaline was administered (1-2 μg/min). Atropine (according to bodyweight) was used when isoprenaline failed. Fluoroscopy time and procedure time were noted. The RF energy output, length of application and temperature were individually titrated. After ablation, 30-45 minute waiting period was kept along with isoprenaline and atropine for re-induction.

Acute success of RF ablation was defined as failure to induce causal arrhythmia after application of adequate number of RF energies. Failure was defined when tachycardia remained inducible at the end of the procedure.

There were two subsets, *viz.* unable to ablate the tachycardia source/circuit, or unable to deliver RF energy due to apprehension of complication or due to mechanical stunning of the pathway. Relapses/recurrence was defined as recurrence of same clinical arrhythmia after acute success of RF ablation.

Follow-up was done by reviewing the patients' medical records, outpatient visits and telephonic conversation. Follow-up period varied from 2-16 years.

Statistical analyses: The SPSS software was used for database organization and statistical calculations. The discrete variables were compared using Chi-square test, considering *P* value below 0.05 as significant.

RESULTS

A total of 2980 cases underwent the procedure during study period – 229 (8%) were performed in patients aged younger than 18 years [mean (SD) age, 12.5 (4.6) year]. In 11 patients the data was incomplete; and another 4 patients did not have inducible tachycardia.Finally, data of 214 children (62% males) undergoing RF ablation were analyzed for this study.

Table I Tachycardia Substrates in Children Undergoing Radiofrequency Ablation (*N*=211)*

	≤6y (n=33)	*7-12 y (n=53)*	*13-18 y (n=135)*
Males	18	32	84
LVEF, %#	70 (9)	67 (9)	65 (10)
Upfront ablation			
Parental preference	1	5	22
Tachycardiomyopathy	1	1	2
AVNRT	8	22	49
Manifest AP (WPW)	14	15	31
Concealed AP	2	11	16
Atrial tachycardia	5	5	11
Fascicular VT	1	0	17
Outflow VT	3	0	7
Miscellaneous	0	0	4

**211 substrates in 214 children; #mean (SD); LVEF: Left ventricular ejection fraction; AVNRT: Atrioventricular nodal reentrant tachycardia; WPW: Wolff-Parkinson-White syndrome, AP: Accessory pathway; VT: Ventricular tachycardia.*

These 214 patients had a total of 211 arrhythmia substrates. The commonest tachycardias found were APs in 85 (39 %) and AVNRT in 79 (36 %) patients. The most common arrhythmia with APs was orthodromic atrio ventricular re-entrant tachycardia (AVRT) followed by antidromic tachycardia (ADT) and pre-excited atrial fibrillation. Ventricular tachycardia was found in 28 patients (13 %), and atrial tachycardia (AT) in 21 patients (9.6%). Three patients had automatic junctional tachycardia and one patient had atrial flutter (previous surgery for atrial septal defect). Four patients had multiple tachycardia mechanisms and three patients had multiple APs.

We categorized them age-wise into three subgroups (***Table* I**). In younger children, AP was the most common mechanism, but above 12 years, AVNRT emerged as the most common tachycardia mechanism. Fascicular VT was by far commoner in Group C. Among the 85 patients with APs, we detected 89 APs; of them there were nine right free wall Mahaim-like (atrio-fascicular) APs with antidromic tachycardia. Other than these, only two other patients had antidromic tachycardia, one of whom also had associated orthodromic AVRT. The left lateral location was the commonest (31/89, 35%). Left sided APs were more common in concealed APs (18/29, 62%) than in WPW group (13/60, 21%, $P<0.001$).

The overall immediate success rate **(*Table* II)** was 95% (204/214). For AVNRT, 98.7% (78/79) were ablated by slow pathway modification. Among the APs, immediate success rate was 96.4% (82/85); failure was most commonly seen in Ebstein anomaly and with Mahaim-like pathways (***Web Table* I**).The success rates in the three groups were similar. There were no major or minor

Table II Success Rate of Radiofrequency Ablation in Children With Tachyarrhythmia

	Total	*Success*	*Fluoroscopy time (min)**	*Mean procedure time (min)*	*No. of RF lesions**	*Maximum temperature* (°C)
AVNRT	79	78	10.9 (5.9)	78	4.7 (2.5)	60
Accessory pathway (AVRT)	85	82	14.6 (7.1)	90	5.1 (3.3)	55-60
Atrial tachycardia	21	19	19.3 (10.2)	117	4.3 (2.0)	50-60
Outflow tract VT	10	10	17.5 (13.3)	103	5.9 (3.1)	60
Fascicular VT	18	15	21.1 (11.1)	130	6.5 (2.5)	50-60
Miscellaneous	4	3	15 (7.2)	90	3.5 (2.2)	60

**Values are expressed as mean (SD); AVNRT: Atrioventricular nodal re-entrant tachycardia; VT: Ventricular tachycardia.*

WHAT THIS STUDY ADDS?

- Ablation in children using conventional radiofreauency energy was safe and effective, with similar success rate among those younger or older than six years.

complication. The recurrence rate was 2.9 % (6/205); 2 had AVNRT, 3 had APs and 1 had AT.

We sub-categorized those who had prolonged procedures, arbitrarily defined more than two hours. There were seven such patients; three had atrial tachycardia, three had APs and one had VT. Five of them required left sided ablation; all these procedures were finally successful.

Among patients undergoing the procedures, six had congenital heart disease (three had atrial septal defect, two had Ebstein's anomaly and one had ventricular septal defect). Four more patients had tachycardiomyopathy, among whom three had incessant AT.

DISCUSSION

We found AVRT to be the most common tachycardia below six years; above this age, AVNRT and AVRT were comparable.This is in contrast to older studies [6], which found that accessory pathway was the most prevalent finding between age range of 2-18 years, with AVRT in 65%, AVNRT in 30%, ventricular tachycardia in 4%, and atrial tachycardia in 0.7%.

Previous report shave demonstrated that RF ablation can safely and effectively be performed in pediatric patients [2-4,6]. After 1-16 year follow up, the overall success rate was also higher than older studies [1]. With the advent of cryoablation, studies revealed, AV block was less with cryoablation, though recurrence was significantly higher [7]. We have performed only conventional RF for all age groups as cryoablation was unavailable at our center. Van Hare, *et al*. [1] reported a success rate of 95.7% with RF ablation in AVRT and AVNRT in pediatric patients. Simao, *et al*. [8] reported slightly lower success rate of 91.7% in AVNRT and 83.5% for APs. Our study is in concordance with these previous results [2-6]. Our study revealed better immediate success rate of 95% and recur-rence rate of only 2.9%. After successful ablation we could withdraw anti-arrhythmic drugs and the majority remained asymptomatic without recurrence.

In our cohort, infants were few and hence we did not compare or analyze the results separately. A unique finding in our study was higher incidence of Mahaim (atriofascicular) pathways (9/89, 10%). Compared to reports of only 3% of accessory pathways [9]. Another unusual finding in our study was that idiopathic VT comprised a significant proportion (12.9 % of all tachycardias), where we had a good success rate (25/28, 89%). A study [10] comparing RF ablation in neonates and children between 1 and 18 months of age, found that neonates had significantly higher structural heart disease and yet the success rate and complications were surprisingly similar in both subsets. The comparable success rates in our cohort could partially be due to the fact that ablations in smaller children are more likely to be attempted by more experienced pediatric electro-physiologists and experience has been shown to be an important factor in successful pediatric RF ablation procedures [11].

This was a hospital-based retrospective analysis and suffers from the risk of bias and lack of generalizability. Infants and very small children were avoided unless pressing indications, hence these were few subjects in that age range.We did not have cryoablation, hence comparison was not possible between RF and cryoablation.

We believe RF ablation can be considered for pediatric arrhythmias, especially when they are recurrent and in children above 5 years of age. Whether RF ablation can be a primary treatment modality for young children is still a debatable issue,this can perhaps be addressed by more data from other Indian centers.

Ethical clearance: Institutional ethical committee of Holy Family Hospital; ECR/196/INST/MH/2013/RR-16, dated September 14, 2019.
Contributors: DB: analysed data and drafted the manuscript; VV:collection of data, designing study; CR: manuscript scrutiny and helped in data analysis; RS: helped in writing the manuscript and develop images; NB: performed echocardiography for majority of the patients and helped in data analysis; YL: concept of the study, supervised cognitive and behavioral assessments, supervised manuscript preparation.
Funding: None; *Competing interest*: None stated.

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Web Table I Details of Children With Failed Ablations (*N*=10)

Age, y	*Diagnosis*	*Cause of failure*
14	WPW/Left lateral AP	Broad pathway, Epicardial location*
13	Junctional tachycardia	Proximity to AV node#
10	AVNRT	Proximity to AV node#
04	AT (right atrial)	Remained inducible*
16	AT (right superior pulmonary vein)	Remained inducible*
14	Fascicular (upper septal) VT	Proximity to his bundle#
15	Fascicular (upper septal) VT	Proximity to his bundle#
14	Ebstein's anomaly	Broad AP, could not be ablated completely*
14	Mahaim atrio-fascicular accessory pathway	Stunned by catheter contact and then could not be mapped#

*Cause of failure: *Unable to ablate the tachycardia source/circuit; #Unable to deliver RF energy due to apprehension of complication or due to mechanical stunning of the pathway; AVNRT: Atrioventricular nodal re-entrant tachycardia, AP: Accessory pathway, AT: Atrial tachycardia, WPW: Wolff-Parkinson-White syndrome, VT: Ventricular tachycardia.*

RESEARCH PAPER

Detection of Immunoglobulin M and Immunoglobulin G Antibodies Against *Orientia tsutsugamushi* for Scrub Typhus Diagnosis and Serosurvey in Endemic Regions

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Objectives: To estimate the regional cutoff of optical density (OD) values for immunoglobulin M (IgM) antibodies against *Orientia tsutsugamushi* in serum and cerebrospinal fluid (CSF) for clinical diagnosis of scrub typhus and immunoglobulin G (IgG) antibodies in serum for sero-epidemiology in Gorakhpur, Uttar Pradesh, India. **Methods**: We used data from a serological investigation of acute encephalitis syndrome patients (*n*=407) during the 2016 outbreak in Gorakhpur, India to determine the cutoff for OD values for IgM antibodies, and from community-based serosurveys (*n*=1991) to estimate the cutoff for OD values for IgG antibodies. **Results**: We determined regionally relevant cutoff for OD values of 0.76 for IgM antibodies in serum and 0.22 in cerebrospinal fluid for scrub typhus diagnosis. For serosurveys, IgG antibody cutoff was 1.5. **Conclusions**: We have proposed locally relevant cutoffs for scrub typhus endemic regions, which may be useful for correctly classifying infected population.

Keywords: *Acute encephalitis syndrome, Diagnosis, Epidemiology, Immunoassay.*

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Scrub typhus, caused by *Orientia tsutsugamushi* (OT), is the most common re-emerging rickettsial infection in India and many other South East Asian countries [1]. Although, various labo-ratory tests are available for diagnosis of rickettsial infection, Enzyme-linked immunosorbent assay (ELISA) based tests, particularly immunoglobulin M (IgM) capture assays can be made available at secondary and tertiary levels of healthcare [2]. The IgM ELISA manufactured by InBios (Scrub Typhus Detect, InBios International Inc., Seattle, USA) is considered as an alternative to the gold standard immunofluorescent assay (IFA) for diagnosis of acute infection [3].

IgM ELISA is meant for diagnostic purposes only, whereas IgG antibodies indicate recent and/or past exposure. IgG seroprevalence surveys are conducted to measure endemicity of OT infection in an area. In India, InBios IgM ELISA and IgG ELISA are commonly used for diagnosing scrub typhus as well as measuring endemicity of infection [4-10]. The manufacturer's instructions recommend calculation of regional cutoff for optical density (OD) values based on geographically representative serum samples [11,12]. Moreover, the IgM assay is recommended for diagnostic purposes using serum [11]; however, its applicability in cerebrospinal fluid (CSF) is not known. The present study was conducted to estimate the regional cutoff of OD values for IgM antibodies against OT in serum and CSF specimens for clinical diagnosis, and IgG antibodies in serum for sero-epidemiology.

METHODS

For this study, we used data collected during our previous two studies [5,13] in Gorakhpur, Uttar Pradesh, India, a highly endemic area for scrub typhus. The first was on 407 inpatients (aged ≤14 years) with a clinical diagnosis of acute encephalitis syndrome [14] during August to October, 2016. Blood and CSF samples were available for serological investigations for 389 and 374 patients, respectively. Sera and CSF were tested for IgM antibodies against OT using Scrub Typhus Detect ELISA. CSF was diluted in 1:10 proportion for detection of IgM antibodies [5]. The other was data from two community-based serosurveys conducted in Gorakhpur district to estimate prevalence of OT infection [13]. These surveys were conducted among healthy individuals in two

separate groups of villages in Gorakhpur district. Blood samples from 1991 individuals aged between 6 and 45 years were collected in these serosurveys, including 1085 during the phase-1 serosurvey, and 906 during the phase-2. Sera were tested for IgG antibodies against OT using Scrub Typhus Detect ELISAs following manu-facturer's instructions.

Statistical analyses: We used the following methods for deciding the cutoff for OD values of IgM and IgG antibodies against OT: (*a*) To determine the cutoff for OD values of IgM antibodies against OT in serum, we plotted the frequency distribution of OD values. The OD value corresponding to the anti-mode was considered as the cutoff. This method is often used for differentiating distribution of infected and un-infected individuals in tuberculosis infection surveys [15]. (*b*) We considered 356 AES patients for whom both serum and CSF samples were available for analyses [5]. We estimated the regression equation between OD values of IgM antibodies against OT in serum and CSF. Using this equation, we calculated the cutoff for OD value for CSF corresponding to the cutoff for serum OD. (*c*) We plotted the frequency distribution of OD values from healthy individuals enrolled in phase 1 and 2 of the serosurveys [13]. There was a bimodal distribution, with segregation of values at the two ends and a central portion of OD values close to the baseline. We considered OD value corresponding to anti-mode of distribution in phase-2 serosurvey and OD value corresponding to the beginning of distribution of infected individuals in phase-1 survey as cutoffs.

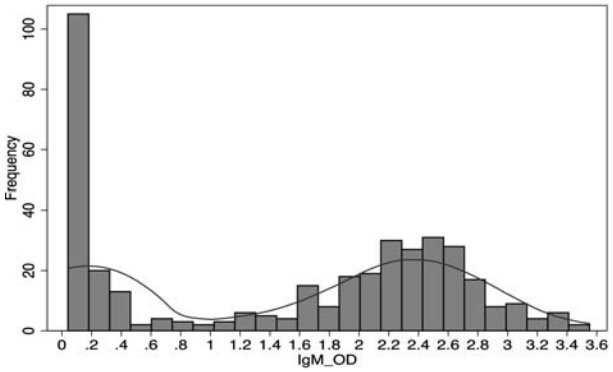


Fig. 1 *Frequency distribution of OD values for IgM antibodies against OT among 356 AES patients, Gorakhpur, Uttar Pradesh, 2016.*

RESULTS

The frequency polygon of OD values of IgM antibodies against OT in 389 AES patients showed a bimodal distribution, with anti-mode at 0.76. This was considered as cutoff for OD values against OT in serum IgM (***Fig.* 1**). A scatter diagram for the paired observations for OD values of IgM antibodies in serum and CSF showed a very strong positive correlation with a correlation coefficient of 0.83 (95% CI 0.79-0.86) (***Fig.* 2**). On linear regression analysis, the relationship between the OD values of IgM antibodies in serum and CSF was serum OD (Serum)=(1.07*CSF OD)+0.52. Based on this equation, for OD value of 0.76 for IgM antibodies in serum, the corres-ponding OD value for IgM antibodies in CSF was 0.224.

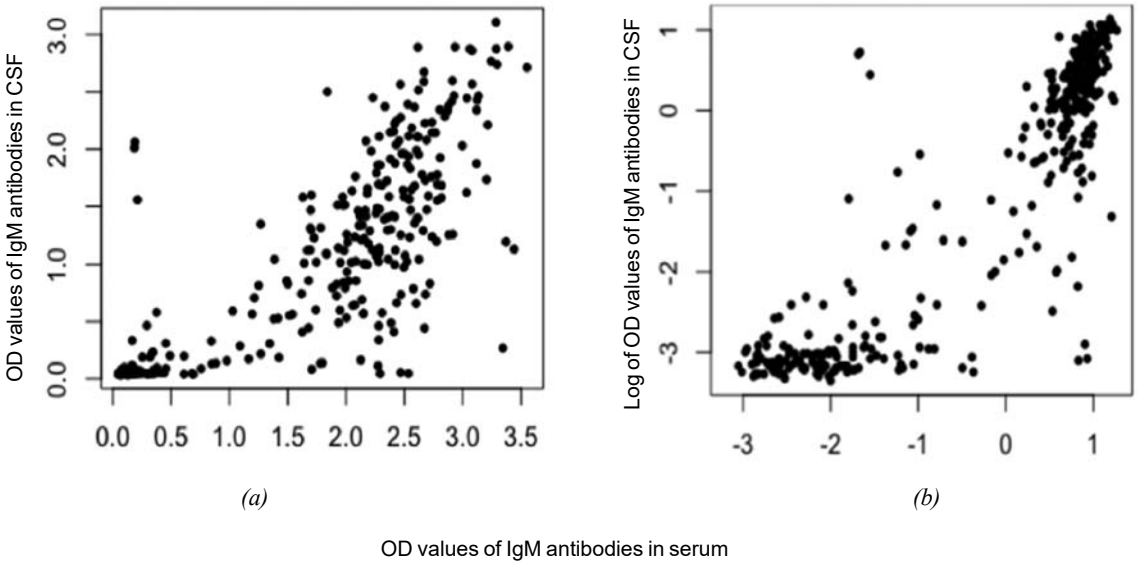
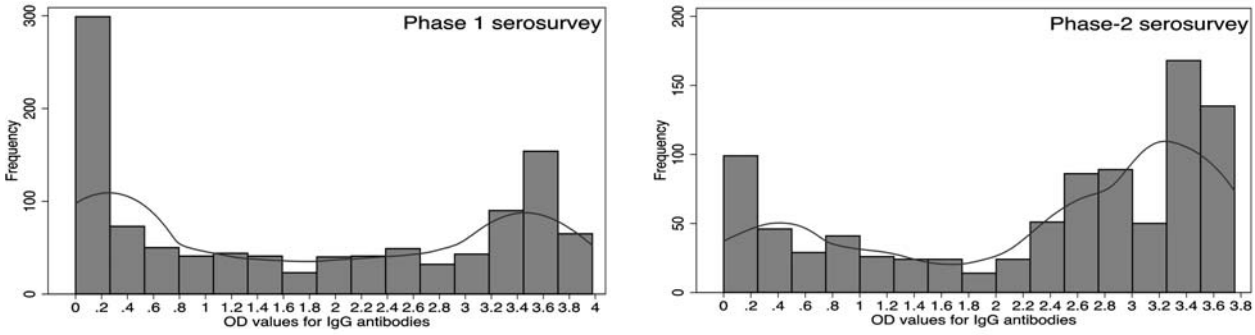


Fig. 2 *Scatter diagram showing (a) OD values and (b) log of OD values of IgM antibodies against OT in CSF and serum (n= 356).*



(a) *(b)*

Fig. 3 *Frequency distribution of OD values for IgG antibodies against OT in (a) phase-1 and (b) phase-2 surveys, Gorakhpur, Uttar Pradesh, 2016.*

The distribution of OD values from phase-2 survey showed an anti-mode at 1.5; however, the distribution from phase-1 survey did not reveal a clear demarcation between infected and uninfected individuals. The central portion between the two peaks was comparatively flat with OD values ranging from 0.6 to 2.5. OD value >2.5 in phase 1 corresponded to the distribution of infected individuals. In phase-1 and phase-2 serosurveys, 155 (14.3%) and 133 (14.7%) observations were between OD values of 1.5 and 2.5 (***Fig.* 3**).

DISCUSSION

Previous studies using Inbios ELISA kit have used OD value of 0.5 as the cutoff for IgM as well as IgG antibodies [4-10]. The manufacturer's instructions recommend calculation of cutoff value by determining the average of OD plus three times of the standard deviation (SD) of sera from healthy individuals and/or sera from persons with unrelated infections. It is further recommended that the end users calculate their cutoff using geographically relevant serum samples [11,12].

The phase-1 and phase-2 serosurveys were conducted among apparently healthy individuals at two different periods of transmission of scrub typhus infection in the community. However, using the OD values from children aged ≤14 years, the cutoff for IgM antibodies as per the kit recommended method, was 0.68 and 1.26 during the phase-1 and phase-2 surveys, respectively. The corresponding OD values for IgG anti-bodies was >3 in both the surveys. Higher cutoff obtained even during phase-1 survey, when the OT transmission in the community is expected to be low, indicates that the population included for sero-survey was not an unexposed population to OT. In view of this, we decided to consider the distributions of OD values for IgM among AES patients and IgG among healthy children for finding out the optimal cutoff.

The cutoff for IgM antibodies determined by us is higher than the cutoff of 0.5 observed by Blacksell, *et al*. [3] but comparable to the cutoff of >0.8 identified in another endemic area in India [18]. For IgG antibodies, A cutoff OD value of ≥1.5 in phase-1 serosurvey would have misclassified 14.3% individuals as infected, while a cutoff OD value of ≥2.5 in phase-2 serosurvey would have misclassified 14.7% infected individuals as uninfected. Since the primary objective of seroepidemiological studies is to estimate the disease burden, certain amount of misclassification in unavoidable with either cutoffs. The amount of misclassification; however, was not different with either cutoff. We therefore suggest an OD value of ≥1.5 as cutoff for classifying individuals as infected with OT for sero-epidemiological studies in Gorakhpur. With this cutoff, it was still possible to see clear transition for OT infections from 50.6% to 70.1% from phase-1 to phase-2 surveys. Trowbridge, *et al*. [16] have recommended a cutoff of >1.8 for IgG antibodies based on the community-based survey conducted in another high endemic setting in India.

Although the kit is recommended for detecting IgM antibodies only in serum samples, we observed good correlation between OD values for IgM antibodies against scrub typhus in serum and CSF. In comparison to serum where dilution of 1:100 is used, for CSF we used dilution of 1:10, as previously reported [17]. Since IgM antibodies cannot cross the blood brain barrier, the presence of such antibodies in CSF indicates that these antibodies are produced by antibody secreting cells in the central nervous system and hence presence of IgM antibodies against OT is more specific of scrub typhus infection. The calculated cutoff for CSF would require further evaluation before being used as a diagnostic criterion.

Our study has certain limitations. We did not use any gold standard test to compare the performance of Inbios

ELISA to calculate the cutoff for IgM and IgG antibodies. It was also not possible to calculate the cutoff based on manufacturer recommended procedure of mean (3 SD) based on endemic normal indivi-duals, in view of high endemicity of infection in the area.

In conclusion, we have calculated regionally relevant cutoffs for OD values of IgM in serum and CSF for clinical diagnosis, as well as cutoff for OD values for IgG antibodies for sero-epidemiological surveys in areas where OT transmission is endemic. Further evaluation of these methods may be used to find out accurate cutoffs in endemic areas, to correctly classifying infected population.

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Contributors: MDG: conceived the study; MDG, SK, MM: designed the study protocol and were involved in sample/data collection; AM, SS, VB, JD: carried out laboratory investigations; MG, MDG: analysed the data; MDG, MG, DG, MM: inter-preted these data; MG, MDG: drafted the manuscript; DG, MM: critically revised the manuscript for intellectual content. All authors read and approved the final manuscript, and agree to be accountable for; all aspects of the manuscript.

Ethical clearance: The institutional ethics committee of National AIDS Research Institute, Pune; No. NARI EC/2015-24 dated 13 August, 2015 and NARI EC/2016-15 dated 12 September, 2015. National Institute of Epidemiology, Chennai; No.NIE/IHEC/201507/-01 and dated 20 July, 2016.

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RESEARCH PAPER

Prevalence of Non-Exclusive Breastfeeding and Associated Out-of-Pocket Expenditure on Feeding and Treatment of Morbidity Among Infants Aged 0-6 Months in an Urban Slum

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Objective: To estimate the prevalence of non-exclusive breastfeeding (NEBF) and quantify the out-of-pocket expenditure (OOPE) associated with NEBF and treatment of morbidity among infants up to six months of age. **Methods**: Community based in an urban slum, among 172 mother-infant dyads selected by systematic random sampling. Current breast-feeding practices and OOPE over last one month was recorded using a pre-validated, interviewer administered schedule. Independent sample t-test subsequent to bootstrapping was used to test the statistical significance of the difference in mean out of pocket expenditure between NEBF and exclusively breastfeeding (EBF) infants.The main outcome measures was non-exclusive breastfeeding rate and out of pocket expenditure associated with infant feeding and treatment of morbidity. **Results**: 67 (38.9%) infants were found to be non- exclusively breastfed. The median (IQR) total monthly OOPE incurred on non-breastmilk feeding and healthcare was found significantly higher among NEBF infants vs EBF infants [440 (80-982) *vs* [0 (0-290); *P*<0.001]. The median (IQR) monthly OOPE incurred on healthcare was also significantly higher among NEBF infants than EBF infants [INR 140 (0-540) *vs* 0(0-150); *P*=0.002].**Conclusion**: The prevalence of NEBF was high, and it was associated with higher financial burden on the families.

Key words: *Breastmilk, Feeding practices, Healthcare costs, Health expenditures*.

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Non-exclusive breastfeeding increases the risk of diarrheal disease, respiratory illness, malnutrition and mortality among infants [1]. Attempts have been made to estimate economic costs associated with suboptimal breast-feeding. The estimated economic loss with suboptimal breastfeeding was reported to be 302-341 billion dollars annually, globally [2,3]. It is from 7.23 billion dollars in low-income countries and 218.27 billion dollars in low- and middle-income countries [3].

Researches have attempted to measure actual cost difference between non-exclusively breastfed infants and exclusively breastfed infants. The cost of formula feeding, and healthcare cost was reported higher in NEBF infants than in EBF infants in certain developed countries [4]. A study from India conducted a decade earlier, quantified the cost of infant feeding among NEBF infants which also included the cost of the foods consumed by the mother [5]. It seems obvious that non-exclusive breastfeeding will lead to increased economic burden due to two reasons. One, the costs associated with non-breastmilk feeding and the other, associated with health-care utilization which is higher in such infants as compared to those on EBF. However, studies on out-of-pocket expenditure (OOPE) associated with NEBF are lacking.

In this study, we estimated the prevalence of non-exclusive breastfeeding and assessed OOPE associated with non-breastmilk feeding and healthcare utilization due to infant morbidity, among infants up to six months of age.

METHODS

This community-based survey was conducted from November, 2017 to February, 2019 in an urban slum in East Delhi. Mother-infant dyads with the infant less than six months of age, from families residing in the area for at least six months, were included in the study. The sample size was calculated on the basis of 50% prevalence of NEBF in the literature [6]. With 50% prevalence, 15% relative error and 95% confidence interval, sample size obtained was 172. The approximate population of the slum was 80000. The estimated number of families based on the family size of 5 was 16000. Based on, crude birth

rate (20 per thousand) [7], the estimated population of infants under 6 months age came out to be 800. So, about one-fourth of the 800 eligible families (the families having an infant under 6 months) were to be selected to obtain the sample size of 172. At the community level, every 80th family was selected to be included in the study. In case of refusal, the immediate next family was surveyed without disturbing the original allotment.If more than one infant of less than six months age was found in a family, then one of them was selected randomly.

Ethics approval from institutional ethics committee was obtained prior to start of the study. Written informed consent was obtained from the mothers and face-to-face interviews were held. In situations, where mothers did not know about the infant feeding and healthcare associated expenditures, the father of the child was interviewed regarding that aspect. A semi-structured, pre-validated, pre-tested, interviewer administered schedule was used to collect the data. The breastfeeding status assessment questions were adapted from the World Health Organization (WHO) recommendation [8]. Socioeconomic status is presented as monthly family income and categorization was done using BG Prasad Scale with Consumer Price Index of 2017 [9]. Breast-feeding status was assessed by 24-hour recall method.

The data on OOPE within last one month was collected regarding the following components *viz.,* (*i*) Non-breastmilk feeds: included the cost incurred on powdered milk, formula milk and animal milk, and bottles, nipples and vessels used for non-breastmilk feeding of the infants; (*ii*) Outpatient care: It included the consultation fees, investigations, medicines and transport; and (*iii*) Hospitalization: It included the bed charges, consultation fees, investigations, medicines and transport. OOPE was recorded from available payment receipts. If receipts were not available, it was recorded as per report of parents.

Statistical analyses: The data was entered in MS Excel and analyzed using SPSS 20.0. Categorical variables such as NEBF status and sociodemographic characteristics are presented as proportions. Non-parametric data such as OOPE is presented as median and interquartile range (IQR). Since, the IQR for the frequency of morbidity episodes and frequency of healthcare facility visits were zero in most of the cases, we have presented it as median and range. Non-normally distributed data such as morbidity episodes and number of healthcare facility visits in last one month were compared between NEBF and EBF infants using Mann Whitney *U* test. Chi-square test was used for comparing proportions such as type of hospital facility accessed by NEBF and EBF infants who were sick. Fisher exact test was used for comparing hospitalization rates between NEBF and EBF infants. For OOPE data comparisons, the recommended statistical method is independent sample *t*-test subsequent to bootstrapping [10,11]. Therefore, instead of the Mann Whitney *U* test, this method was used to compare OOPE among NEBF and EBF infants.

RESULTS

Out of 195 participants approached, fifteen refused to give consent for the study and eight did not give complete information; thus, 172 mother-infant dyads were included in the study giving a response rate of 88.2. The mean (SD) age of the infants was 98.3 (54.5) days. About half of the mothers were educated up to or below the primary school level. The median (range) monthly family income was INR 15000 (INR 4000 to INR 150000). Most (72.1%) of the families belonged to the upper lower and lower middle socio-economic class as per BG Prasad scale using October 2017 Consumer Price Index (CPI).

Around two-fifths (*n*=67, 38.9%) of the infants were practicing NEBF. Among NEBF infants (*n*=67), 58.2% (39/67) were givenjust water in addition to breastmilk, whereas, 41.8% (28/67) were given animal milk,(10.5%, (7/67) infant formula, 0.3% (2/67) powdered milk and 0.3% (2/67) juices.

There was no statistically significant difference between the median monthly family income of the EBF and NEBF infants (*P*=0.64). The prevalence of morbidity and outpatient care visits was significantly higher among NEBF than EBF infants (***Table* I**).

The median (range) episodes of morbidity and healthcare facility visits among NEBF and EBF infants is given in ***Web Table* I**. Private healthcare facility was accessed by 51.2% of NEBF and 58.7% of EBF infants who had any morbidity and there was statistically no

Table I Prevalence of Morbidity and Healthcare Utilization Among Infants in Last One Month (*N*=172)

Morbidity status	*NEBF (n= 67)*	*EBF (n=105)*	*P value*
Any, *n*=92	46 (68.7)	46 (48.8)	0.001
Fever, *n*=37	22 (32.8)	15 (14.3)	0.004
Diarrhea, *n*=30	15 (22.4)	15 (14.3)	0.172
ARI, *n*=54	26 (38.8)	28 (26.7)	0.094
Healthcare utilization			
Outpatient care, *n*=86	43 (64.2)	43 (41.0)	0.003
Hospitalization, *n*=8	6 (9.0)	2 (1.9)	0.057

All values in no. (%); NEBF: Non-exclusive breastfeeding; EBF: Exclusive breastfeeding, ARI: Acute respiratory infection.

WHAT THIS STUDY ADDS?

- This study provides quantification of the out-of-pocket expenditure estimates of non-breastmilk feeding and healthcare utilization among non-exclusive breastfeeding infants as compared to exclusive breastfeeding from a community-based setting.

significant difference in the types of health facilities accessed by sick NEBF and EBF infants (P=0.21).

Average monthly OOPE (mOOPE) on non-breastmilk feeding, and on morbidity treatment is shown in ***Table* II**. The median (IQR) total mOOPE on non-breastmilk feeding, and on morbidity treatment was significantly higher in NEBF *i.e*. INR 440(80-982) than EBF *i.e*. 0 (0-290) infants (P<0.001). The median (IQR) mOOPE on outpatient care was significantly higher *i.e*. INR 100 (0-520) among NEBF than EBF infants *i.e*. INR 0 (0-150) (P=0.04).

DISCUSSION

This study aimed to find out the burden of NEBF, and the associated OOPE on non-breastmilk feeding and on healthcare utilization.

In our study, around two-fifths of the infants were found to be non-exclusively breastfed. Similar prevalence of NEBF was also found in a study in an urbanized village of Delhi [6,12] and in Gujarat [13]. At national level the prevalence in urban areas was found to be higher 47.9% as per NFHS-4 [11], as also reported in another study from Delhi [9]. Higher prevalence of NEBF has also been reported from Southern India [15]. As our study area had a nongovernment organization working actively in providing primary healthcare and health education related to promotion of breastfeeding, it might have been the reason for lower prevalence of NEBF in our study, as compared to these studies.

The mean total OOPE on non-breastmilk feeding and health care was found significantly higher among non-exclusive breastfed infants than exclusive breastfed infants. Similar findings were reported from a follow up study in Delhi in 1996, and a cohort study in Italy in 2006 [4,5]. The mean OOPE on non-breastmilk feeding was found significantly higher among non-exclusive breastfed infants than exclusive breastfed infants.

The difference in mean OOPE on both outpatient and hospitalization was found significantly higher among non-exclusively breastfed infants than exclusively breastfed infants. These findings are consistent with findings of other studies [4,5]. The difference in mean OOPE on outpatient care was found significantly higher among non-exclusively breastfed infants then exclusively breastfed infants. Similar finding was reported from another study in Italy [4]. Our findings support the hypothesis that NEBF causes more events of morbidity, thus more out of pocket expenditure on treatment of illnesses.

No significant difference was found in OOPE on hospitalization between non-exclusively breastfed infants than exclusively breastfed infants. While, a study in Italy had reported higher expenditure on hospitalization among non-exclusively breastfed infants [4]. In our study this might be becauseall the hospitalized patient availed their services from government health facilities and the OOPE on healthcare utilization in the government health facilities are very low.

So, there is a significant difference in cost incurred on non-breastmilk feeding and healthcare between exclusive breastfeeding and non- exclusive breastfeeding.

Table II Average Monthly Out-of-Pocket Expenditure on Non-Breastmilk Feeding and Healthcare (in INR)

Variables	*NEBF (n=67)*	*EBF (n=105)*	*Mean difference (95% CI)*
Non-breastmilk feeding*	207.9 (284.8)	0.0 (0.0)	207.9 (145.33-280.69)
Outpatient care*	327.1 (489.2)	180.0 (402.5)	147.0 (18.99-295.83)
Hospitalization	60.3 (267.4)	3.6 (34.2)	56.7 (8.34-112.78)
Total healthcare*	387.4 (587.39)	183.6 (402.8)	203.8 (61.10-355.97)
Wages lost	125.4 (505.6)	61.0 (259.4)	64.3 (-33.01-189.08)
Man-hour loss	17.9 (63.2)	3.0 (6.1)	14.8 (3.83-26.84)
Total (on feeding and healthcare)*	720.6 (838.1)	244.6 (491.8)	475.9 (282.61-683.95)

*All value in mean (SD); NEBF: Non-exclusive breastfeeding, EBF: Exclusive breastfeeding; *P<0.05.*

This study is a direct assessment of OOPE incurred on non-breastmilk feeding and healthcare utilization, thus provides a tangible evidence of cost saving with exclusive breastfeeding. However, the study involves only OOPE *i.e*. expenditure borne by families, it didn't assess the costs of healthcare which was not paid by the users at the point of delivery.

The study has certain limitations. Being a cross-sectional study, it is possible that the observed relationship between high expenditure and NEBF may be due to certain confounders such as prematurity or low birth weight. Another limitation was that the sample size was not calculated to detect a difference in OOPE or prevalence of morbidities between NEBF and EBF infants. For the variables, where the difference in the OOPE were not found to be statistically significant, it is possible that for those variables, the sample sizes were not enough to detect the observed difference.

NEBF is associated with higher morbidity events than exclusively breastfed infants. The OOPE associated with NEBF is two-fold; the OOPE associated with non-breastmilk feeding, and the OOPE associated with higher morbidity events. Thus, NEBF is associated with higher financial burden borne by the families. EBF should be supported and promoted. Investments in supporting and promoting EBF will cut the out of pocket expenditure at the community level.

Ethics clearance: Institutional Ethics Committee (Human Research), UCMS and GTB Hospital; No. IEC-HR/2017/32/25 dated October 17, 2017.
Contributors: AK: concept and design, analysis, interpretation of data, drafting the article; AMK: concept and design, interpretation of data, drafting the article, revising it critically; NKS: concept and design, interpretation of data, revising it critically for important intellectual content; DS: concept and design, interpretation of data, revising it critically for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Web Table I Episodes of Morbidity and Healthcare Utilization Among Infants in Last One Month (*N*=172)

	Total	*NEBF (n=67)*	*EBF (n=105)*
Morbidity status			
Fever	0 (0-2)	0 (0-2)	0 (0-2)
Diarrhea	0 (0-3)	0 (0-3)	0 (0-3)
ARI	0 (0-4)	0 (0-3)	0 (0-4)
Total	0.5 (0-4)	1 (0-4)	0 (0-4)
Healthcare utilization			
Outpatient visits – public	1 (1-3)	1 (1-3)	1 (1-3)
Outpatient visits – private	1 (1-3)	1 (1-3)	1 (1-3)
Outpatient visits – total	0.5 (1-4)	1 (0-4)	0 (0-3)
Hospitalization (duration in h)	0 (0-217)	0 (0-195)	0 (0-217)

All values in median (range); NEBF: Non-exclusive breastfeeding; EBF: Exclusive breastfeeding; ARI: Acute respiratory infection.

RESEARCH PAPER

Lung Function in Adolescents Exposed to Environmental Contamination and Brickworks in Guadalajara, Mexico

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Objective: To compare the pulmonary function in adolescents exposed to different concentrations of air pollutants in two different zones. **Methods:** Two zones based on monitoring of environmental pollutant concentration as high (zone 1) and low (zone 2) were chosen. The lung functions of apparently healthy adolescents (12-15 years) residing in two zones were measured for forced vital capacity (FVC), forced expiratory volume in first second (FEV1), FEV1/FVC ratio, and forced expiratory flow $(FEF)_{25-75}$. **Results:** A total of 302 adolescents (142, zone 1 and 160, zone 2) resided in the study area, with higher than permissible concentrations of PM10 and ozone at both places. Abnormal lung functions were seen in a higher proportion of adolescents in zone 1 than zone 2 (23% and 14%; *P*=0.04). A significantly lower mean (SD) FEV1 was seen in adolescents in zone 1 than zone 2 [2.9 (0.5) *vs.* 3.2 (0.4) L, *P* = 0.04]. A higher proportion of abnormal FEV1/FVC ratio% was seen in zone 1 than 2 (12% *vs.* 6%, *P*=0.04), suggestive of an obstructive pattern on spirometry. Higher risk (β 95% CI) for abnormal lung functions was seen with the zone [2.2 (1.1-4.2)], diagnosis of asthma [5.74 (2.4-13.2)], and living within 500 meters from a brickwork [1.8 (1.0-2.5)]. **Conclusion:** High exposure to PM10, ozone and living near brickwork were associated with reduced lung function in adolescents.

Keywords: *Air pollution, Asthma, Ozone, Particulate matter, Spirometry.*

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Around 92% of the global population lives in areas with environmental contamination that exceeds the limits recommended by the World Health Organization (WHO), which includes 300 million children [1,2]. The last phase of pulmonary development occurs during adolescence with the lungs being vulnerable to the effects of environmental contami-nation [3]. This may be associated with chronic obstructive pulmonary disease and lung cancer if persistent in adulthood, including among non-smokers [2,4].

Previous studies [5-7] have demonstrated the link between environmental contamination and decrease in lung function in children, with scarce data in adolescents. In the metropolitan area of Guadalajara, located in the western region of Mexico, environmental contamination related to automobile traffic is the primary source of ozone and particulate matter with an aerodynamic diameter of<10μm (PM10), which exceed the WHO limits in few areas [8]. The objectives of this study were to compare the lung functions of adolescents exposed to different concentrations of atmospheric pollutants and associate with the proximity to artisan brick factories (brickworks) and major roadways.

METHODS

This cross-sectional study was conducted during 2016-2017 in the metropolitan area of Guadalajara, Mexico. Adolescents between 12 to 15 years of age of either gender who were attending public secondary schools were enrolled. Those with active smoking, acute exacerbation of asthma or acute respiratory infection in the last two weeks were excluded. The protocol was approved by the Research and Ethics Committee of the Mexican Social Security Institute.

The metropolitan area of Guadalajara has ten fixed stations for environmental monitoring which measure PM10, ozone, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO). Two stations were selected centered on their concentrations of air pollution (the highest and lowest), based on the 2016 official report of air quality [8]. Google earth was used to locate the schools within a 2 km radius from the monitoring station, and to measure the distance between the subjects' homes and brickwork or a major roadway. The adolescents were randomly selected from a list obtained from the district's Department of Education. The study period was from

September to October, 2016 and March to June, 2017 as the mean values of ozone and PM10 remained stable with maximum of 10% variation during this period [8].

Written informed consent was obtained from the parents and assent from the adolescents. Parents completed an ad hoc questionnaire which included demographic details, clinical details for chronic diseases, asthma and allergies, and environmental exposures like prenatal smoke, secondhand tobacco smoke, wood and charcoal smoke, proximity (<500 meters) to a major roadway and/or brickworks from their house.

Height was measured using SECA portable stadiometer (SECA GMBH & Co., Hamburg, Germany; model 206), and weight by Tanita scale (Tanita UK Ltd Middlesex, United Kingdom; model UM-061) to calculate the body mass index (BMI). The spirometer equipment used was Easy-One Spirometer (NDD, Techopark, Zurich Switzerland) which was calibrated daily with a 3L syringe (Sensor Medics) prior to data collection. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio, and forced expiratory flow 25-75 (FEF25-75) were measured. Readings were performed at the school during morning and early afternoon to record at least three acceptable spirograms which were reproducible. The spirometric measurements were checked with the 2019 American Thoracic Society (ATS) criteria for acceptability and reproducibility [9]. The lung function parameters were calculated as mean (SD) and percentage of the predicted value. Reference values of National Health and Nutrition Examination Survey III for Mexican-Americans were used to calculate the percentage of predicted values [10].

Air pollutant concentrations were measured for ozone as 8-hour means in parts per million (ppm), PM10 as 24-hour means (μm/m^3), NO_2 as 1-hour means (ppm), SO_2 as 24-hour means (ppm), and CO as 8-hour means (ppm). The permissible concentrations were defined as per WHO [11], for ozone, PM10, NO_2, SO_2, and CO as <0.050 ppm, <50 μm/m^3, <0.106 ppm, <0.008 ppm and <8.73 ppm, respectively. Environmental air pollution was considered high (zone 1) or low (zone 2) according to the median concentrations of pollutants in the two respective zones.

Sample size and statistical analysis: The sample size based on a power of >80% and a two-tailed α of 0.05, to detect at least an 11% difference [12] in predicted percentage of FEV1, FVC, and FEV1/FVC ratio between the two zones was 129 adolescents in each zone.

The analysis was conducted using SPSS V.22 (License by IBM). Comparisons for continuous data between groups were done with Student t-test, and for proportions by chi-square test. Logistic regression analysis was done for risk of abnormal lung functions for factors like zone, diagnosis of asthma, and living <500 meters from a brickwork. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 317 adolescents were enrolled, out of which four children with asthma, two with active smoking and nine with poor reproducibility on spirometry were excluded to finally include 302 adolescents. The mean (SD) age in zone 1 (*n*=142) and zone 2 (*n*=160) was 13 (1) and 13 (0.9) years, respectively, with BMI of 21 (3) and 21 (4) kg/m^2, respectively.

The mean (SD) concentrations of pollutants in both zones are shown in ***Web Table* I.** The levels of PM10 and ozone were higher than the permissible limits in both zones. A higher proportion of adolescents lived within 500 meters from brickworks in zone 1 than zone 2 (31% *vs.* 16%, *P*= 0.001), respectively. A lesser proportion of those with allergic rhinitis (2% and 7%, *P*=0.03) and asthma (6% and 14%, *P*=0.03), respectively were reported in zone 1 than zone 2. There were no significant differences for any other environmental exposures.

The lung functions of adolescents in both groups are shown in ***Table* I.** A higher proportion of adolescents in zone 1 had abnormal spirometry results than zone 2 [23% *vs*. 14%, OR (95% CI) 1.8 (1.0-3.2); *P*=0.04]. Significantly

Table I Lung Function in Adolescents According to Air Pollution Exposure Zone in Guadalajara, Mexico

Spirometry variables	*Zone 1 (n=142)*	*Zone 2 (n=160)*	*P value*
FEV_1, L	2.9 (0.5)	3.2 (0.4)	0.04
FVC, L	3.4 (0.6)	3.3 (0.6)	0.08
FEF_{25-75}, L/s	3.7 (0.6)	3.9 (0.5)	0.4
% Predicted			
FEV_1 %	91.2 (9)	93.6 (10)	0.03
FVC %	90.4 (10)	91 (0.9)	0.2
FEV_1/FVC %	86.3 (6)	86.2 (5)	0.9
FEF_{25-75}%	89.2 (3)	90.1 (4)	0.6
n (%)			
FVC <80	16 (11)	9 (6)	0.07
FEV1 <80	14 (10)	6 (4)	0.03
FEV1/FVC ratio	17 (12)	9 (6)	0.04
FEF_{25-75} <80	12 (8)	8 (5)	0.3

Continuous data expressed as mean (SD); FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; FEF 25-75: Forced expiratory flow 25-75.

WHAT THIS STUDY ADDS?

- Adolescents exposed to high concentrations of PM10, ozone, and living <500 m from a brickwork have reduced lung function.

higher odds ratio (95% CI) for abnormal lung function were recorded for the zone, diagnosis of asthma, and living <500 meters from a brickwork as [2.2 (1.1-4.2)], [5.7 (2.4-13.2)], and [1.8 (1.0-2.5)], respectively.

DISCUSSION

Almost one-third of the adolescents presented abnormalities on spirometry, chiefly as a decrease in FEV1 and predicted FEV1%, which represents obstruction of the medium and large airways. The pollutants in both the zones were predominantly PM10 and ozone, both exceeding the WHO recommendations.

Our study has several limitations. First, we relied on fixed-site environmental measurements which could introduce exposure misclassifications. Second, we did not measure PM 2.5, which accounts for a larger proportion of the combined effects of PM10 and PM 2.5 [13]. PM 2.5 contains more small particles that can absorb toxic components from the air and penetrate deep in the lungs [14]. Third, socioeconomic status might be a determinant of lung function in our population which was not assessed. Fourth, the questionnaire for pollutant exposure was not validated. Fifth, we did not perform the reversibility test on spirometry. Six, multilevel logistic models should have been adjusted for potential confounders like height, BMI, sex, age, and passive smoking.

In this study, up to one third of the adolescents in zone 1 lived <500 meters from a brickwork. The brickworks are an artisanal and unregulated industry, initially located on the periphery, but nowadays found alongside inhabited zones which emit contaminants like SO_2, NO_2, CO, particulate matter (PM10 and PM2.5), and black carbon. These can cause health problems for their workers, in the nearby surrounding and even distant communities [15]. The generated gases induce an inflam-matory response in the airways, with excessive mucous production, broncho-constriction, and deterio-ration of lung function [16]. The exposure to PM10 and ozone induces oxidative stress and inflammation of the airway generating a decrease in lung function in children [17].

Our results are pertinent when compared to the ESCAPE study [6], from Europe which observed spirometry alterations in 6.8% to 10.4% children with an annual PM10 ranging from 3.0-31.4 $\mu g/m^3$. The decrease in FEV1 % was associated with high concentrations of NO_2 and PM2.5 [6]. Similarly, the Southern California Children's Health Study [5], confirmed alterations in FEV1 and FVC, and progressive loss of FEV1 <80% of predicted at 15 years of age in 3.6% to 6.3% and 7.9% adolescents on follow-up [5]. Similar reductions in FEV1 and FVC were associated with exposure to ozone, PM10, and NO_2 in children in an earlier study [12], as also reported by us. Exposure to higher NO_2 and PM levels during preschool was associated with reduced FEV1 at 16 years of age, but not with FVC which was not modified by asthma. This suggested that pollutant exposure during early life was influential to cause increased airway obstruction but not reduced lung volume in adolescence [18]. The increase in morbidity and mortality associated with brief exposure to environmental contamination is also documented [19].

To conclude, the high exposure to PM10, ozone, and living in close proximity to brickwork was associated with reduction in lung function in adolescents from the metropolitan area of Guadalajara. Follow-up studies to determine the impact of air pollution on lung function during adulthood are required.

Ethics approval: Comité Local de Investigación en Salud (CLIS); No. R-2016-1302-031, dated March 06, 2016.
Contributors: RHR, ATP: conception and designed of the study; RHR, VM: collected the data; RHR, OMC: analyzed the data; RHR, ATP: wrote the manuscript. All authors read and approved the final manuscript.
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RESEARCH PAPER

Clinical Profile of SARS-CoV-2 Infected Neonates From a Tertiary Government Hospital in Mumbai, India

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Objectives: To describe the clinical and laboratory profile of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected neonates. **Methods:** This is a review of hospital records, conducted in a tertiary care public hospital. Medical records of neonates born from 1 April, 2020 to 31 May, 2020 were reviewed. Women admitted in labor were screened for SARS-CoV-2 infection based on the guidelines issued by Indian Council for Medical Research. Neonates were tested for SARS-CoV-2 infection once mother tested positive, which was after day 2 of life. Demographic, clinical features, laboratory tests and chest radiographs of SARS-CoV-2 infected neonates were reviewed and neonates were telephonically followed up till the age of 2 months. **Results:** Out of 1229 mothers, 185 tested positive (15.05%); 12 neonates (6.48%) tested positive for SARS-CoV-2 infection. All neonates were exclusively breastfed. Symptoms, if any, were mild and self-limiting. Serum lactate dehydrogenase and liver enzymes were elevated. All neonates were healthy and thriving well on follow-up. **Conclusion:** SARS-CoV-2 infected neonates are mostly asymptomatic and thrive well on exclusive breastfeeding.

Keywords: *Breastfeeding, COVID -19, Management, Outcome.*

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Reports of SARS-CoV-2 infections in neonates are still emerging. There is little literature available about the clinical features, outcomes and the mode of transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in neonates, especially from India. Recently, a meta-analysis has described 58 SARS-CoV-2 positive neonates from across the globe [1]. We present the clinical and laboratory profile of SARS-CoV-2 positive neonates admitted to a tertiary-care public hospital.

METHODS

This was a review of case records of SARS-CoV-2 positive neonates, conducted in a tertiary care hospital in Mumbai, India after obtaining approval from Institutional ethics committee. Medical records of neonates born between 1 April, 2020 and 31 May, 2020 were reviewed. All neonates who tested positive for SARS-CoV-2 infection during the birth-admission or readmitted anytime in the neonatal period were included in the study.

During this period, Indian Council for Medical Research (ICMR) recommended that all pregnant women in labor or who were likely to deliver in the next 5 days, residing in clusters/containment areas or in large migration gatherings, from hotspot districts should be tested for SARS-CoV-2 infection with Real time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab, even if asymptomatic [2]. Mothers readmitted for post-partum complications were also tested. Neonates were tested for SARS-CoV-2 by RT-PCR on a nasopharyngeal swab sample if mother tested positive. All babies showing symptoms suggestive of coronavirus disease (COVID-19) were also tested. The usual turnover time for the test was 24 hours, which was the same for mother and baby. All the SARS-CoV-2 positive neonates were retested after 5 days. If negative on repeat testing, they were discharged. Those who continued to test positive on day 5 were discharged on day 10, if asymptomatic, without repeating the test.

Stable neonates, whether positive or negative, were roomed-in with their SARS-CoV-2 positive mothers in a separate COVID postnatal ward as recommended by Federation of Obstetric and Gynaecological Societies of India (FOGSI) and National Neonatology Forum (NNF) guidelines on the management of perinatal SARS-CoV-2 infection [3]. Neonates and mothers were kept on the same bed due to space constraints. Mothers were encouraged to breastfeed immediately after birth and educated about

maintenance of proper hand and respiratory hygiene. Lactation counseling and support were provided in person by a trained counselor. All the neonates were monitored twice daily for development of any COVID related symptoms like fever, hypothermia, respiratory distress, lethargy, cough, rhinorrhea, irritability, rash, diarrhea and feeding intolerance. If the neonates became symptomatic, they were shifted to the isolation area and managed.

Data regarding epidemiologic, demographic, clinical features, laboratory tests and chest radiographs of COVID positive neonates were recorded. Telephonic follow up of these neonates was done till 2 months of age. General health status, need for re-hospitalization, feeding status, weight gain and immunization were enquired about.

Descriptive statistics were used and outcomes expressed as proportions. Calculations were done using Microsoft Excel software.

RESULTS

Out of the total 1229 tested mothers, 185 (15.05%) tested positive for SARS-CoV-2 infection. Three (1.7%) mothers had fever and two of these three also had mild breathless-ness and responded favorably to treatment in the COVID ward (***Fig.* 1**). Twelve neonates (6.48%) tested positive for SARS-CoV-2 infection; 75% of these at 48 to 72 hours of life during the birth-admission. Three neonates were re-admitted with their mothers on day 13, 15 and 20, respectively for maternal complications and tested subsequently. All these neonates were roomed-in with their mothers in the COVID postnatal wards. The clinical and laboratory profile of all the SARS-CoV-2 positive neonates have been summarized in ***Table* I**.

Telephonic follow up was done for all positive infants till 2 months of age. Two infants received their 6-week immunization at 9 weeks, delayed by 3 weeks due to concerns of safety of visiting a health center during the pandemic and lockdown. All positive neonates were healthy, exclusively breastfed at 2 months follow up and did not require re-hospitalization after discharge following their SARS-CoV-2 infection.

Table I Characteristics of SARS-CoV-2 Infected Neonates (*N*=12)

Characteristics	*Value*
Male, *n* (%)	8 (66.6)
Gestation (wk), median (IQR)	38 (37.8, 39.3)
Birthweight (g)^	2734.1 (346)
Caesarean section, *n* (%)	10 (83.3)
APGAR at 1 min, median (IQR)	8 (8, 8.2)
Breastfeeding, *n* (%)	12 (100)
Feeding difficulty, *n* (%)	2 (16.6)
Fever, *n* (%)	3 (25)
Phototherapy, *n* (%)	3 (25)
Pre-ductal SpO_2 (%), median (IQR)	98 (97.7, 98)
Hospitalization (d), median (IQR)	13 (12,14)
*Hemoglobin (g/dL) ^	14.8 (2.4)
*leukocyte count ($\times 10^9$/L) ^	10.5 (3.3)
*Absolute neutrophil count ($\times 10^9$/L) ^	4.6 (1.4)
*Absolute lymphocyte count ($\times 10^9$/L)^	5.02 (1.8)
#AST (IU/L), median (IQR)	75 (65,88)
#ALT (IU/L), median (IQR)	29 (25,39)
#CRP (mg/L), median (IQR)	5 (4.2,7)
#Creatinine (mg/dL), median (IQR)	0.4 (0.3, 0.6)
‡LDH (IU/L), median (IQR)	1462 (1148.2, 1604.5)

*Values in ^mean (SD) or as detailed; Investigation carried out in *11, #9 or ‡8 neonates; No baby had respiratory symptoms or lethargy/ neurological symptoms; AST: Aspartate transaminase, ALT: Alanine transaminase, CRP: C reactive protein, LDH: Lactate dehydrogenase.*

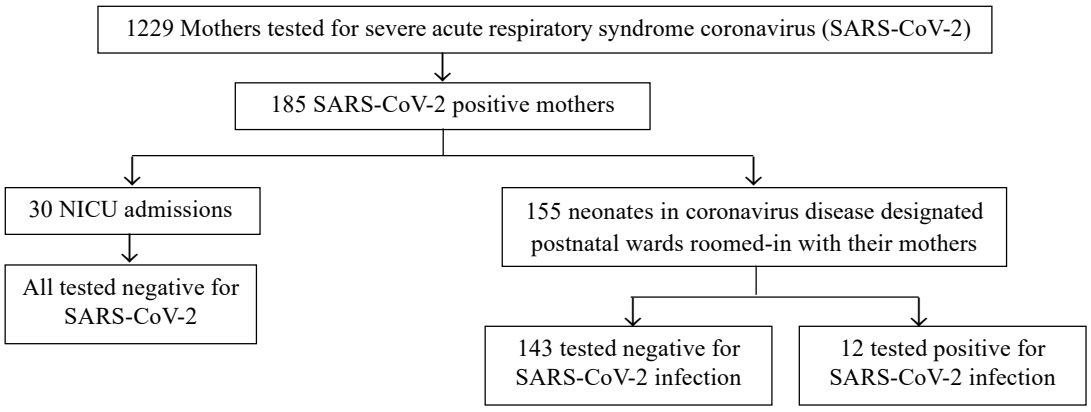

Fig. 1 *Flowchart showing patients during the study period.*

WHAT THIS STUDY ADDS?

- The clinical features of SARS-CoV-2 infection in neonates are mostly mild/asymptomatic, and such mother-baby dyad can be successfully roomed-in and breastfed.

Thirty (16.2%) neonates required NICU admission for neonatal problems and all of them tested negative for SARS-CoV-2 infection. The remaining 143 (77.2%) neonates tested negative and continued to be roomed-in with their mothers.

DISCUSSION

This is one of the earliest reported cohorts of COVID positive neonates from India. The exact incidence of SARS-CoV-2 infection in neonates is largely unknown. The proportion of SARS-CoV-2 positive neonates in our study was 6.5% as compared to 3.9% in a meta-analysis of 58 neonates [1].

Although a few authors have reported vertical transmission in neonates, there is still controversy regarding the same [4]. To prove intra uterine viral infection, testing of RT-PCR assay on tissue samples derived from placenta, amniotic fluid, cord blood and neonatal pharyngeal swab in the immediate post-partum period is required [5]. In our study, the maternal reports were available after 24 to 48 hours of delivery. Hence 50% neonates were tested at 48 hours, 25% neonates at 72 hours and the three re-admitted neonates were tested between 13-20 days. The median gestational age was 38 weeks in this study and the ratio of male to female was 2:1, similar to that described by Bernardo, *et al*. [6].

Mode of delivery does not impact transmission of the infection to the baby [3]. Still, the caesarean section rates have been found to be higher among SARS-CoV-2 infected mothers, and in our study too it was 83.3%. Respiratory problems requiring ventilation have been reported as the most common presenting symptom amongst SARS-CoV-2 positive neonates [1]. However, none of babies in this cohort had respiratory symptoms. We found mild and self-limiting symptoms in our cohort, with 3 neonates having fever. However, two out of these three neonates also had feeding difficulties and excessive weight loss, which responded to improved feeding practices and supplementary feeding with expressed breast milk. Hence, these could be cases of dehydration fever and may not be related to SARS-CoV-2 infection. One neonate had mild fever, which could not be attributed to any cause, therefore we presumed that the fever was caused by SARS-CoV-2 infection.

Very few studies have described laboratory abnormalities in SARS-CoV-2 positive neonates. The study by Henry, *et al*. [7] in pediatric COVID patients described lymphopenia, raised liver enzymes and raised LDH levels as the common lab abnormalities. Raised LDH levels in adult studies on SARS CoV-2 infection suggest greater severity of illness [8]. In our study, marked elevation of LDH levels and mild transaminitis were observed in the SARS-CoV-2 positive neonates. However, the significance of raised liver enzymes and LDH in neonates is yet to be understood. Bernardo, *et al.* [6] has reported radiological abnormalities in 44% of SARS-CoV-2 positive neonates but we did not find any radiological abnormalities in our study. Current evidence does not recommend any blood or radiological investigations in any asymptomatic SARS-CoV-2 positive neonates.

The World Health Organization and most professional bodies recommend rooming-in of asymptomatic mother-baby dyad, exclusive breastfeeding and maintaining a distance of 6 feet between them [3,9,10]. All stable neonates in our study were not only roomed in but also bedded in with their mothers and exclusively breastfed. Maintaining a distance of 6 feet was not possible due to lack of space in our hospital. In the study by Salvatore, *et al*. [11], despite rooming in, there was no horizontal transmission of SARS-CoV-2 infection as these babies were kept in Giraffe isolette incubators. Around 6.5% of our neonates had possible horizontal trans-mission due to prolonged close contact with their SARS-CoV-2 positive mothers during bedding in.

There is no conclusive evidence that the virus is transmitted through breastmilk [12,13]. Also, the benefits of breastfeeding far outweigh the negligible risk of transmitting the virus. In our center, we counselled and encouraged mothers to follow strict hand hygiene and respiratory hygiene all the time, especially while breastfeeding, but the exact compliance was not studied.

The limitations of our study were its retrospective design and small number of subjects. The manifestations in SARS-CoV-2 positive preterm neonates and those born to severely symptomatic mothers is not known and needs to be further explored. Exclusive breastfeeding is an integral part of neonatal care and has to be strongly promoted.

Ethics clearance: Institutional Ethics Committee Human

Research, Lokmanya Tilak Municipal Medical College and General Hospital; No: IEC/28/20 dated June 11, 2020.
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Immunization During the COVID-19 Pandemic: Recommendations From Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices

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During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, immunization practices of all age groups, especially routine childhood vaccines, have been interrupted. Immunization is considered an essential health activity, which needs to be resumed as early as possible. This pandemic has created several unique issues related to routine immunization of individual children at clinics, which needs to be addressed. In this communication, the Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics addresses the common questions and issues related to SARS-CoV-2 and routine immunization services. This also includes the recommendations for routine immunization of SARS-CoV-2 suspect and positive children, and for the logistics to be followed for immunization services.

Keywords: *COVID-19, Guidelines, Missed Vaccination, Routine immunization*.

The coronavirus disease (COVID-19) pandemic has negatively impacted every aspect of life. The economic sector has been the most affected and preventive health services have been almost kept on hold. Primary health care services, including immunization, have been disrupted, putting women and children at risk for vaccine-preventable diseases (VPDs), such as measles, rotavirus, and tetanus. Several districts and blocks in India have had partial or complete lockdown on-and-off, affecting movement of people. Fear of getting the infection, social distancing norms and other infection prevention control practices have adversely affected health seeking behavior and routine visits to health care facilities. The primary focus of public health has been diverted towards preparedness and containment of COVID-19 pandemic in the country, and all other preventive health activities have been relegated to the background.

The immunization services had to bear the brunt of these unprecedented circumstances and various on-site and community immunization services were severely affected. In April 2020, the health management and information system data reported a decrease in the number of routine immunization sessions relative to the previous year. The number of fully immunized children also decreased over the same time period. It is to be emphasized that any flare of VPDs will additionally burden already stressed health care systems.

The severe acute respiratory infection 2 (SARS-CoV-2) pandemic has created several unique issues related to vaccines and immunization services. ACVIP has taken on itself to address the common questions and issues related to COVID-19 and routine immunization services in a question-answer format, with an objective to guide pediatricians on these important issues.

Should children be vaccinated during the pandemic?

ACVIP recommends that all routine vaccinations be administered as scheduled, even during the COVID-19

pandemic as it is an essential health activity [1]. The benefits of immunizations far outweigh the associated risks. The importance of continued immunization activities is further emphasized by the observation that during the 2014-2015 Ebola outbreak, the increased number of deaths caused by measles, malaria, HIV/AIDS and tuberculosis attributable to health system failures, exceeded deaths from Ebola itself. In a benefit-risk analysis of health benefits versus excess risk of SARS-CoV-2 infection, in Africa, it was estimated that in a high-mortality scenario, for every one excess COVID-19 death attributable to SARS-CoV-2 infections acquired during routine vaccination clinic visits, 84 (95% CI 14-267) deaths in children could be prevented by sustaining routine childhood immunization. The advantages of sustained immunizations extended to their siblings (<20 years) and to other family members also [2]. In the private practice settings, the existing ACVIP Guidelines are to be followed for routine immunization.

Is my child at an increased risk for getting infected with SARS-CoV-2 by the hospital/clinic visit for immunization?

If SMS (social distancing, mask, sanitization) is strictly followed, and the recommended COVID-19 related norms are observed in the immunization session, the risk is minimal.

Is there any risk from immunizing a child during the pandemic?

There is no documented risk of immunizing a well child during the COVID-19 pandemic. COVID-19 is still an evolving disease and hence we need to monitor strictly for any increased adverse events following immunization (AEFI).

Is there a risk if we vaccinate a child during the incubation period of COVID-19?

Currently there is no evidence that there is any risk to the vaccinee if vaccination is done during the incubation period of COVID-19. The efficacy and safety of the administered vaccines would be the same.

Does vaccination increase a child's risk of becoming infected with SARS-CoV-2 or of developing COVID-19?

In general, vaccination against one disease does not weaken the immune response to another disease. As of now, there is no evidence that vaccination would increase the risk of a child becoming infected with COVID-19 or affect the course of the disease in a child who has been inadvertently vaccinated during the asymptomatic phase or incubation period [3].

Is there a change in the existing immunization schedule during the pandemic?

There is no information about the effect of COVID-19 on responses following immunization. ACVIP recommends that in private practice settings, the existing ACVIP Guidelines are to be followed for routine immunization [4]. There is currently no need for a change in the immunization schedule.

How is area categorization being done by the Government during the COVID-19 pandemic for providing immunization services?

Based on World Health Organization (WHO) guidelines, the Government of India (GOI) has categorized areas (district/sub-division/municipal corporation/ward/any other appropriate administrative unit) into Red and Orange zones with active COVID-19 cases, and Green zones with no active COVID-19 cases [5]. Areas where COVID-19 cases are reported and surrounding areas with risk of COVID-19 spread are classified as Containment zone and Buffer zone respectively; whereas areas outside the buffer zone are identified as Area beyond buffer zone. The categorization of containment and buffer zones is a dynamic process updated on a weekly basis or earlier. In alignment with the area categorization, immunization services are classified into two heads: Immunization in containment and buffer zones, and immunization in areas beyond buffer zones and green zones.

How are immunization services to be conducted in containment zones and buffer zones?

Traditionally, immunization services in India get delivered through the following modes: Birth dose vaccination (at delivery points), Health facility-based sessions (at fixed health facilities), and Outreach sessions (as part of Urban/village health sanitation and nutrition day services). The birth dose vaccination at all health facilities should be provided to all the eligible babies. A child reporting to the health care facility due to any reason should not be denied immunization and every opportunity must be utilized for vaccinating the beneficiaries. The health facility-based immunization services should be provided only on demand to walk-in beneficiaries. The outreach immunization sessions should not be undertaken in these areas. However, the facility-based as well as outreach immunization activities can be started after two weeks of delisting of the area as containment or buffer zone, after being assessed for the COVID-19 risk by the district authorities [6].

What are current recommendations for immunization services in the area beyond buffer zone and green zone?

All areas beyond the buffer zone and in the green zone need to follow similar guidelines. In these areas, the health facility-based immunization services should be provided to all the beneficiaries. The outreach (modified) immunization sessions can also be undertaken at a predetermined site having adequate space and in a modified way. Such a modified outreach session is to be planned for less than 500 people, with a number of beneficiaries not more than 10-15 per session. Less than five persons should be present at the session site while maintaining a distance of 1 meter from each other. Organization of such sessions will be at the discretion of the district administration, with clear planning for social distancing and hand washing at session site [6].

Should children from containment or buffer zones be vaccinated if they report for vaccination in a facility outside those areas?

Since the residents of the containment or buffer zones are considered as suspects, they should not be encouraged to go out of containment zones, as per government instructions. Active immunization activities are not allowed in such areas. However, when any child from such areas reaches the healthcare facilities, he/she should be offered immunization as per the requirement of the child.

What logistics are required while setting up immunization practices during COVID-19 times?

The logistics may be divided into preparation of the space, personnel, vaccinee, maintaining the waiting area and post vaccination care (***Box* I**).

What should be done if certain due vaccines are missed?

This is a common situation in the COVID-19 pandemic. The parents have to be reassured that the vaccination schedule can be resumed without any need to restart the series. Multiple vaccines in one sitting and using the minimum permitted interval between two doses of the same inactivated vaccine can be practiced to complete the schedule in the shortest possible time.

The vaccination services should be restarted as early as possible. Missed vaccines have put the society at an increased risk of VPDs. Multiple epidemics of measles occurred in 2015 in Guinea because of the interrupted immunization during the Ebola outbreak [7]. The vaccine provider should track the cohort of children who have missed the vaccine and immunize them, as soon as the vaccination becomes feasible. Public awareness should also be done to sensitize them about the catch-up vaccination. The parents should be reassured; that there is a window period in which the vaccines could be given; and once given, it would have similar efficacy in future. Following principles need to be followed:

- The birth dose of hepatitis B vaccine should be administered within 24 hours of birth and OPV, and BCG vaccines should be given as early as possible after birth. If for any reason this is not done, these vaccines should be administered at the first contact with the healthcare facility.
- The primary vaccination series and the vaccines for outbreak prone diseases should be prioritized for example DPT, hepatitis B, Hib, OPV/IPV, rotavirus, PCV, influenza, varicella and MR/MMR. Postponing these vaccines is to be avoided.
- The pneumococcal and influenza vaccine should also be given to the vulnerable groups.
- The age specific recommendations of giving vaccines e.g. for pneumococcal, meningococcal and rotavirus vaccine should be followed.
- Multiple vaccines can be administered in the same session without fear of any increased adverse effects.
- Typhoid conjugate vaccines may be clubbed with the influenza vaccine at 6 months or MR/MMR at 9 months.
- Inactivated JE vaccines (where applicable) can be administered at 1 year.
- We may use the shortest acceptable interval between two doses of the same vaccine if the prospective vaccinee reports to a health facility; and is unlikely to come for follow-up. For inactivated primary vaccines this is 28 minus 4 days i.e. 24 days.
- The vaccination of healthcare personnel should be up to date in their age appropriate vaccinations.
- When missed (because of the logistic issues of transport etc.), hepatitis A vaccines and HPV vaccines may be administered after the priority vaccines have been given.
- When missed (because of the logistic issues of transport etc.), the booster dose(s) may be given at the next earliest available opportunity.
- If a child is in a healthcare facility for any reason, and eligible for immunization, this opportunity should be utilized for administering eligible vaccines.

What schedule should be followed for vaccination at birth?

The vaccination at birth depends upon the COVID-19

Box I Logistics for Immunization Preparedness During COVID-19

Preparation of the vaccination area

- Exclusive vaccination sessions are recommended in separate vaccination rooms. If the same floor/ building is used for other patients, provision should be made for separate entry and exit paths for the prospective vaccinees to avoid mixing with the general patients.
- Adequate well-ventilated seating space having one meter distancing from another person should be available. The area should have exhaust fans for adequate air circulation, and windows should be kept open.
- Sanitizers, soap and running water should be made available in adequate amounts at the entry point of the vaccination area.
- Vaccination staff, having any Flu like symptoms, should not be allowed to vaccinate.
- It is essential that the doctor and supporting staff utilize adequate PPE. A mask (N95 mask preferably and three-layered surgical mask when N95 is not available), gloves, and face shield along with scrupulous hand hygiene are likely to protect from aerosol generation by a crying child.
- New clean gloves (non-sterile) should be donned before each vaccination.
- Hand hygiene with alcohol-based hand sanitizers containing minimum 60% alcohol, for a minimum 20 seconds is to be practiced before and after each vaccination. Gloved hand should also be sanitized.
- COVID-19 awareness material should be displayed in the vaccination area.
- Continuous training should be imparted to the health care personnel engaged in vaccination practices.

Vaccinee logistics

- The vaccinee should preferably be called by appointment although no opportunity should be missed for vaccination.
- Overcrowding should be avoided. Physical distancing of 1 meter should be observed.
- Utilize every healthcare visit for immunization, provided there are no precautions/ contraindications and the interval between vaccines are maintained as per published guidelines.
- Minimum number of attendants preferably single (maximum two) should only be allowed in the premises.
- The accompanying individuals should be screened for fever and respiratory symptoms and if symptomatic, they should not be allowed in the vaccination area and should be advised to get examined at the health care services.
- Attendants who are more than 60 years of age or have comorbid conditions should be requested not to accompany the vaccinee.
- All caretakers and children, except infants should wear a triple layer mask and provision should be made for providing these at the entrance of the vaccination area.
- The accompanying persons should be made aware of the social distancing, hand washing/sanitizing and respiratory hygiene during the visit.

Waiting area

- The number of waiting persons both before and after the vaccination should not be more than the capacity of the area while maintaining the distance of 1 m between two persons.
- Post vaccination, the vaccinee must be observed for 15 minutes for development of any immediate AEFI.
- This waiting period should be used for group counselling. Key preventive messages pertaining to precautions during COVID period, strengthening of hand hygiene, social distancing, breastfeeding, dietary advice, and danger signs could be discussed during this period.
- The informative written material can also be kept in the waiting areas.

Logistics post vaccination

- The furniture used should be thoroughly cleaned with appropriate sanitizers.
- Proper sanitization of the anthropometry equipment should be ensured immediately after each use.
- The biomedical waste generated should be disposed of at source.
- Digital payment is to be encouraged.

status of mother as well as the neonate, and the clinical condition of the baby [8]. The recommendations are given in ***Table* I**.

What is to be done if the vaccinee is suspected or diagnosed to have SARS-CoV-2 infection?

ACVIP recommends that if the prospective vaccinee has been infected with COVID-19 or is under quarantine, the vaccination is to be done only after the quarantine period is over and the clinical condition of the baby is stable. If the child has any symptoms suggestive of COVID-19 infection, vaccination is to be avoided till the symptoms resolve. It is also emphasized that the presence of fever may interfere in the differentiation between the disease progression and vaccine induced adverse events. Therefore, it is best to wait for the resolution of symptoms before vaccinating in COVID times. Standard guidelines given in IAP guidebook on Immunization 2018-2019 (vaccination in special situations) should be followed if children develop 'Multisystem inflammatory syndrome' during COVID infection and require intravenous immunoglobulin or steroids [9]. It is not mandatory to document a negative COVID test before vaccination.

Do Bacille-Calmette-Guérin (BCG) or MMR vaccines have some role in controlling the ongoing COVID-19 pandemic?

Epidemiological studies have suggested a negative association between national BCG vaccination policy and the prevalence and mortality of COVID-19. Observational studies have also suggested that countries with recent MMR campaigns or established MMR vaccinations in their national programs have generally reported lower mortalities due to COVID 19.

Table I Birth Dose Vaccination Recommendation During COVID-19

Scenario	*Mother*	*Neonate*	*Status*	*Schedule*
A	No clinical suspicion of COVID-19 infection	No clinical suspicion of COVID-19 infection	Normal	• Hepatitis B: At birth or as early as possible within 24 h • BCG: At birth or as early as possible • OPV: At birth or as early as possible within15 d
B	Suspected but COVID unconfirmed	No clinical suspicion of COVID-19 infection	Normal	Same as above
Ca	COVID positive	Asymptomatic but not tested	Contact of confirmed case	Same as above
Cb	COVID positive	Symptomatic but not tested	Contact of confirmed case	• Hepatitis B: At birth or as early as possible within 24 h • BCG: At time of discharge • OPV: At time of discharge but less than 15 d
Da	COVID positive	COVID positive but asymptomatic or mildly symptomatic	Confirmed case, capable of trans-mitting disease	• Hepatitis*: At time of discharge but less than 15 d • BCG: At time of discharge • OPV: At time of discharge but less than 15 d
Db	COVID positive	COVID positive but severely symptomatic	Confirmed case, capable of trans-mitting disease	• Hepatitis[#]: At time of discharge but less than 15 d • BCG: At time of discharge • OPV: At time of discharge but less than 15 d
E	No clinical suspicion of COVID-19 infection	Symptomatic but COVID status unknown	Suspect	• Hepatitis**: At time of discharge but less than 15 d • BCG: At time of discharge • OPV: At time of discharge but less than 15 d

**In infants born to HBsAg/HBeAg-positive/Hepatitis B status unknown mother, hepatitis B vaccination to be given within first 24 hours or as soon as possible, hepatitis B immunoglobulin (HBIg) as per schedule. [#]In infants born to HBsAg/HBeAg-positive/Hepatitis B status unknown mother, if the baby is clinically stable, hepatitis B vaccination to be given within first 24 hours or as soon as possible, HBIg to be given as per schedule. Schedule adapted from Ref No 8.*

As of now, there is no evidence that BCG vaccine has a protective role against occurrence of SARS-CoV-2 infection [10]. Based on the current evidence, ACVIP does not recommend use of BCG or MMR vaccine for the protection of individuals against COVID-19 infection [10-12]. Various attributed potential nonspecific effects of the BCG vaccine in preventing COVID-19 as of now remain a hypothesis, because of multiple confounding factors [13]. Clinical trials are underway and the recommendations would be updated once more evidence is available.

Disclaimer: These guidelines are meant for practicing pediatricians in their office set up or hospital. These guidelines are based on the available knowledge of COVID 19 as on date. Any further guidance based on evolving scenarios will be issued accordingly. Members are informed that these are only recommendations and they should be taken in context with local advisories issued by health authorities in the areas where the member provides medical services.

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Indian Academy of Pediatrics Guidelines on School Reopening, Remote Learning and Curriculum in and After the COVID-19 Pandemic

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Justification: With the unprecedented COVID-19 pandemic and the resultant school closure, children all over the country are undergoing a lot of educational, psychosocial, and physical problems. There is an urgent and deep felt need to offer scientific and concrete guidance for these concerns and support children in their educational development during these testing times. **Objectives**: To review the guidelines and recommendations given by various international agencies and formulate guidelines in the Indian context on (*a*) how and when to reopen the schools; (*b*) ways and means of remote learning; and (*c*) to identify the contents of curriculum that need restructuring in context of the current situation. **Process**: Indian Academy of Pediatrics (IAP) formed a task force of pediatricians, educationists and technological experts who connected through various video and social platforms. They gathered and exchanged information and thoughts. The writing committee drafted the guidelines and got approval of all the members of the task force. **Recommendations**: Schools can be reopened only when the local epidemiological parameters are favorable, the administration is equipped with adequate infrastructure and health care facilities, and the stakeholders (teachers, students, parents, and support staff) are prepared for the new normal. In the meanwhile, remote learning (media-based and /or otherwise) should reach to the last student to maintain uninterrupted education. The curriculum needs to be revised, with focus on revision and core contents. Informal learning of psychosocial empowerment and daily living skills should be encouraged rather than stressful formal learning.

Keywords: *Education, Distance learning, e-learning, Lock down, Screen time*.

Nearly 240 million school going students in India are homebound owing to the coronavirus disease 2019 (COVID-19) pandemic [1]. The loss in learning in pandemic is estimated to be up to 50% of the expected academic level [2]. The impact could be life long and likely to be most significant for the disadvantaged and marginalized children [3].

Schools provide a safe and stimulating environment to children for learning, education, physical activities, socialization, and cater to their nutritional needs through mid-day meal program. UNICEF's 'Lives Upended' report describes the consequences of the pandemic on nearly 600 million children in South Asia, including India [4]. School closure has resulted in stress among the children and their families and they are more likely to suffer from anxiety, depression and post-traumatic stress disorder during and after COVID-19 epidemic [5-7].

As of now, there is a lot of uncertainty and confusion about when and how to start the schools, in all sectors of the stakeholders including the government, school authorities, teachers, parents and the civil society. Efforts to continue education through remote learning are falling short in reach [8] and academic outcome, and children are also missing the socialization, which schools entailed [9]. Additionally, online learning is proving to be a big challenge for many. School closure has initiated the concept of digital remote learning, which is being popularized extensively, with due credit to the digital technology. However, it is now being realized that online

learning is causing a lot of stress to the children and families [10].

Academics has always been a big burden for the Indian children [11]. They are occupied for one third of their day in the school and related academic activities. Schoolwork generates negative emotional states like low mood, low motivation, feeling of compulsion and anxiety [12]. The National Education Policy of Government of India, 2020, emphasises on the holistic development of children. It recommends easing out the academic stress and incorporating co-curricular activities in the mainstream education [13]. Children are placed at the centre of Sustainable Developmental Goals [14,15]. Being the advocate of holistic health of children and adolescents, the Indian Academy of Pediatrics tried to address these issues with a scientific and evidence-based temper.

OBJECTIVES

These guidelines are framed with the following objectives:

1. To recommend how and when the schools can be safely opened
2. To describe various ways and means of remote learning
3. To define appropriate contents of learning for students in the current times

PROCESS

The Indian Academy of Pediatrics, in June, 2020, constituted a task force on 'School reopening and remote learning' to address the issues outlined above. The members comprised of practicing pediatricians, teaching faculty, developmental and behavioural experts, epidemiologists, educationists, and technology experts. The members of the task force remained in touch telephonically, via emails and through social networking sites. Regular meetings were held periodically on video networking platform, the first being held on 21 June, 2020. Taking into consideration, the pressing need of the time, the issue of 'when to reopen the schools' was urgently addressed by the task force. The interim guidelines on the same were released and disseminated to the concerned authorities on 4 July, 2020 [16].

The members were divided into four subgroups to address four subsets of the objectives viz (*i*) when is it safe to open the schools, (*ii*) how should the schools reopen safely, (*iii*) ways and means of remote learning during the school closure and (*iv*) contents of learning in the current times.

Review of literature was conducted by the members and they shared in their subgroups relevant scientific material and research studies obtained from various authentic sources. The main areas addressed were: (*i*) epidemiology of COVID-19, (*ii*) clinical presentation and transmission of COVID-19 in children , (*iii*) effect of non-pharmacological measures in mitigating the transmission of Corona virus, (*iv*) psychosocial impact of pandemic and school closure on children, (*v*) ways and means to reduce the stress and (*vi*) various modes of distant education.

School opening Guidelines given by the World Health Organization (WHO), United Nations Children Fund, Centers for Disease Control and Prevention (CDC), and American Academy of Pediatrics (AAP), were thoroughly studied. PRAGYATA guidelines (on remote learning) by the Government of India, as well as guidelines from various educational boards of national significance were searched and studied. A pan-India survey was conducted to get inputs from the parents and teachers regarding their perspective on different aspects of school closure [10].

Box I Principles to Guide the Formulation of School-reopening Guidelines

- A total redressal of the education system is the need of the present crisis. However, physical and psychosocial health of children is more important than formal learning.
- School reopening should be based on the local epidemiological indices at the district level, the administrative preparedness to handle the consequences, if any, the school preparedness, the compliance of the society to the new physical hygiene norms and the parental willingness to send the children to school.
- All efforts should be made to retain the connect of students with the educational system, while the schools are closed. Various modes of remote learning should be blended to reach till the last student.
- Education should be stress free, meaningful and empowering for the present and future adversities.
- Relevant infrastructural changes in the education system, including manpower recruitment and training, need to be urgently addressed.

Among the members, a leader was assigned for each subgroup. S/he collected all the inputs from other members and drafted their part of the guidelines. This draft was circulated in the subgroup inviting opinions and suggestions from other members. Accordingly, all four parts of the guidelines were redrafted by the respective subgroups. All the four parts of the guidelines were then collected and compiled together. These guidelines were then e-mailed to the members of the task force for critical comments. All the comments and suggestions were reviewed and incorporated in the guidelines. Differences of opinion were sorted out by re-referring the scientific studies and consulting experts from the concerned field. These redrafted guidelines were circulated to all the members. A virtual meeting of all the task force members was organised for final discussion. Consensus on all the points was reached by discussion. The final draft of guidelines was written. This final version was circulated to all the members by mail and everyone approved of it.

The task force agreed upon the following guiding principles (***Box* 1**) based on the framework for reopening the schools, jointly given by UNESCO, United Nations Children Fund, World Bank and World Food Programme in June, 2020 [17,18]. The framework of the guidelines is depicted in ***Fig*. 1.**

GUIDELINES

A. When to Reopen the Schools

It has been amply demonstrated by various studies that COVID-19 poses very low risk to the physical health of the children as compared to adults [19]. Many studies are showing that children remain asymptomatic but carry significant viral load and can potentially spread COVID-19 in the general population [20]. Hence, school reopening needs to be considered with utmost care [17, 21]. Looking at the diverse sociocultural conditions and varying COVID-19 epidemiology across India, decision about opening of schools should be taken by the local authorities at the district level [22,23], and not at the national or state level. The following

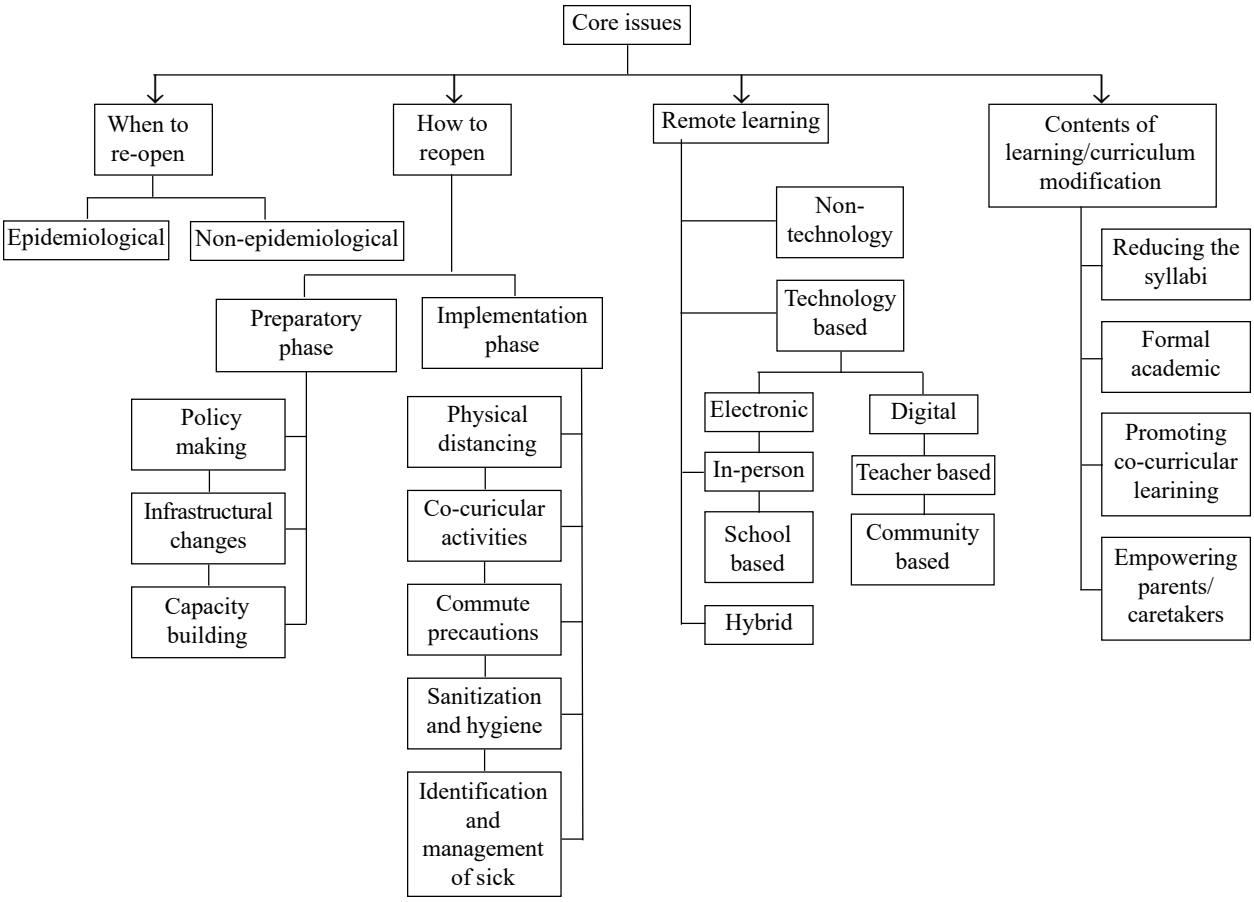

Fig. 1 *Framework for IAP-school reporting guidelines*.

epidemiological parameters should be met with in the district, before the administration declares reopening of the schools [18,24]:

- The number of new cases of COVID-19 detected in the district should be steadily decreasing for the preceding two weeks.
- The case positivity rate should be less than 5 (that is, less than 5% of the total COVID-19 tests performed in the district per day turn out to be positive) for the preceding two weeks [25,26].
- The number of new cases in the district per lakh population per day should be less than 20 in past two weeks.

Schools should be ready with the new norms of the infrastructure, training of the staff and health and hygiene facilities. Schools should have sorted out their timetable, and distributed the students in shifts to facilitate physical distancing [27]. An alliance should have been established between the schools and the local administrative and health authorities to guide, help and support the school staff [28]. The health department should be adequately equipped with enough testing capacity (75%; 59-87% as per the reference study, of the symptomatic contacts to mitigate a second wave), contact tracing, isolation, hospital beds and facilities to fight any eventuality [29].

The awareness drive on physical distancing, masks and sanitization should be ongoing and effective with citizens adequately adhering to these norms. The transport system should be functional. All the aforementioned conditions should be scrupulously reviewed periodically (every two weeks), and the decision to continue the physical schooling should be redressed.

B. How to Reopen the Schools

As per WHO, the school reopening should be undertaken in a stepwise manner starting with policy making, infrastructural changes and manpower training. The process has to be individualized for every school [28,30,31]. Standard operating protocols (SOP) should be in place before the school reopens [32].

I. Preparatory Phase (before the students are called)

Policy making: The school administration should designate responsible staff member(s) to define and execute standard operating protocols, keeping in tandem with the local administration guidelines. The policy should mandatorily include redressing the curriculum, curtailing the school hours, staggering the students and disinfection and hygiene protocols. The school reopening should mainly aim for school connectedness, psychosocial well-being and stress-free learning of the children. Adequate staff including a counsellor and a medical nurse should be recruited. Staff above 60 and those with co-morbidities should be adjusted in work from home mode. The policy of 'Staying home if not well' should be in place for everyone.

Infrastructural changes:

- The entire school premises should be thoroughly cleaned and sanitised. New hygiene rules should be displayed in pictorial and child friendly manner in the premises.
- All the rooms including classrooms, staff rooms, libraries etc. should be airy and well ventilated. Furniture should be arranged with adequate spacing. Reception area should preferably have plexiglass guards.
- Toilet facilities and free flowing potable water should be made amply available.
- A sick room should be identified and kept ready with basic medicines and personal protection equipment.

Capacity building of staff, parents and students: Authentic scientific information regarding COVID-19 (symptoms, physical distancing, proper wearing of a mask, hand sanitization, coughing and sneezing etiquettes, and refraining from touching eyes, nose, mouth and face) should be shared with all staff members and parents and students using mails, telephonic calls, letters, pamphlets etc. All should be well informed about the new standard operating protocols.

The schools should encourage completing the routine vaccination of children and taking influenza vaccine for the staff members and the students. Those suffering from chronic illnesses like diabetes, asthma etc. and those on regular medications should be advised to consult their physicians before resuming the school.

It should be made clear to the staff and teachers that school reopening is mainly for school connectedness, psychosocial well- being and stress-free learning of the children. Schools should try to imbibe a sense of social responsibility required in Covid times, among its staff, parents and students.

II. Implementing Phase

Measures for physical distancing in classroom and beyond:

- School should open in batches with older students joining first. The students should be divided and

called in different batches, in different shifts / alternate days and in staggered times.

- The classrooms should be kept ventilated by opening the doors and windows and air conditioners should be put off. Outdoor spaces like school ground should preferably be utilised to conduct classes.
- A distance of at least 1 meter should be strictly maintained between any two individuals in the school premises. Mingling should be permitted only among the small groups of selected individuals (Bubble class or cohorting). School gates, assemblies, corridors, toilets, libraries, gyms, locker rooms etc. and break times should be strictly monitored to avoid overcrowding.
- Children should bring minimal commodities like stationary, wrist watches, mobiles etc. and be discouraged from sharing the same. Eating during school hours and sharing food/water should be discouraged. Money transfer in lieu of mid-day meal is advisable.
- Visitors should be restricted. Communication with parents should be carried out digitally/postally.

Co-curricular activities: Group activities and team sports, National Cadet Corps (NCC), scouts, cultural and scientific meets etc. should be discouraged. Individually played non-contact games like badminton, athletics etc. and art activities like drawing, painting, dancing, may be allowed ensuring all safety precautions. Swimming pools should not be opened. Vocal singing, flute, mouth organ etc should be discouraged.

Precautions during commute: Respiratory, hand hygiene and physical distancing measures should be adhered during the commute. School buses should be disinfected after every trip, before picking up the new batch of students. The driver and the staff should wear masks and face shields. They should not belong to the high-risk category for COVID-19. Drop and pick up in personal vehicles by parents (and not by elderly/ co morbid care takers) should be encouraged. For older students, bicycles should be encouraged.

Maintaining sanitation and hygiene:

- School buildings and classrooms, gyms, sports centres, toilets etc. should be cleaned and sanitised at regular intervals and in between the two shifts. Places of frequent hand touch like door knobs, desks, benches, switches etc. should be disinfected repeatedly. A record of these activities should be maintained.
- Foot-operated hand sanitisation equipment with 70% alcohol-based sanitizer, foot-operated covered dust beans, soap, water, masks of suitable sizes etc. should be available appropriately and freely, at various places like classrooms, toilets, gyms, sports centres etc. Students and staff should be encouraged to use them frequently.
- Three layered cotton masks should be compulsory for all students, teachers, all school employees and visitors. Mask donning and doping and other mask manners should be thoroughly taught to all staff members and students. Children below five should be assisted and watched carefully (for breathing difficulties) while using mask.
- Spitting should be strictly banned and signage for the same displayed.

Screening and management of the sick:

- Those with body temperature raised beyond 37.3^0C or 99.4^0F or those who report a history of fever or 'feeling feverish' in the previous 24 hours, should be denied entry in the school and referred for medical care. If some student or employee falls ill during schooltime, he/she should be isolated in the sick room having support staff equipped with adequate PPE.
- The testing for COVID-19 should be undertaken in every suspected individual who has attended the school, like one who is suffering from the classical symptoms of fever, cough and breathlessness, a close contact of a positive case, or fitting into any other criteria as per the norms laid down by the local health authority.
- Should a student/staff/visitor be positive SARS-CoV-2, the government authorities should be informed, and (s)he be asked to stay away from school for at least 14 days. Resuming the school should necessitate a fitness certificate from a registered practitioner.
- The school officials should extend full cooperation to the Government protocols like contact tracing, testing, isolation, disinfection etc.
- The school authorities should be liberal and considerate about absenteeism and leaves of their staff and students during Covid times.
- Discrimination against SARS-COV-2 positive staff/ students should be discouraged and they should be dealt with empathy.

C. *Remote Learning Guidelines*

Remote learning, or distant education [33], is a term used for the teaching-learning process wherein students are not

in physical proximity of the teacher as against class-room setting and communicate using different means. The teacher-learner separation is by space or time, or both. Various types of media, both print and technology are used to maintain the communication [34]. Remote Learning could be technology-based or non-technology based. Technology based learning is offered through electronic media like radio and television, or through digital platform as in massive open online courses (MOOCs*),* group or individual digital classes or through (preloaded) gadgets. Non-technology-based learning is offered *via* print media as in correspondence education and external studies.

Depending on the availability of various technological resources (like radiofrequency penetration, DTH (direct to home)/cable connections, internet access) and that of gadgets (like radio set, mobile handset, TV set, computer, laptop, smartphone, preloaded tablets), technology based remote learning can be offered in several options. It could be asynchronous, wherein, a one-way communication from the teacher to the student takes place, or synchronous where learners can participate actively during remote learning [35].

Electronic technology-based learning makes use of basic phone, radio and television systems, and is predominantly asynchronous, whereas digital technology is internet or gadget dependent. Different types of modes using digital technology are either Interactive sessions (using online digital platforms, a virtual classroom with face to face interaction between the teacher and the students, the synchronous learning) or One-way teaching (where pre-recorded sessions reach the students either by sharing the link or preloaded in a tablet, pen drive, social media etc. It could be video, audio message, power point presentation, document etc., the asynchronous learning).

PRAGYATA guidelines of Government of India, vividly describe the various ways of imparting distant education with the help of technology [36]. AAP recommendations on media time can be used to avoid overuse of on-screen teaching and pave a way for blended learning [37,38]. When remote learning is combined with in person learning, it is called hybrid learning.

UNESCO's distance learning strategies in response to COVID-19 school closures [42] and 'crisis-sensitive educational planning', emphasize that all ways and means should be implemented to maintain the continuity of education for each and every child, in the times of complete/partial school closure [39]. The World Bank in its guidance note or remote learning and COVID-19, states that the non- technology based remote learning modes are very beneficial in settings with limited access to technology [40]. Here, print media is used to deliver the contents either by post or other delivery services, and is very pertinent to India.

Hybrid learning: Remote learning and In-Person Learning

All types of remote learning methods should be blended with one another appropriately as and when feasible, to make the learning more adaptable to all types of learners, to break the monotony and to overcome the shortcomings of individual modes of learning. Some scope for in person learning should be always sought after, keeping into account, all safety measures. The guidelines and recommendations for various types of remote learning are listed in ***Box* 2, *Table* I** and ***Table* II.**

D. Content of Learning in COVID Times

This part showcases IAP's advocacy on the nature of formal as well as informal educational contents that should be prioritized for the children in these testing times. Various studies are pointing to the fact that pandemic is causing a lot of stress and psychosocial burden on the children and adolescents [41]. Hence, it is imperative that the academics this year, should be made as stress free as possible. Every attempt should be made

Table I Recommendations on Time Allotment for Screen-based Remote Learning

Standard/class	*Pre-primary*	*1-2*	*3-5*	*6-8*	*9-10*	*11-12*
Screen time per session (min/d)	30	30	30	30 - 45	30 - 45	30 - 45
Maximum sessions per day	1	2	2	3	4	4
Days/wk	3	3	5	5	5	6
Content						
Curricular	-	< 25%	25%	50%	75%	75%
Co-curricular/general	100%	> 75%	75%	50%	25%	25%

All values denote maximum recommended upper limits; presence of parents/adult supervisor is mandatory for pre-primary and those up to 2nd grade; preferable for grade 3-5; and optional for older children; use a judicious mix of synchronous/asynchronous modes of learning; interactive learning is to be preferred.

Box II Guidelines for Remote Learning During the COVID-19 Pandemic

General guidelines

1. The focus should be on developing skill sets such as 'learning to learn' and the curriculum should be adapted suitably.
2. Hybrid and synchronous options should be preferred as far as possible.
3. Special care should be taken to involve marginalized children in remote learning
4. The problems arising out of the new ways of learning should be looked for and dealt with timely.

Non-technology based remote learning

1. This should be mandatorily included in all schools, and for all classes even though the facilities of online classes are available.
2. Learning material should include books, worksheets, hand-outs and practical activity guides (with kits). They should be student friendly, attractive, and easy to follow.
3. These materials could be delivered to and (assignments collected) from the students by post, other delivery systems or could be collected and dropped by parents from the school, taking all the precautions of physical distancing. Teachers should similarly convey their feedback and provide further individualized guidance depending on the evaluation.

Technology-based remote learning

A. Electronic technology-based learning

1. Government should come up with exclusive channels on radio and television and with good bandwidth for smooth dissemination till the remotest places. Local cable networking services should be utilized.
2. Educationists and broadcasters should establish a fair alliance for carrying out the delivery.
3. All pre-recorded available resources in the form of audio, video lessons should be tapped and aligned to cover the curriculum.
4. Interactive telephonic calls or SMS should be used for easy communication and feedback.
5. This mode of learning could be used for a group of students residing in a close community, following all the physical distancing norms.

B. Digital technology-based learning

1. Teachers should be trained periodically and evaluated for delivering the academic contents online in an interesting manner.
2. It should be ensured that the students have access to suitable gadgets, they are supervised and helped in learning digitally. No child should be denied his/her right of education, or de-enrolled from the school, even if (s)he is unable to use this mode of learning.
3. The age-specific norms for duration of use of digital/screen-based media should be followed meticulously (***Table I***). Digital technology-based learning should always be blended with various other modalities.
4. A virtual help desk should be created for students/parents/teachers/school authorities, to enable two-way communication, for smooth implementation of the digital learning.
5. Cyber safety rules should be repeatedly taught to the students.

Guidelines for in-person learning

A. Teacher-based learning

- A teacher takes the responsibility of a group of students, like a mentor.
- The teacher selected for such a job should not be a high-risk person and should preferably be staying in the close vicinity of the allotted (10-15) students.

Continued...

Box continued...

B. Community based learning: *Mohalla* schools

- A motivated willing educated adult should take this responsibility. Qualified youth, or elder students, preferably from the community should be oriented and assigned the job. A school like platform should be created and only a handful of students should be engaged for limited days/time in open spaces like parks, playgrounds etc. following all the safety precautions.
- The teaching-learning process could be carried out in person or using common media resources, public address systems, and digital equipment as feasible.

C. School-based learning

- Schools should provide an opportunity for the students to remain in touch with the teachers and promote school connectedness.
- With prior appointments, students/parents should be able to meet the teachers, following physical distancing norms, and sort out their problems.
- Exchange of learning materials/ assignments, library books should be carried over.

to keep the students connected to the educational system and to mitigate dropouts.

It appears prudent to involve the students in some-thing that is attractive and engaging yet enriching for them. Easing out on formal learning and emphasizing on informal co-curricular learning, is highly likely to prove to be a key to this. Students are more likely to find such contents of learning interesting and easy to follow through. This will increase their chances of continuing in the educational stream and reduce dropouts. The lessons learnt through the informal need-based learning will equip them with abilities to fight their current and future psychosocial issues. Empowering them with age appropriate daily life skills and vocational training, will go a long way in making them competent to face their future productively [43]. This is also in line with the National Education Policy, 2020, of Government of India [13].

I. Reducing the Academic Burden of Formal Learning

- The Educational Boards should undertake 50% trimming of the syllabi for all the subjects of all the classes so that there is stress free and appropriate learning of the designated portion of syllabus while taking care that no part of the core contents of any subject of any class is deleted. The quantity and portion to be cut should be reviewed and readdressed from time to time.
- Revisiting and revising already covered portions from previous academic sessions should be aimed at to get a feeling of ease and accomplishment. New concepts should only be gradually introduced.
- Formal teaching learning should be restricted to graded subjects only, that is the languages, the mathematics and the science. Simple self-learning modules of other subjects should be made available to the students in the print form.
- All teaching should be child centred. Activity based participatory learning and observational learning should be promoted, rather than rote learning. It should stimulate thinking processes, should highlight applied aspects of the contents and give a sense practical utility.
- Due care should be taken to facilitate all types of learners like visual, auditory, tactile etc.
- The students should be evaluated intermittently so as to judge and improve the effectiveness of the new teaching-learning process.

II. Recommendations for Imparting Formal Academic Content

Pre-Primary (3-6 years): Teaching should be totally informal adapting play-way learning through rhymes, songs, dance, short stories, simple activities etc.

- Introduction to colours, shapes, animals, birds, day to day objects and their uses, pairing etc should be given.
- Reading should be introduced step wise after 4 years and pencil holding after 5 years of age. It should be limited to recognition and writing of alphabets and few small words/ two digits numbers.
- The students should be encouraged to assist their parents in the household work/kitchen work under their vigilant supervision.

Table II Age and Stage Specific Guidelines on Suggested Contents of Technology Based Learning

Age groups	*Guidelines*
3-6 y	• Teacher- child connection: video chats, once in a week or fortnight
	• Parent-child interaction- Co-viewing of activities like fun videos, games, phonics, numbers etc.
	• Children to watch and follow: yoga/play etc. (in the prescribed time limits), always co viewed and facilitated by parents
7-8 y (Standards I-II)	*In addition to the above*
	• Introduce formal learning along with co- viewing and explanatory conversations.
	• Parents' capacity building sessions to improve developmental skills and early literacy skills in children in an activity-based manner.
9-11 y (Standards III to V)	*Co-viewing: desirable*
	• Introduce pre-recorded lessons on digital media followed by an interactive time with the teachers.
	• Promoting 'Learning to learn' through various modes of learning.
	• Introducing cyber rules.
	• Encourage to follow ergonomic practices
12-14 y (Standards VI to VIII)	• Encourage independent learning
	• Gradual introduction of new concepts
	• Assignments: online plus paper pencil work
15-18 y (Standards IX to XII)	• Introducing newer modalities of remote learning: searching different search engines, online submissions etc.
	• Encouraging projects related to creative media use, equipping with nuances of technology for wider use

Contents: 3-6 years: Play, story, rhymes, games, cartoons, creative art activities etc; 7-8 years: all the above and music, do it yourself activities, documentaries.

- Exposure to various home commodities, play items, art forms and to nature should be encouraged to promote learning thereof. Development of hand eye coordination and motor skills should be encouraged.
- Parents should actively talk and interact with children to empower them with language and communication skills.

Primary classes – Standards I to V:

- The focus should be to attract them towards formal learning environment and help develop age appropriate skill sets.
- Gross and fine motor skills should be encouraged through activities like play dough, beading, make and break toys etc.
- Early literacy and math skills should be introduced in an activity-based manner. Two letters word writing and calculation of numbers with two digits should be introduced and regular practice should be encouraged.
- Languages and mathematics should only be taught formally using simple colorful picture-based textbooks.

Upper primary – Standards VI to VIII:

- Independent learning should be promoted with emphasis on basic conceptual learning.
- Languages, mathematics and science should be included in formal education through practical/ activity-based approach.
- Basic linguistic skills like use of dictionaries, finding meaning of difficult words, antonyms, synonyms, understanding spellings and pronunciation should be taught in a child friendly manner. Similar strategies should be applied for science and mathematics.
- Regular small assignments should be given to maintain continuity in learning.

Secondary and senior secondary classes: Standards IX to XII :

- Self-dependence and responsible behaviour regarding schoolwork should be promoted in these

senior students. SMART (specific, measurable, achievable, rewarding, time bound) goals should be given.

- They are at the crucial age and stage of learning, hence, hand holding as needed should be done meticulously to see them achieve their educational targets. Every effort should be made to see that they are prepared enough for the coming career formative years.
- The basic core concepts of the three subjects, languages, mathematics and science should be thoroughly undertaken in an online/hybrid/distant learning mode. The learning material should be thoughtfully divided into 'must know', 'need to know' and 'nice to know' topics and subtopics. Teaching should be ensured by priority to the must know portions, to begin with, and need to know, if feasible.
- Projects, models and activity-based submissions should be encouraged to get the practical touch to the knowledge. Literary reviews, essays, articles should be given as assignments.
- Research based work like collecting information from electronic or print media should be assigned.
- Small groups of students should be formed who could stay in touch with one another through gadgets (or in person following physical distancing norms), to help and motivate each other.
- The teachers should be contactable through audio, video calls, mails/e mails, or through interactive radio/TV platforms.
- Laboratories, libraries and in person teaching for practical classes, for tough topics and for solving difficulties could be arranged, following all physical distancing norms.

III. Promoting Co-curricular Learning

More emphasis should be given on imparting various co-curricular skills in age appropriate manner. This will make the children better equipped to face their present and future [44]. Other relevant topics could be added to the options in ***Box* 3** and ***Fig*. 2.**

IV. Empowering the Caretakers

Periodical training sessions of teachers and parents should address on how to help the children during the pandemic and how to identify children with psychological problems. Youth from the community should be trained in giving educational, psychosocial, informational and referral support to students and their families. They could act as one-point service resource for all Covid related daily life problems of the community.

THE WAY FORWARD

The Indian Academy of Pediatrics believes that the holistic and healthy development of children is fundamental for our nation's progress. The present guidelines on school reopening, remote learning and contents of learning are scientifically designed with an idea of helping children along with their caretakers and the society at large, especially keeping in mind the present unprecedented situation. We have tried our level best to answer most of the basic dilemmas related to education of children and the possible prejudices that may be present in the parents' minds given the current situation.

These guidelines are drafted with the sole purpose of helping the policymakers, school authorities, and other stakeholders to take appropriate and justifiable decisions. We have worked hard to ensure that these guidelines will be useful for ministries of central and state governments as well as district authorities to plan their course of action regarding school reopening. Educational boards and societies should also get guidance regarding contents and modes of teaching in the COVID-19 pandemic. The school authorities will find them immensely useful so as to take decisions while framing their new standard operating protocols. Teachers and parents will also get an understanding of how to help children in these testing times.

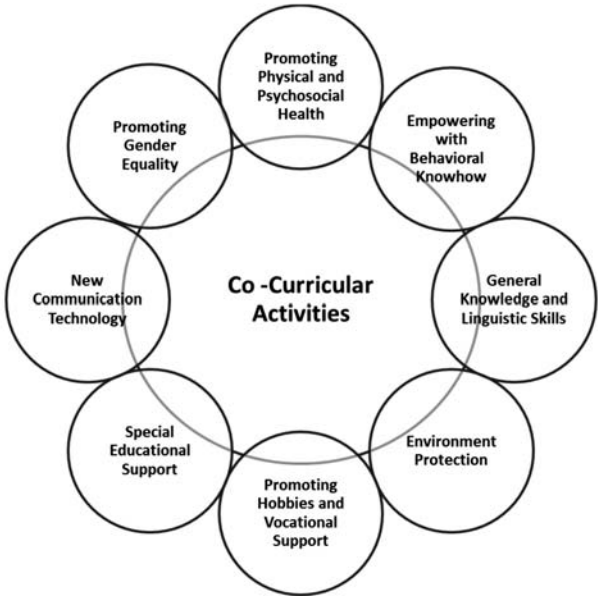

Fig. 2 *Suggested co-curricular activities in the modified curriculum framework.*

Box III List of Suggested Co-curricular Activities and Their Components

Promoting physical health: Health and hygiene, nutrition, healthy lifestyle, COVID-19 related information, first aid, physical training etc.

Promoting psychosocial health: Life skill lessons, self-development, moral science, Social service, art appreciation, yoga, meditation, self -defence, indoor games, art and craft, reading biographies, self- help books

Empowering with behavioural knowhow: Age appropriate activities of daily living, basics of home science, economics, civic rules, road traffic rules, work experience, gardening

General knowledge: Encouraging reading newspaper, encyclopaedia, knowledge bank books etc., watching educational films, documentaries, channels etc

Word power and language building: Use of dictionaries, thesaurus, scrabbles, fictions, writing, learning new languages

Environment protection: Awareness drives, best out of waste activities

Promoting hobbies: General reading, music, dance, drawing, painting, art and craft, poetry, story writing, mono acting and other indoor activities

Imparting vocational support: To adolescents, plumbing, carpentry etc

New communication technology: Practically oriented lessons, learning tools and apps (like play games, chess, number games on free websites), Cyber safety lessons and healthy media usage guidance

Gender equality: Sexuality education, Protection of children from sexual offence (POCSO) act

Development promoting tasks for pre-schoolers: Fine motor skills, Hand eye coordination, balancing etc

Special educational support for children with special needs: Individualised education plan for every child

IAP plans to distribute and disseminate the guidelines nationwide to all these stakeholders. The task force assigned with this job plans to review these guidelines after a period of six months. They will be re-addressed depending on the latest epidemiological conditions and the resultant feedback and gaps that may have been identified during the running of this program.

Contributors: All authors were part of the IAP Task Force on School Reopening and Remote learning that formulated these Guidelines. BJP, GVB, PG and SG: conceived the Guidelines, prepared the agenda, and executed administratively. PG: led the discussions and all the members actively participated. YK, SPV, PRN: contributed extensively on educational and technological angles of the guidelines. SSK and MN; guided on the epidemiological aspects. BJP, RKT, UB, PB, SS, SK, PN, SP, CHS and SG: reviewed the literature. UB, PG, PB, RKT and SG: worked on the survey to generate Indian data on the topic. RKT, PRN, SS, SP, CHS and SG: wrote the first draft of respective sections assigned to them. Review of literature and the first drafts were peer reviewed by PG, PB, SK, YK and SPV. PG, PB, SSK: provided intellectual inputs and overall guidance at every step. BJP, GVB, PG: provided the administrative support from the Indian Academy of Pediatrics and coordinated between the team and executive board members of the Academy. The final document was drafted by SG and RKT; and edited by PG. All authors approved the final recommendations of the guidelines.

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SPECIAL ARTICLE

COVID-19 in Neonates: A Call for Standardized Testing

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The limited evidence on neonatal coronavirus disease (COVID-19) suggests that vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rare, and most neonates seem to acquire the infection postnatally through respiratory droplets and contact. Testing of neonates with perinatal or postnatal exposure to COVID-19 infection plays a vital role in the early diagnosis, management and institution of infection prevention measures thereby cutting off the chain of epidemic transmission. A recently concluded online neonatal COVID-19 conference conducted by the National Neonatology Forum (NNF) of India and a nationwide online survey pointed to substantial variation in neonatal testing strategies. We, herein, summarize the relevant literature about the incidence and outcomes of neonatal COVID-19 and call for a universal and uniform testing strategy for exposed neonates. We anticipate that the testing strategy put forth in this article will facilitate better management and safe infection prevention measures among all units offering neonatal care in the country.

Keywords: *Nucleic acid testing, RT-PCR, Rapid antigen test, SARS-CoV-2.*

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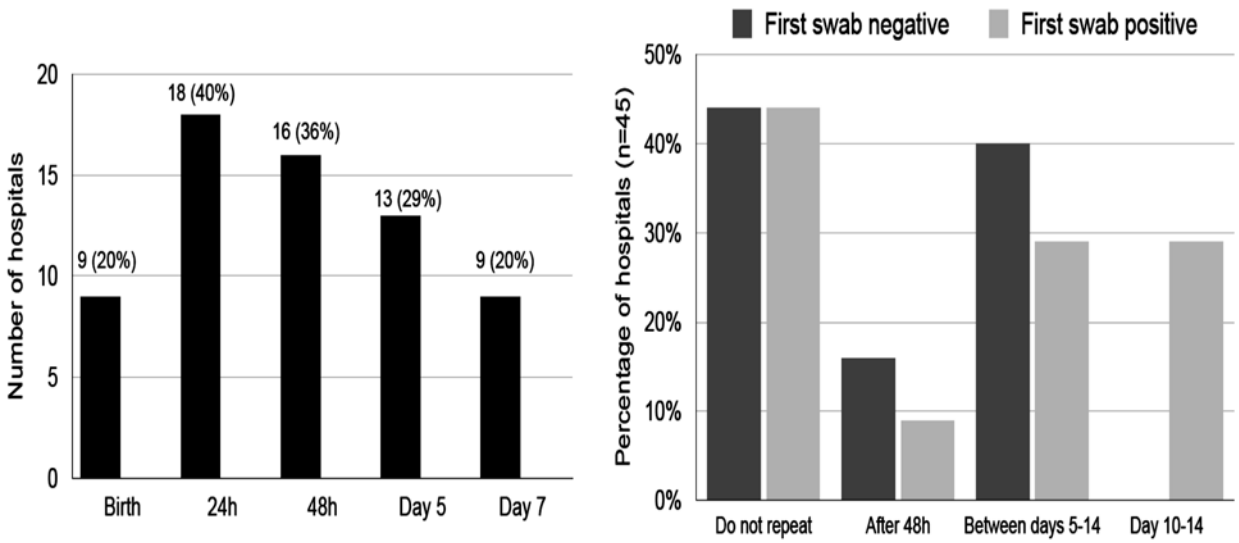
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected over 41 million people globally and has caused more than 1 million deaths [1]. Pediatric cases account for 2-8% of diagnosed coronavirus disease (COVID-19) [2], and three-quarters acquire the disease from an infected family member. While the disease is generally milder in children when compared to adults, a small proportion require hospitalization or intensive care, and there is an increasing recognition of a Multisystem inflammatory syndrome related to COVID-19 illness in children (MIS-C), a severe condition with potential long-term consequences [3,4]. The infection rate in this vulnerable group is increasing [5], and the reported burden is likely an underestimate due to a higher proportion of asymptomatic infections, and lack of standardized testing protocols. Amongst neonates, the risk of vertical transmission is rare and most cases are reported to be acquired horizontally from infected contacts [6]. However, the modes of transmission and the impact of COVID-19 among neonates is less well characterized.

The National Neonatology Forum (NNF) of India in collaboration with Federation of Obstetric and Gynaecological Societies of India (FOGSI), and Indian Academy of Pediatrics (IAP) has published evidence-based recommendations for perinatal-neonatal COVID-19 [7]. In an online NNF COVID-19 conference held on 10 July, 2020, substantial variability in testing strategy for SARS-CoV-2 exposed neonates between centers was evident. Following this, NNF India conducted a cross-sectional nationwide online survey in July-August, 2020 to investigate this variability further. The call for participation was made via email and social media. A total 45 hospitals responded till 20 August, 2020, of which 25 were COVID-designated hospitals. All hospitals tested neonates born to COVID-19 positive mothers once or at multiple time points; 9 (20%) tested neonates at birth, 18 (40%) by 24 hours, 16 (36%) by 48 hours and 49% between days 5-7 (***Fig.*** **1**). While 44% did not do repeat testing, others repeated it after varying time periods irrespective of initial results. The majority (97%) used reverse-transcriptase polymerase chain reaction (RT-PCR) test on oro-nasopharyngeal swab. Among neonates presenting to a health facility with symptoms, 11 (25%) of the hospitals tested all such neonates while others selectively tested based on certain criteria like history of contact, respiratory symptoms or as screening prior to surgery.

Lack of standardized testing protocols has important implications for the management of the neonate, infection prevention and control practices, as well as for



(*a*) Timing of first RT-PCR testing (*b*) Timing of repeat RT-PCR testing

Fig. 1 *Testing strategies adopted by 45 participating hospitals managing neonates with perinatal or postnatal COVID-19 exposure Results of NNF cross-sectional online survey (July-August, 2020).*

understanding disease epidemiology. In this article, we review the available evidence on neonatal SARS-CoV-2 infection and make a case for uniform and universal testing of COVID-19 exposed neonates.

NEONATAL SARS-COV-2 INFECTION

Incidence

Neonates, like infants and children have a lower incidence of SARS-CoV-2 infection. In a systematic review, Dhir, *et al*. [6] reviewed the outcomes of 1141 neonates born to COVID-19 positive women reported in 45 case series. Two-thirds were delivered by cesarean section, a quarter were preterm, and among 1005 (88%) neonates tested, 39 (3.9%) were found to be positive by RT-PCR. In the perinatal COVID-19 registry of the American Academy of Pediatrics, 2962 mother-infant dyads had been enrolled till 29 August 2020 from 264 centers across the United States of America (USA) [8]. In this registry, 2561 (86%) neonates underwent testing by RT-PCR and 45 (1.8%) tested positive for SARS-CoV-2. Two-thirds of the infants were delivered vaginally, and about a half were roomed-in with their mothers, and were breastfed directly or with expressed milk by mothers themselves. Of 26 neonatal deaths in this cohort, none were related to COVID-19. In a large series from Mumbai, India, only 3 out of 131 (2.2%) neonates born to COVID-19 mothers tested positive within 24 hours of birth [9]. These neonates subsequently turned negative when retested on day 5. In this series, 50% of the infants were delivered vaginally and rooming-in and breast-feeding were encouraged. Reports from other national databases have shown a variable risk of perinatal transmission; 2 (4.9%) out of 41 tested from Kuwait [10], 12 (5%) out of 240 tested from the UK Obstetric Surveillance System (UKOSS) [11], 9 (6.1%) out of 147 tested from the Italian Obstetric Surveillance System (ItOSS) [12], 4 (3.3%) of 120 tested from Turkey [13], and 1 (2.7%) of 36 tested (2.7%) from France [14].

Mode of Transmission

SARS-CoV-2 infection can pass from mother to fetus/neonate through trans-placental route or during delivery from exposure to maternal blood or secretions. Post-natally, the infection can be transmitted from infected mother or caregivers through aerosols or direct contact. Initially, with limited information, there was no consensus on the type of samples (maternal and neonatal), and timing and type of testing to categorize if the COVID-19 infection was congenital, or acquired at birth or postnatally. Some experts have put forth classification schema, but none is universally accepted currently [15,16]. Generally, these are complex and mandate serial testing to rule out surface contamination with maternal fluids [15] or additional serological evidence of infection [16]. Broadly, intrauterine transmission can be reasonably confirmed, if the mother has been positive for SARS-CoV-2 within 14 days before or 2 days after birth and, the virus has been detected in amniotic fluid, placental tissue, neonatal blood or respiratory specimens collected within first 12 hours of birth, as well as in repeat neonatal blood or respiratory samples after 24 hours. If

the amniotic fluid, placental tissue and early neonatal samples are negative but subsequent ones after 24 hours are positive, it is likely that the virus was acquired intrapartum or in early postpartum period.

Vivanti, *et al*. [17] made a strong case for transplacental transmission in a neonate who manifested neurological symptoms on day 3 of birth. The authors demonstrated the E and S genes of SARS-Co-V-2 in the maternal blood and amniotic fluid along with high viral load in the placenta and histological evidence of placental inflammation. The nasopharyngeal and rectal swabs of the neonate collected 1 hour after birth, and then repeated on day 3 and 18 were positive for the two SARS-CoV-2 genes [19]. The neonate improved with symptomatic treatment and was discharged home. In another case of a symptomatic neonate whose nasopharyngeal swab was positive by RT-PCR at 24 and 48 hours after birth, SARS-CoV-2 nucleocapsid protein and viral particles were demonstrated in the placental syncytiotrophoblast [18]. The neonate was separated at birth from its COVID-19 positive mother and subsequently recovered. Added to this conundrum is the demonstration of SARS-CoV-19 virus-specific antibodies (IgM and/or IgG) in the neonatal serum despite negative nasopharyngeal swabs in a few cases [19]. While IgG antibodies can passively transfer across the placenta, the presence of IgM is intriguing. Whether the elevation and rapid decline of IgM antibody level noted in the above case represents fetal viremia that had subsequently cleared or signaled a false-positive result due to cross-reactivity with other viruses is a matter of debate.

Breastmilk is unlikely to be a route of transmission. Among 48 milk samples from 32 infected women, only one tested positive for SARS-CoV-2 virus [20]. In two samples produced by a single woman, IgG but not IgM antibodies against SARS CoV 2 were detected. Chambers, *et al*. [21] showed that mere detection of viral RNA does not equate to infectivity, because the viral particles failed to replicate in tissue culture [21]. Recently, secretory antibodies against SARS-CoV-2 were demonstrated in a high proportion of human milk samples from 41 mothers with unknown COVID status during the pandemic [22]. Possibilities include an antibody response secondary to COVID-19 infection or the inherent characteristics of milk antibodies to have cross-reactive and poly-reactive properties against coronavirus and other related viruses. Thus, human milk might have a protective role against COVID-19 illness. In the AAP registry, the risk of COVID-19 infection among neonates isolated at birth (22/1123; 2%) and those roomed-in (21/974; 2.2%) was similar [7]. The data from various national, population-based studies indicate that rooming-in and direct breastfeeding of infants born to mothers with confirmed or suspected SARS-CoV-2 infection do not increase the risk of infection if proper contact and droplet precautions are followed [9,11].

Clinical Manifestations in Infected Neonates

Most neonates born to COVID-19 positive women are asymptomatic and carry only a small risk of acquiring the infection from mother [11,23,24]. However, they are at a higher risk of being born preterm (30%) or by cesarean section (50% or greater) and may require intensive care for management of prematurity and other co-morbidities [6]. The incidence of symptoms in neonates varies as per proportion of preterm deliveries among different case-series and reviews. Among 58 neonates with confirmed SARS-CoV-2 infection, 22% were asymptomatic, 41% presented with respiratory symptoms and 15% with fever [6]. Less common symptoms included poor feeding and lethargy (10%) and gastrointestinal symptoms (9%). The illness manifested beyond 24 hours of age, and most improved with symptomatic treatment. However, 38% (22 of 58 positive neonates) required admission to neonatal unit and 17% required respiratory support. In the AAP registry, 30% of infected neonates (n=43) manifested COVID-19 related symptoms. The duration of hospitalization was also longer in this group compared to COVID-19 negative neonates. Due to the overlap of usual morbidities of preterm and term neonates, it is difficult to tease out the contribution of SARS-CoV-2 infection to the reported symptoms and morbidities. Neonatal deaths due to COVID-related illnesses are uncommon [8,11]. However, follow-up has been reported only till hospital discharge and long-term outcomes are not known.

Infectivity and Risk of Transmission of COVID-19

Viral loads in children who are asymptomatic or have mild illness have been shown to be higher than hospitalized adults with severe disease [25]. Prolonged fecal excretion of SARS-CoV-2 has also been shown in children and could play a significant role in the transmission of COVID-19 disease [25,26]. Infected neonates may pose a higher risk to healthcare providers and family members, especially elderly who come in close contact with them or their excreta during caregiving activities. Face masks are not recommended for infants, and their care inherently requires close and repeated contacts.

TESTING STRATEGY FOR COVID-19

***Web Table* I** provides a list of diagnostic modalities for COVID-19 and their application. The RT-PCR test to detect SARS Co-V-2 viral genome is the preferred diagnostic modality in all age groups, but the test should

be interpreted along with clinical context. When the pre-test probability of COVID-19 infection is high, a single negative RT-PCR test (sensitivity, 70%; specificity, 99%) does not help in ruling out an infection and the test needs to be repeated. Automated RT-PCR systems (CBNAAT or TrueNat) can be used where RTPCR testing is not available or quick turnaround is required *e.g.* emergency surgery. Rapid point of care antigen-based tests (RAT) on respiratory samples may have a role in triaging and rapid diagnosis. However, because of low sensitivity, if index of suspicion is high and test result is negative, confirmatory RT-PCR testing is recommended [27]. Due to fewer numbers of neonatal and pediatric cases, these recommendations are extrapolated from adult data [28].

Optimal Testing Time in Neonates

We examined the data extracted from published reports on neonates born to women with COVID-19 infection maintained by the Cochrane Gynecology and Fertility group [29]. Similar to the findings in the NNF survey, there were variations in the timing of testing. Therefore, the optimal testing time proposed in this article is derived from the knowledge of the viral infectivity and disease course in adults and children, and the testing recommendations by the National COVID-19 task force [27].

In neonates born to COVID-19 mothers, ideally a test should be done as early as possible after birth, within 12 hours (to find out vertical transmission, only for research purpose) and again after 5-10 days (as the initial test may

Table I Suggested Testing Strategy in Neonates Exposed to COVID-19 Infection

Rationale

1. Infected neonates requiring intensive or special care need to be isolated from other neonates
2. Health care workers and other caregivers need to take special precautions and wear appropriate personal protective equipment
3. Family members esp. elderly need to take special measures at home
4. Contributes to better understanding of neonatal SARS-CoV-2 epidemiology

Choice of test

- RT-PCR for SARS-CoV-2
- TruNat/CBNAAT
- Rapid antigen test (RAT) can be used as point of care(POC) test for triaging and rapid diagnosis. However, because of low sensitivity, a negative RAT needs to be confirmed with RT-PCR in symptomatic cases and if index of suspicion is high.

Serologic testing is not recommended to diagnose acute infection in neonates

Samples

- Combined naso-oropharyngeal swab or tracheal samples, if intubated

Interpretation of positive test

A positive result by RTPCR or TrueNat/CBNAAT or RAT is confirmatory

Scenario	*Timing of test*	*Repeat testing after initial negative test*
Suspected perinatal transmission Mother with COVID-19 infection detected within 14 d before or within 2 d after delivery	At birth or as soon as possible within 12 h of birth. Rooming-in should not be postponed if testing is delayed.	If the first test is negative, a repeat test is recommended after 5-10 d of birth. Test earlier if neonate becomes symptomatic.
History of exposure to COVID-19 positive persons (including mother or family member or healthcare provider)	Asymptomatic high-risk contacts to be tested once between day 5 and day 10 of coming into contact. If symptomatic- see below	If symptoms develop following a negative RAT test, a repeat testing by RT-PCR or RAT should be done.
Symptomatic neonates (irrespective of history of exposure) with onset at or beyond 48 h of life and presenting with acute respiratory (respiratory distress or apnea with or without cough, with or without fever) or sepsis like illness (fever, lethargy, poor feeding, seizures or diarrhea).	At the time of first evaluation	If negative, repeat the test in 24-48h if the index of suspicion is high. If positive, repeat the test only in severe illness. No re-testing is recommended prior to discharge from a COVID-19 facility after clinical recovery including transfer from a COVID facility to a non-COVID facility.

CBNAAT: Cartridge-based nucleic acid amplification test; COVID-19: Novel Corona virus disease; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-Co-V-2: Severe acute respiratory syndrome coronavirus 2; TruNat: Chip-based RT-PCR test.

have false negatives and mother-infant dyad are generally roomed-in). However, for those neonates who are asymptomatic and otherwise fit to be discharged, the test can be scheduled as a pre-discharge sample at 24-72 hours of age (to avoid delay in discharge and missing sampling). Centers for Disease Control and Prevention, USA has also given similar guidelines [30]. The family should be advised to report to the nearest health facility for a repeat test if the neonate develops any symptoms or signs. In symptomatic neonates reporting to emergency, the test should be done at presentation. Based on the available evidence on neonatal SARS-CoV-2 transmission and the recommendations put forth by the National Task Force on COVID-19, we propose a testing strategy that is applicable for India in ***Table* I**.

CONCLUSION

Although data on the incidence and outcomes of neonatal SARS-CoV-2 infection continue to emerge, there is much more to be learned. The evidence so far suggests that vertical transmission is uncommon and a greater proportion acquire infection postnatally through respi-ratory droplets or contact with infected mother or care-givers. Majority of neonates do not develop symptoms due to SARS-CoV-2 but the morbidities related to prematurity may necessitate intensive care and support. All neonates born to mothers with suspected or confirmed COVID-19 infection, regardless of presence of symp-toms should be tested. The awareness about neonatal COVID status promotes opportunities to implement infection prevention and control measures. Cases missed through lack of clinical suspicion or under-testing may facilitate the transmission of SARS-CoV-2 infection because asymptomatic infected neonates may serve as reservoirs of infection.

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Web Table I Diagnostic Characteristics of Tests Used for SARS-CoV-2 Infection

Test	*Method and requirements*	*Diagnostic characteristics*	*Advantages/disadvantages*	*Reasons for false negative test*	*Application*
Real time reverse transcriptase PCR (RT-PCR)	Detects viral genome using approved primers. Needs specialized laboratory and biosafety precautions.	Gold standard test. Good analytical sensitivity (detects even few copies of viral genome) but sensitivity [30] in the clinical setting is around 70% and specificity 99%.	Pros: Gold standard; can process up to 90 samples in a single run Cons: Turnaround time is 4-5 hours and may be longer if test is run in batches/samples need to be transported to laboratory	Swab taken early in the course of illness, improper collection of sample and samples with lower viral load (oropharyngeal swab) or laboratory errors	Diagnosing a current infection
Nucleic acid amplification tests	Detects viral RNA but does not utilize the conventional PCR technique. It is an automated cartridge-based system. Example: TrueNat and CBNAAT test.	82-97% sensitivity [31] (depends on test kit).	Pros: Widely available; Quick turnaround time (30 -60 min); Less biosafety hazard. Cons: Limited samples (less than 50) can be tested in a day; Equipment, reagents, and expertise needed; Swabs must be taken correctly and transported in viral transport medium	Same as RT-PCR	Rapid test to rule-in COVID-19 but a single negative test cannot be used to rule out infection especially in samples with lower viral loads.
Rapid point-of care (PoC) antigen detection test	Example: Standard Q COVID-19 Ag kit	Moderate sensitivity but high specificity	Pros: Does not require a specialized machine and can be interpreted with the naked eye Cons: Need to be validated before being approved for use	Lower sensitivity than RT-PCR as there is no amplification of the viral nucleic acid	Testing in the containment zones as well as hospitals in combination with the gold standard RT-PCR test. All symptomatic negative patients should be essentially tested with a RT-PCR test for COVID-19
Serological tests (IgM and IgG antibodies) [32]	Point of care tests: Qualitative detection and differentiation of IgM and IgG antibodies to SARS CoV-2 within 15-20 min	Sensitivity 85-99% Specificity 85-100%	IgG becomes detectable 3 days after symptom onset or at least 7-10 days after infection and lasts several months. IgM is detected earlier but wanes rapidly	Testing early in the course of illness. Asymptomatic and milder infections may have a lower level of antibodies	IgG based assays are currently recommended only for serological surveillance and not for diagnosis

CBNAAT: Cartridge-based nucleic acid amplification test; COVID-19: Novel Corona virus disease; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TruNat: Chip-based RT-PCR test.

What Is New in the Management of Childhood Tuberculosis in 2020?

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The Government of India has developed a National Strategic Plan for tuberculosis (TB) elimination by 2025, five years ahead of the global target set by the World Health Organization (WHO). For achieving these targets there has been a paradigm shift in the diagnostic and treatment strategies of TB at all ages. This update summarizes the specific changes in pediatric TB management in light of the guidelines developed by National Tuberculosis Elimination Program and Indian of Academy of Pediatrics.

Keywords: *Diagnosis, End TB strategy, National strategic plan, National Tuberculosis Elimination Program.*

World Health Organization (WHO) announced the End TB strategy with the target of reducing tuberculosis (TB) deaths by 90% and 95%, and, incidence by 80% and 90%, by 2030 and 2035, respectively [1]. However, Government of India has decided to aim TB elimination from our country by 2025, ahead of the global target [2]. Childhood TB is an important area of intervention while drawing the road-map to end TB. National Tuberculosis Elimination Program (NTEP) and Indian of Academy of Pediatrics (IAP) have partnered to develop updated guidelines and training program for management of childhood TB in the country. The salient updates are detailed below.

NEW PARADIGM OF TB DIAGNOSIS

There is a paradigm shift in diagnostic strategy from conventional smear microscopy to molecular methods of diagnosis due to their higher sensitivity. NTEP approved rapid nucleic acid amplification tests (NAAT) like Xpert Rif/Truenat have made it possible to detect *Mycobacterium tuberculosis* (MTb) with much higher sensitivity as compared to smear and rapidity than culture. The testing turnaround time for rapid NAAT is 2 hours. These tests are also nested for establishing rifampicin resistance - a surrogate for multi-drug resistant (MDR) TB.

In addition, NTEP also recommends Line probe assays (LPA) – which are multiplex NAAT- to test for resistance to rifampicin, isoniazid and other second line drugs (flouroquinolones and second line injectables). Unlike rapid NAAT, LPA due to its relatively lower sensitivity can be used directly only in smear positive specimens or else after isolating MTb on culture, and has a turnaround time of 3-4 days.

So, TB diagnostics have now graduated to upfront testing every likely patient for presence of MTb as well as rifampicin resistance under the strategy called universal drug sensitivity testing (U-DST) [3].

How Does It Impact the Diagnosis of TB in Children?

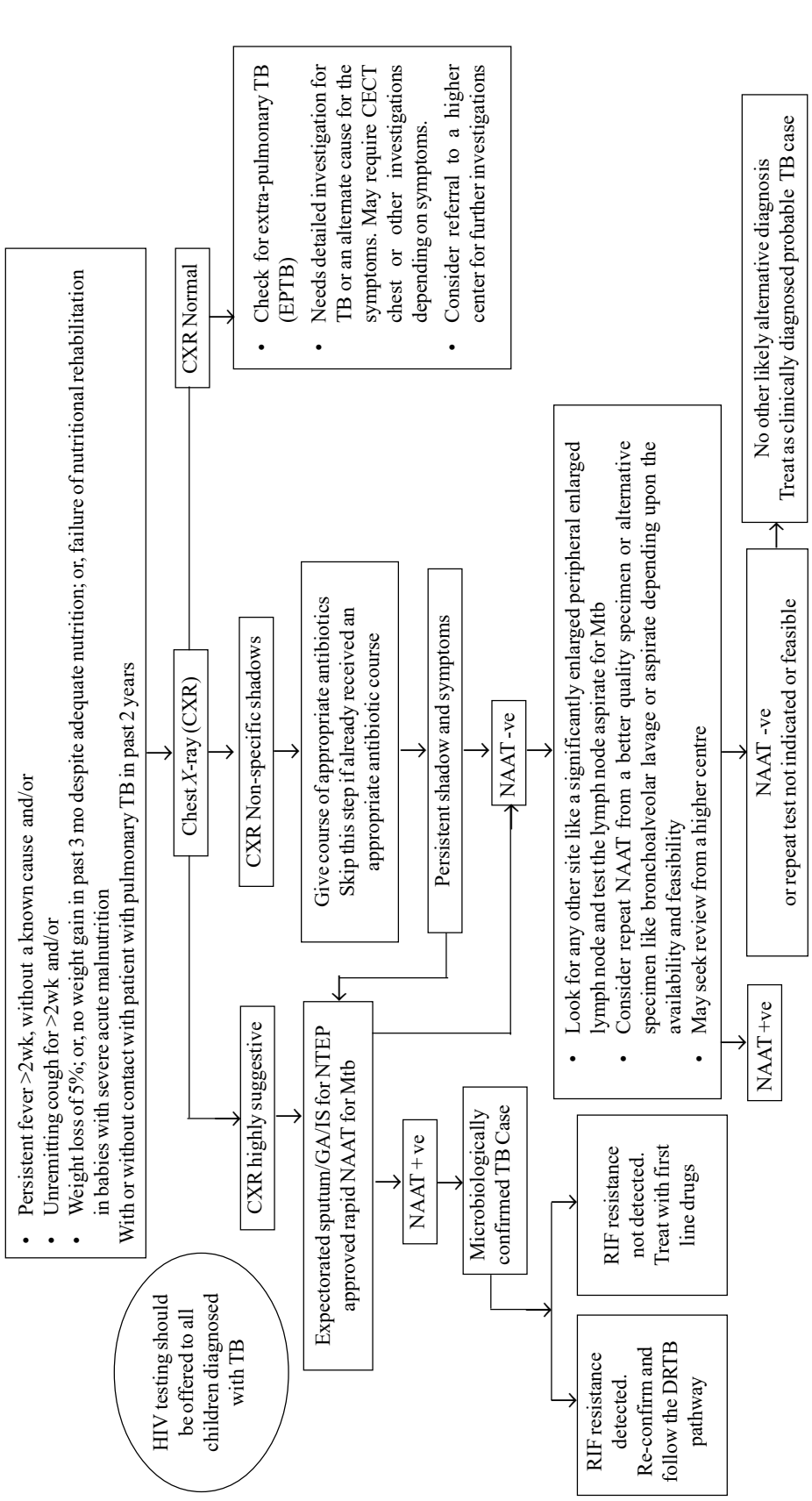
Conventional TB diagnostics for children involved appropriate use of clinical details, chest radiology and tuberculin skin test, with much less focus on microbiology, due to poor yield (AFB smear) or access issues (MTb cultures). U-DST strategy has led to change in the diagnostic pathways to include NAAT for every patient where a biological specimen can be procured. Routine chest imaging is done as initial screening test as testing of respiratory specimens from radiologically positive cases improves the yield of NAAT [4,5].

While NAAT has higher sensitivity than the smear, yet it fails in many paucibacillary cases. It is good only as a 'rule in' test and a negative NAAT does not rule out TB. The conventional methods of clinical diagnosis still need to be relied upon among those who are not confirmed by molecular tests. Current algorithm for evaluation of a child with pulmonary TB is shown in ***Fig.* 1**.

MANAGEMENT OF CHILDHOOD TB

What Is New in Treatment?

Treatment of TB has also evolved from erstwhile standard regimens based on the likely risk of drug resistance (new *versus* retreatment cases) to regimens based on identification of key resistance. The evidence available earlier in 70s suggested that the retreatment cases could be treated with a simpler 5 drug category II



Chest X-ray shall be done upfront in cases who are suspected to have TB but if a recent good quality chest X-ray is available, it need not be repeated. Highly suggestive chest X-ray refers to miliary shadows, or lymphadenopathy (hilar or mediastinal), or chronic fibro-cavitary parenchymal lesions; Non-specific chest X-ray: refer to patterns other than highly suggestive like consolidations, in-homogenous shadows or bronchopneumonia, etc.; NTEP approved NAAT shall be preferred over smear examination in all children. Available NTEP approved NAAT include Xpert Rif™, TrueNat™ and Line probe assay – If a specimen is positive by any of these methods, the case is labelled as microbiologically confirmed TB; At the initial step, if self-expectorated sputum is available and imaging /NTEP approved NAAT test is not available or delayed, smear may be done (for ease of availability and low cost); Whenever smear is used for diagnosis at least 2 samples should be tested while a single sample is sufficient for more sensitive NTEP approved NAAT; If a specimen is negative by NTEP approved NAAT (or smear), the second aliquot or a fresh good quality specimen should be submitted for a repeat NAAT and liquid culture; In case of Rif resistance is detected on NAAT, in a new case without any risk factors, a reconfirmation is desirable; Antibiotics of choice include amoxycillin or co-amoxyclav: Antibiotics like Linezolid or anyfluoroquinolone should not be used as they have anti-TB action; in case antibiotic trial has already been given in adequate dose and duration, it may not be repeated; Clinically-diagnosed probable TB case : Is a patient with a high clinical suspicion for TB disease based on suggestive symptoms, radiology and often supportive circumstances (history of exposure to a TB case) or evidence of infection (positive skin test for TB or positive IGRA) BUT the rapid microbiological tests are negative. Such a case may be treated as clinically diagnosed patient provided common alternative diagnoses have been ruled out. Where facilities exist, send one aliquot of the specimen for liquid culture, if the NAAT is negative for MTb.

DRTB: Drug resistant TB; GA: Gastric aspirate, NAAT-Rapid nucleic acid amplification test; NTEP: National tuberculosis elimination program.

Fig. 1 *Algorithm for pediatric intrathoracic tuberculosis (TB) among children with no risk factors for drug resistance.*

regimen. However, post implementation operational research and meta-analysis showed that this strategy was associated with increased risk of treatment failure with amplification of resistance to other companion drugs, particularly, if the patient was initially harboring rifampicin resistance [3,6]. With the feasibility of upfront rapid testing for rifampicin resistance, use of standard regimens without sensitivity testing is no more recommended for both the new as well as retreatment cases.

Likewise, the non-responders to initial regimen for drug sensitive TB (by 4 weeks) should be assessed again for presence of drug resistance (rifampicin and isoniazid at least). Non responsive cases with resistance to rifampicin and/or isoniazid are also tested for resistance to second line drugs like fluoroquinolones and the injectable aminoglycosides to provide the most suited regimens depending on the resistance pattern. The effort is to manage the cases as per the sensitivity to key drugs, thus improving outcomes and preventing further amplification of drug resistance. Retreatment cases with-out rifampicin resistance are now treated again with initial 4 drug regime while being tested for isoniazid resistance. In case of isoniazid (mono- or poly-) resistance, 6 month uniphasic 4 drug regime, where isoniazid is replaced by levofloxacin, is recommended. The IAP NTEP 2020 TB treatment guidelines are shown in ***Table* I** and **II**. The algorithm for evaluation of children with suspected drug resistance is shown in ***Fig.* 2**.

What Else Is New in Management?

NTEP has introduced daily therapy with dispersible tablets in fixed dose combinations (FDC) for children.

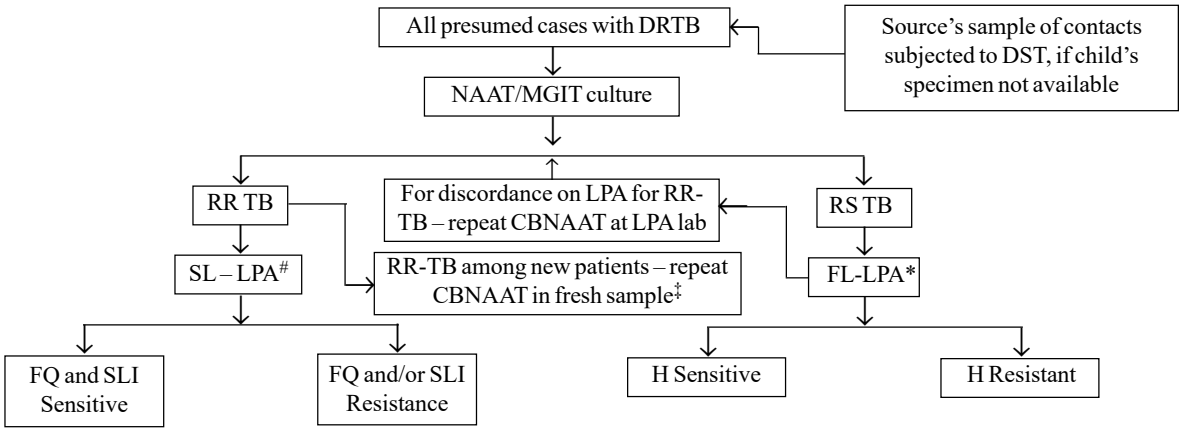
Table I Drug Regimen for Rifampicin-Sensitive Tuber-culosis as per IAP-NTEP Guidelines, 2020

*Type of patient**	*Regimens*
New microbiologically confirmed pulmonary TB	2HRZE+
New clinically diagnosed pulmonary TB	4HRE[#]
New microbiologically confirmed extra-pulmonary TB	
New clinically diagnosed extra-pulmonary TB	
Previously treated TB ^(recurrence, treatment after loss to follow up, treatment after failure)	

*H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; *Molecular testing for rifampicin resistance shall be done in all new cases in children with suspected TB at diagnosis; [#]In case of neurological, bone, joints and spinal TB the continuation phase is extended to 10 months. In disseminated forms, the continuation phase might be extended to 7 months; ^All retreatment cases are to be evaluated as per DR-TB Algorithm. They were earlier treated with CAT II or retreatment regimen, which is now withdrawn. Their treatment should be based on drug sensitivity, particularly for R and I. In case they are found to be drug sensitive, they shall be started on the above regimen as for a new case.*

Younger children get 3-drug FDCs (HRZ) along with 100 mg ethambutol tablets. Older children can also get, in addition, 4-drug FDCs (RHZE) to meet their drug dosages (***Table* III**). Isoniazid and rifampicin are in a ratio of 2:3 and the average dose of isoniazid is around 10 mg/kg/day. These drugs are given free of cost in public sector and the private sector can also access these drugs for free through various partnership schemes that the program offers.

Experts now also recommend addition of pyridoxine (10 mg/day) with isoniazid containing regimens because of the risk of peripheral neuropathy due to higher dosages



**First Line LPA (FL-LPA) may be done directly if smear positive; else, send for MGIT followed by FL-LPA to evaluate for R and H resistance; [#] Second Line LPA (SL-LPA) may be done directly if smear positive; else, send for MGIT followed by SL-LPA or Liquid culture DST (Mfx 2.0, Km, Cm, Lzd); [‡]If Rifampicin Resistant on repeat test, DRTB regimen is initiated; If repeat test shows Rifampicin resistance not detected or If result is unavailable, DSTB regimen is initiated.*

Fig. 2 *Algorithm for evaluation of children with suspected drug resistant tuberculosis (DR TB).*

Table II Drug Regimen for Pediatric Drug-Resistant Tuberculosis as per IAP NTEP Guidelines, 2020

Type of tuberculosis	*Treatment regimen*	*Special considerations*
RR/MDR-TB without additional drug resistance to FQ and/or SLI* (Conventional Short Regimen – Initial regime for pulmonary TB & isolated pleural effusion or lymph node TB)	*Intensive phase* (4-6) Mfx^h Km Eto Cfz Z H^h E *Continuation phase* (5) Mfx^h Cfz Z E	• Recommended for pulmonary cases or non severe forms of EPTB like isolated lymph node disease or pleural effusion, etc. • Not exposed to reserve drugs • Send tests for SLI and FQ class resistance, continue this regimen only if sensitive to these two drug classes
MDR TB / MDR TB + FQ resistance / XDR – TB#, $, ‡ (All oral regime for children above 6 y)	*Intensive phase* 6-8 Dlm (Bdq) Lfx (Mfx^h) Lzd Cfz Cs *Continuation phase* 12 Lfx (Mfx^h) Lzd (l) Cfz Cs	• Not for severe EPTB like intracranial TB or disseminated TB • Not for children <6 y • Bdq to be replaced by Dlm in 6-17y age • Lfx to be replaced by Mfx^h if FQ class resistance
MDR TB(EP)/ Or MDR TB + FQ resistance/XDR - TB And Not eligible for all oral regime above	*Intensive phase* (6-9) Amika Mfx^h Lzd Cfz Eto Cs *Continuation phase* (18) Mfx^h Lzd (l) Cfz Cs	Disseminated or severe extra-pulmonary disease
Resistance to INH (with or without any non-rifampicin first line drug resistance) ^	*Uniphasic regime* (6) Lfx R E Z	Can be extended to 9-12 mo in extensive pulmonary disease and extrapulmonary disease like bone or intracranial

*RR: Rifampicin resistant; MDR: Multidrug resistant; XDR: Extensively drug resistant; EPTB: Extrapulmonary TB; FQ: Flouroquinolones; SLI: Second line injectables; Mfxh: High dose moxifloxacin; Km: Kanamycin; Eto: Ethionamide; Cfz: Clofazimine; Z: Pyrazinamide; Hh: High dose isoniazid; E: Ethambutol; Dlm: Delaminid; Bdq: Bedaquline; Lzd: Linezolid; Cs: Cycloserine; Lfx: Levofloxacin; *Shorter MDR TB regimen is of 9-11 mo with 4-6 mo of IP containing injectables and 5 months of CP. If the IP is prolonged, the injectable is only given three times a week in the extended intensive phase; #All oral longer MDR TB regimen is of 18-20 months; $New drugs like Bdq and Dlm would be given for 6 months duration while the dose of Lzd will be tapered to 10mg/kg/d (max 300 mg) after the initial 6-8 mo of treatment; ‡This regimen will also be used for treatment of XDR TB patients with 20 mo duration; ^All oral H mono/poly DR TB regimen is of 6 mo with no separate IP/CP.*

of isoniazid and high prevalence of malnutrition amongst the affected.

Table III Tuberculosis Drug Formulations and Dosages for Children As per IAP NTEP Guidelines, 2020

Weight band (kg)	*Dose from 0-18 y**
4-7	1P + 1E
8-11	2P + 2E
12-15	3P + 3E
16-24	4P + 4E
25-29	3P+3E+1A
30-39	2P+2E+2A

*H-Isoniazid, R-Rifampicin; Z-Pyrazinamide, E-Ethambutol; *number preceding the letter denotes number of pediatric or adult formulations; IAP: Indian Academy of Pediatrics; NTEP: National Tuberculosis Elimination Program; Pediatric formulation (P) H50, R75, Z150 + E 100 (E separate tab); adult formulation (A) H75, R150, Z400, E275; Children (aged 0-18 y) upto the weight of 39 kg should be managed as per this table; children (aged 0-18 y) ≥40 kg would be managed as per the various weight bands described for adults.*

Current Status of Preventive Treatment

Goal to eliminate TB cannot be achieved timely unless the pool of cases with latent infection is treated. TB preventive treatment may now be extended to all household contacts of an infectious case after ruling out disease by symptom screening in line with WHO guidance. For children above 5 years, if facilities exist, one may test for presence of latent infection and then treat. But it is not mandatory to test for infection due to lack of simple and affordable point of care tests. TB preventive treatment is also recommended for any tuberculin skin test positive child who is receiving immunosuppressive therapy (children with nephrotic syndrome, acute leukemia, *etc.*), and a child born to mother who was diagnosed to have TB in pregnancy but has no evidence of disease [7].

Isoniazid is recommended for TB preventive treatment at a dose of 10 mg/kg/day for six months. No drugs are currently recommended for TB preventive therapy for the contacts of MDR TB cases but a close follow up for two years after exposure is recommended for timely

identification of those developing disease among exposed [8].

To conclude, the management of TB in children now has undergone a sea change with drug sensitivity directed therapy becoming the corner pillar. NTEP approved rapid NAAT has become the core investigative modality and erstwhile clinic-radiological approach of diagnosis is used only when NAAT fails in a clinically probable case. The pediatricians need also to be aware of the updated guidelines detailing change in regimens and drug dosages so that they can rationally manage TB among children.

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Parental Perspectives on Remote Learning and School Reopening

We conducted this online survey to assess the parental perspectives on remote learning, the associated stress, and school reopening during the COVID-19 pandemic. Of 2694 responses, 2032 (75.4%) parents perceived remote learning to be stressful for the child and 1902 (70.6%) for the family. The mean (SD) duration of remote learning was 3.2 (2.1) hours/day and 5.3 (1.0) days/week. Parents from 1637 (61.7%) families reported headaches and eye strain in children. Starting regular school was not acceptable to 1946 (72.2%) parents.

Keywords: *Covid 19, Education, Online, Pandemic, Stress.*

Worldwide more than 1.6 billion children in 191 countries were affected by school closures due to the ongoing coronavirus disease 19 (COVID-19) pandemic [1]. Most countries including India, limited the disruption in education by shifting to remote learning. With re-opening in full flow, when to reopen the schools is under increasing focus, we conducted this survey to assess parental perspectives on remote learning as an acceptable tool for learning, the stress perceived by them on the child and the family, and their willingness regarding school reopening.

We designed and disseminated a questionnaire on Google Forms, to the teacher groups associated with the Indian Academy of Pediatrics, with a request to share it with the parent groups. Parents across India, whose children were receiving remote learning and who agreed to participate were included. Parents of children with special educational needs were excluded. The responses were received between 17-31 July, 2020. Information was obtained about the type of school and class of the child, remote learning mode, the source used, and duration of remote learning in hours per day and days per week. Parental perception of stress due to remote learning was also collected. Any physical or psychological problem developed during the period, and their willingness to send children to the school, if it reopens, were also collected.

Out of the 2694 respondents, 2383 (88.5%) were from urban areas; 2444 (90.7%) were attending private schools. The source of remote learning was a mobile phone in 1697 (63%). An interactive, live video class was attended by 2171 (80.6%) children. The mean (SD) duration of remote learning was 3.2 (2.1) hours per day and 5.3 (1.0) days per week. The advantages of remote learning (multiple responses allowed) were listed as: safe in the pandemic (89.9%), helps to maintain connect with school (61.6%), not losing out in studies (63.1%), and no need to travel (38.7%). The disadvantages were listed as: causes headache and eye strain (61.7%), does not feel like a real class (60.4%), no physical activity involved (59.5%), hard to maintain concentration (57.1%), needs home environment adjustments (40.8%), and an extra financial burden (30.3%).

Remote learning was perceived to be stressful for the child by 2032 (75.4%) parents while 1902 (70.6%) felt it is stressful for the family. The problems which children developed: eye problems (44.8%), irritability and behavioural issues (42.7%), disturbed sleep (41.8%), headache (34.8%), weight gain (32.5%), decreased appetite (16.7%), bodyache (13.7%) and change in bowel habit (12.7%). Overall, 1946 (72.2%) parents were not ready for school reopening soon.

Similar to a previous survey from US [2] reporting 56% of parents complaining about the affection of the emotional well-being of their children and 52% of the family; parents in this study perceived stress badly. We found the duration of remote learning was higher than that suggested in the PRAGAYTA guidelines and could be an important source of stress not only to the child but also the family (***Table* I**). It may lead to prolonged screen time, increased demand, and sharing of devices and data among the family members.

In June, 2020, a survey [4] showed that 86% of parents believed schools should be opened only; when there would be no new cases for 21 days, or a vaccine has already been introduced. The proportion of parents against the reopening of school may be declining, yet 72% of parents of our study still don't want to send their children to school. This suggests that parents might be getting adjusted to the situation or accepting the situation as the new normal. It has been indicated that COVID-19 illness is less severe in children [5], but the effect of school reopening on children and the community is yet to be seen practically in our country.

Our study had several limitations. Respondents were mainly city-dwellers, and educated parents whose children are studying in private schools offering online remote learning. We did not collect information on additional private tuition/ coaching classes. Perceptions of older children and adolescents would have provided a more comprehensive picture but was not collected. Despite these, we conclude that majority of parents were not ready to send their children to school till the risk of COVID-19 pandemic abates in the country. As most of the remote learning is being conducted on-screen, newer methods need to be explored that do not involve prolonged screen hours.

Ethics clearance: Institutional ethics committee of Hind Institute of Medical Sciences; IEC/IRB No. HIMS/IRB/2020-21/1094, dated July 16, 2020.
Contributors: SG, UB: conceptualized the study; UB, SG, PG: devised the methodology and wrote the protocol; UB, SG, PB, RKT: collected data and reviewed the literature. PG, UB: analyzed the data. UB with RKT and PB wrote the first draft. Final manuscript was edited by PG and SG. All authors approved the final manuscript.
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Table I Remote Learning Duration Frequency in Different Grades (*N*=2694)

Grades	*N*	*Duration h/d*	*Frequency d/wk*
Pre-primary (<6y)	210	1.7 (1.6)	4.7 (1.3)
Primary (Grades I-V)	113	2.7 (2.0)	5.1 (1.1)
Upper primary (Grades VI-VIII)	590	3.6 (1.7)	5.4 (1.0)
Secondary (Grades IX-X)	498	4.1 (2.3)	5.6 (1.0)
Higher secondary (Grades XI-XII)	266	4.3 (2.0)	5.5 (1.0)

All values in mean (SD); Maximum duration as per Pragyata [3] guidelines (h/d); Pre-primary – 0.5, primary and upper primary – 1-1.5; secondary and above – 2-3.

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Comparison of Domiciliary and Hospital-Measured Temperature Amongst Febrile Infants Presenting to an Emergency Department

Childhood fever is one of the commonest reason for medical consultation in children, being responsible for 15-25% visits in primary care, and also presentations to the emergency departments (ED) [1,2], and is known to cause significant anxiety in parents [3]. Most children undergo evaluation for at least one febrile illness before their third birthday [4]. Western studies report good parental awareness about fever [5], but studies from India [6,7] have shown conflicting results. Frequently, parents do not document temperature or record it improperly, leading to undue anxiety and over-crowding of the ED [6-8]. We studied the correlation of temperatures measured at home by parents with recordings done at presentation in the ED among infants with acute illnesses.

This cross-sectional study was conducted from April, 2018 to January, 2019 at the pediatric ED of a public hospital in northern India, after taking clearance from the Institutional Ethics Committee. Febrile children aged 3 month to 2 year, with fever of at least 4 days were considered for enrollment. A febrile child was defined as one with history of fever e"38ÚC recorded at least once at home in previous 24 hours. Those suffering for fever for >7 days, children with any underlying heart disease, and children with any diagnosed immunodeficiency disorder or conditions predisposing to recurrent infections (like type 1 diabetes, vesico-ureteric reflux) were excluded. Consecutive children were enrolled on one pre-decided day every week.

After taking written informed consent, enrolled children were evaluated clinically and initial management provided. Subsequently, based on history, and clinical and laboratory information, they were treated as inpatient or outpatient. For all enrolled children, demographic details, contact information and details of education and income of parents were collected. History was taken regarding highest temperature recorded at home and any associated symptoms, treatment taken if any before presentation, relevant history of co-morbidities, immunization and feeding history. Anthropometric measurements were taken for all included children as per standard guidelines, and Z-scores were calculated using Anthrocalc application.

All the data were recorded in a structured pre-tested form. Rectal temperature was taken at presentation for all enrolled children, The various diagnoses were made and management carried out according to the departmental protocols guided by standard management guidelines [9,10]. Mean (SD) or median (IQR) were calculated for the baseline characteristics. Pearson

correlation coefficient was calculated for temperature documented at home and in the ED. Comparisons were done between children with fever documented in ED, and those without fever documented in ED.

Out of overall study population of 150 children with history of fever of 4-7 days in respective age group attending ED, only 108 (68.3% boys) had documented fever at home. The median (IQR) age of the study population was 12 (3-20) months. The median Z scores for all anthropometric variables (weight, length and head circumference) were greater than –3. Majority (88%) of children belonged to the lower middle (III) and upper lower (IV) socioeconomic classes, and majority of mothers (62%) had at least secondary school education (***Table* I**). Along with fever, the most common presenting complaint was respiratory problems.

Of the children for whom fever was documented at home, nearly half (46.3%) did not have fever at presentation in the ED. Mean (SD) temperatures documented at home and ED were [38.8 (0.16)°C *vs* 39 (0.7)°C; *P*=0.03]. Among those who were febrile in ED, the correlation coefficient (*r*) of fever documented at home and in ED was 0.3 (95% CI, 0 to 0.6), suggesting a weak correlation of axillary fever documented by parents at home and that of rectal temperature documented in ED (***Fig.* I**).

For five children, rectal temperature could not be documented in view of their critical condition at presentation to ED, and axillary temperature was documented in them so as not to hinder required resuscitative measures. Of the illiterate mothers, 42% did not document the fever as compared to 205 of those with a secondary school education (*P*=0.02). There was

Table I. Baseline Characteristics of the Study Population (*N*=108)

Characteristics	*No. (%)*
Weight, Z-score[#]	-2.05 (4.62)
Height, Z-score[#]	-1.525 (2.57)
HC, Z-score[#]	-1.66 (1.64)
I*mmunization status*[a]	
Partially immunized	9 (8.3)
Fully immunized	78 (72.2)
Socioeconomic status[b]	
Upper middle class	13 (12)
Lower middle class	51 (47.2)
Upper lower class	42 (38.8)
Lower class	2 (1.9)
Maternal education	
Illiterate	24 (22.2)
Primary school	17 (15.7)
Secondary school	56 (51.9)
Graduate	11 (10.1)

HC: Head circumference; [b]Modified Kuppuswamy socioeconomic status scale for year 2018. [a]Immunization details not known.

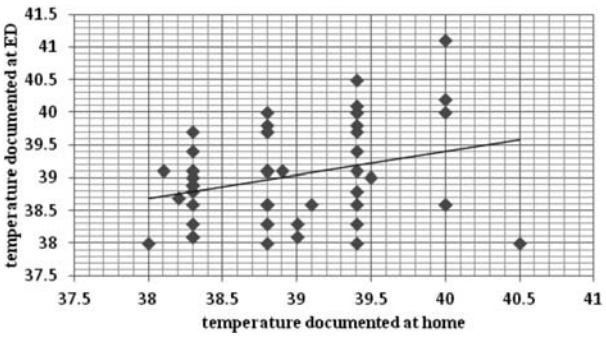

Fig.1 *Correlation between fever documented at home and in ED (r=0.3).*

no increased risk of having a severe infection if temperature is documented at ED *versus* if fever is not documented at presentation [OR (95% CI): 0.96 (0.32-2.85); *P*=0.94].

In our study majority of parents measured temperature at home by axillary or oral thermometry, There was a weak correlation between axillary/ oral temperature measured at home and rectal temperature documented at ED. Findings in our study are in agreement with the internet-based survey done by de Bont, *et al*. [5] in Netherlands, which showed 71.5% parents document fever if their child is ill, although majority documented rectal temperature. None of the parents in our study documented rectal temperature, as home measurement of rectal temperature by parents is uncommon in Indian settings. Other studies from hospitals in various regions in India report conflicting results on proportion measuring temperature of febrile children at home (14.5-71%) [6,7]. These differences may be based on regional socio-cultural factors. The finding of association of temperature documentation at home with higher educational level of mother is in agreement with previous reports [8].

The small sample size in our study may be a limiting factor for applying results of this study to general population. Most of the children had already received antipyretics before presenting to ED, and may have been exposed to varying environmental temperatures while travelling to hospital; thus explaining the poor correlation between temperature documented at home and in ED. Additional analysis could have been done for temperature correlations in different disease groups, but the numbers for individual diseases were less for valid comparisons. Further studies may need to study the relationship of domiciliary temperature measurements and fever at presentation, as triage and evaluation of pediatric patients in crowded EDs is frequently dependent on the presence/absence of fever.

Ethics clearance: Institutional ethics committee of MAM College; No. 17/IEC/MAMC/2017/Peds/07 dated 10 October, 2017.

Contributors: PP: subject assessment, management under supervision, data analysis, and preparing first draft of manuscript; RB: important contribution in study concept, data analysis and manuscript preparation; DM: Study concept, supervision and finalization of manuscript. All authors approved the final manuscript.

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A Unique Case of Cardiac *Echinococcus multilocularis*

Human alveolar echinococcosis (AE) or alveolar hydatid disease is extremely rare in children due to the prolonged incubation period of 5-15 years [1]. A tumor-like infiltrative growth characterizes it. Metacestodes of AE can infiltrate into adjacent areas resulting in its spread to different organs, primarily liver and lungs [1].

We report the case of a 7-year-old child from Iraq who presented with the complaints of cough and breathing difficulty, with progressive worsening over two months before presentation. Parents had also noticed increasing yellowish discolouration of eyes and skin, loss of appetite and weight in the previous month. The patient had a low-grade, intermittent fever for the past 20 days. The child had been diagnosed to be a case of hepatic failure and had been referred for liver transplant. On examination, the child had tachycardia, tachypnea and mild subcostal, intercostal retractions. Breath sounds were absent on the right side. There was non-tender hepatomegaly, with the liver span of 16 cm and smooth surface. Minimal ascites was present. Liver functions were deranged (serum glutamic oxaloacetic transaminase or SGOT/ serum glutamic pyruvic transaminase or SGPT 145 / 345 U/L, gamma-glutamyl transferase or GGT 528 U/L, total bilirubin and direct 6.4/2 mg/dL, total protein 8.1 g/dL, serum albumin 2.8 g/dL). The international normalized ratio (INR) was 1.37. He also had severe anemia (hemoglobin – 5.8 g/dL), with absolute eosinophil count of 2.45×10^9/L and high pro-inflammatory markers. Chest radiograph revealed right-sided pleural effusion with underlying collapse and consolidation. Pleural tap revealed almost bile-like pleural fluid with high bilirubin level suggestive of a trans-diaphragmatic extension of the hepatic disease. Evaluation of the fluid for infection was negative. Contrast-enhanced, multiphasic, multi-detector computed tomographic (MDCT) scan of abdomen revealed hepatomegaly with a large hypodense lesion in the liver, invading the inferior vena cava and serosa of the oesophagus with cystic changes, and was reported by the radiologist to possibly be mitotic etiology of the biliary tract or *Echinococcus alveolaris*. Qualitative Echinococcus (E) IgG was positive. Endoscopy revealed normal esophageal and gastric mucosa. Echocardiography demonstrated inferior vena cava infiltration by a mass extending into the right atrium. Ultrasound-guided liver biopsy revealed an inflammatory pathology with the possibility of mass forming *E. multilocularis*. The child was treated with 15 mg/kg/day divided in two doses of continuous albendazole therapy and other supportive treatment, and was under regular follow up. Unfortunately, the child died 2 months later.

Alveolar echinococcosis, due to *E. multilocularis* is extremely unusual, accounting for < 5% of all cases of hydatid liver disease and, less frequently, lung disease. The mean age of presentation is 55 years [1,2], with children being rarely affected. Liver is the primary site of cyst development in almost all patients. The characteristic feature of *E. multilocularis* is that they behave just like malignant tumors with invasion and destruction of surrounding tissue, spread into contiguous areas and metastasis to distant organs, with the most common organ being lung [3]. Lung manifestations always appear after the involvement of the liver [3]. Cardiac echinococcosis is very rare (0.03%-1% of all cases) [2], with the left ventricle being most frequently affected (55–60%).

We diagnosed our patient to be a confirmed case of alveolar echinococcosis based on clinical findings, contrast-enhanced MDCT, histopathology and serology [4]. We further classified the case as per the WHO-IWGE (WHO-Informal Working Group on Echinococcosis) PNM classification as P4N1M1 [5].

The focus of management in these patients is early diagnosis and radical (tumour-like) surgery, which is followed by anti-infective prophylaxis with benzimidazoles [1,3,4]. However, as in our case, most patients are diagnosed at an advanced stage, when radical surgery (a distance of larval to

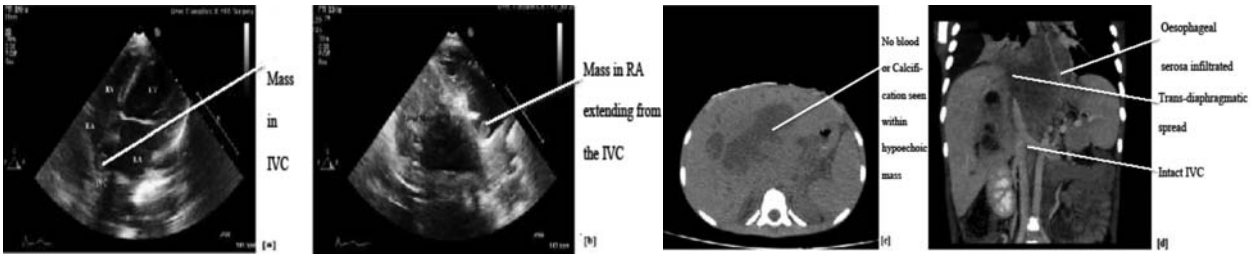

Fig. 1 *(a) 2-D Echocardiography (modified 4 chamber view) showing mass in IVC (b) Modified subcostal view with mass clearly seen in RA (c) CT: Nature of disease seen here – hypoechoic lesion with no blood/calcification within, unlikely to be carcinoma (d) Venous Phase of Triphasic CT: Trans diaphragmatic spread seen into the adjoining tissue, oesophageal serosa infiltrated. IVC, inferior vena cava; RA, right atrium; CT, computed tomography.*

liver tissue of >2 cm) cannot be achieved. Hence, as per current recommendations, the cornerstone of treatment remains the continuous medical treatment with albendazole, with individualized interventional measures at the appropriate time [1,4]. Radical surgery could not be done in our patient as R0 (no residue) resection was not possible. Palliative surgery was not possible as the lesion was unresectable due to invasion into the oesophagus, as well as into a blood vessel, leading to its spread to distant organs (both lungs and heart) [1]. Liver transplant was contraindicated due to the presence of extra-hepatic locations [1].

The first reported case of cardiac alveolar echinococcosis in adults, has been recently published [6]. In another interesting recent case report, E. granulosus causing cystic echinococcosis (CE) in left ventricle has been described in an 8-year-old child [2]. Yet another publication reports a giant hydatid cyst of the left ventricle in an 11-year-old child, also reviewing the 18 cases of cardiac echinococcosis reported thus far, all of which were due to cystic echinococcosis (CE) [7]. This is the first reported case of cardiac AE in children and highlights the need to consider this rare entity in patients with extensive liver disease extending into heart and lungs.

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Deep Vein Thrombosis After Trivial Blunt Trauma at High Altitude in a SARS-CoV-2 Positive Child: Complication of the Hypercoagulable State

Deep venous thrombosis and spontaneous thrombosis have previously been reported among patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a sequelae of hypercoagulable state [1,2]. We report the clinical course of coronavirus disease 2019 (COVID-19) in a 14-year-old boy living at high altitude whose manifestations could primarily be attributed to this hypercoagulable state.

A 14-year-old previously healthy boy, native of high altitude, presented with left thigh swelling for 1 week and breathlessness, chest pain, cough, fever and poor urine output for 5 days following trivial blunt trauma. The thigh trauma had occurred after jumping from a height of around three meters. This child belonged to a COVID-19 containment zone which was located at an altitude of 8000 feet above sea level. He had no significant past or family history suggestive of thrombo-embolism or bleeding disorders. He had no external injury or bleeding after the trauma but had tenderness at the thigh and difficulty in walking. On examination he was sick, lethargic, and febrile with PR=120/min with low volume pulse, respiratory rate of 32/minute, SpO_2 at room air of 78%, blood pressure of 80/60 mm Hg. Chest auscultation revealed bilateral crackles. There was left thigh swelling with tenderness and restriction of movement at the knee and rest of the clinical examination was normal.

Initial *X*-ray thigh was normal and did not reveal any fracture. Doppler ultrasound thigh revealed left common femoral vein thrombus measuring 12.56 cm × 0.79 cm, which was non-compressible with no Doppler flow. The thrombus extended into the left saphenous vein. Chest *X*-ray showed bilateral fluffy shadows. Treatment for suspected SARS-CoV-2 infection was immediately started. High flow oxygen via nasal cannula at 8 liters per minute was initiated. Fluid bolus with normal saline at 20 mL/kg once was given over one hour followed by maintenance intravenous fluid. Intravenous broad spectrum antibiotics and injection dexamethasone 6 mg once daily were started. In view of suspicion of COVID-19 with a differential diagnosis of traumatic deep vein thrombosis with pulmonary thromboembolism, initial treatment comprised of oral hydroxychloroquine, acetylsalicylic acid (anti-platelet dose), and injection low molecular weight heparin (LMWH) 40 mg subcutaneous twice daily. His hemodynamic status improved with fluid resuscitation and he did not require inotropic support. Preliminary investigations showed hemoglobin of 13.3 g/dL, total leucocyte count of 11×10^9/L (polymorphs 84%, lymphocytes 12%), and platelet count of 398×10^9/L. CRP was positive. Blood urea (279 mg/dL) and

serum creatinine (4.7 mg/dL) were raised, with normal serum electrolytes. Prothrombin time was 16 sec with INR 1.6, and activated partial thromboplastin time (APTT) was 17 second. Liver function test was normal. His nasopharyngeal swab RT-PCR for SARS-CoV-2 was positive on day two of admission and he was shifted to the district Covid-hospital. Over the next few days, his respiratory status initially improved and oxygen flow was gradually reduced.

From the second week of illness, the patient developed repeated episodes of hemoptysis and occasional epistaxis and required blood transfusion for symptomatic anemia with hemoglobin dropping to 7.5 g/dL. His PT/INR and aPTT remained normal during this period, and anti-factor Xa was not done. Pulmonary thromboembolism was clinically suspected as the etiology of hemoptysis in the setting of the COVID-19 and DVT. Patient's repeat nasopharyngeal RT-PCR sample tested negative for SARS-CoV-2 on day 10 and rapid antigen test was also negative. Hence, he was shifted back to our center.

High-resolution computed tomography (HRCT) scan of chest could only be done on day 11 of the hospitalization and revealed multiple bilateral nodular paren-chymal opacities with areas of cavitation seen in bilateral lung fields (suggestive of septic emboli) with bilateral pleural effusion (left more than right). Repeat HRCT chest after four days reported bilateral nodular shadowing with multiple cystic bronchiectasis changes in both lung fields, more in upper lobes. Echocardiogram was reported normal. The patient's renal function recovered after the initial fluid resuscitation and did not required dialysis. Other investigations like blood culture, D-dimer, ferritin, IL-6, protein C and S, Factor V Leiden *etc*. could not be done due to non-availability at the facility. From day 20 of admission, his oxygen saturation remained greater than 90% at room air. Repeat USG thigh showed resolution of DVT. Both dexamethasone and LMWH were given for 10 days each. Oral warfarin was started after ceasing heparin but was stopped after onset of repeated hemoptysis. From the third week, he again developed high fever and the thigh swelling worsened. *X*-ray left femur demonstrated signs of acute osteomyelitis of the left femur. Antibiotics were upgraded and pus was drained from the thigh. Pus culture was sterile, as the patient was already on antibiotics. After two weeks of surgical drainage, he became afebrile and was discharged after 40 days of total hospitalization.

In addition to primary lung involvement due to COVID-19, this patient developed a hypercoagulable state with consequent DVT and suspected pulmonary thromboembolism, which greatly increased the comorbidity and duration of hospital stay. Although rarely reported in children [3,4], the hypercoagulable state can result in significant clinical sequelae. High altitude is also a predisposing factor for thromboembolic phenomenon [5].

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Virus-Induced Wheezing With COVID-19

Pediatric coronavirus disease 2019 (COVID-19) has now been documented to be a milder illness worldwide except for the few presenting with pediatric multi-system hyperinflammatory syndrome (PIMS). Viral respiratory tract infections are the most common triggers of wheezing illnesses in children. With the ongoing pandemic, a rapid increase in wheezing-related illnesses may be theoretically anticipated. However, COVID-19 induced wheezing is currently thought to be rare. On a related note, a recently published online survey of members of the Pediatric Asthma in Real Life think tank and the World Allergy Organization Pediatric Asthma Committee [1] also suggested that COVID-19 is not associated with acute onset wheezing in children with underlying asthma. We report our experience with COVID-19 induced wheezing in three children (***Table* I**), who presented to our emergency room with respi-ratory distress.

COVID-19 associated asthma exacerbation [2] is rare; although there is a theoretical risk of COVID-19 causing a virus triggered asthma exacerbation. Previous epidemics of the coronavirus also did not report significant numbers of asthma exacerbations [3].

Table I Associated Wheezing Characteristics of Children With COVID-19

	Case 1	*Case 2*	*Case 3*
Age, known wheezer	4 y, No	1y, Yes	10 y, No
Asthma predictive index	Negative	Positive	Negative
Clinical features	Fever, cough, breathing difficulty	Breathing difficulty	Fever, cough, breathing difficulty
Dxygen saturation	SpO_2 89%	SpO_2 94%	SpO_2 94%
Neutrophil-lymphocyte ratio	7.08	0.44	1.05
C-reactive protein	24	2.88	<2.8
Treatment	Salbutamol metered dose inhaler with spacer, IV $MgSO_4$,	Salbutamol metered dose inhaler with spacer	Salbutamol metered dose inhaler with spacer
Respiratory support	HFNO (@ 2 L/kg flow and 40% FiO_2)	Oxygen by nasal cannula @ 4 L/min	HFNO (@ 2 L/kg flow and 40% FiO_2)
Steroids	IV dexamethasone (@ 0.6 mg/kg/d)	Oral prednisolone (@ 1 mg/kg/d)	Oral prednisolone (@ 1mg/kg/d)
Hospital stay (d)	5	3	5

All children were RT-PCR positive, and had tachypnea, subcostal retractions, and bilateral expiratory wheeze; Chest X-ray showed bilateral lung hyper inflammation in all 3; None of the children had any comorbidity; and HFNO: High-flow nasal oxygen; FiO_2: Fraction of inspired oxygen.

Severe respiratory manifestations of COVID-19, though uncommon in children have been reported and may be presumed to involve clinical presentations related to small airways or alveolar involvement or both. If small airways are predominantly affected, treatment modalities will include bronchodilators, corticosteroids, oxygen supplementation and respiratory support as required. However, bronchodilators are potentially detrimental in a scenario of alveolar disease due to pro-inflammatory effects on alveoli, worsening of ventilation-perfusion mismatch and increased tachycardia [4]. There is no clear-cut separation of these phenotypes and overlap may be expected. Corticosteroids, typically in courses longer than that used in exacerbations of asthma, are currently in use for treating severe COVID-19 [4,5]. The role of antiviral treatment is not precisely known especially in the pediatric context [4].

In our cases, we utilized C-reactive protein (CRP) levels as an indicator of severity of inflammation. In one child CRP was elevated but other markers of inflammation including D-dimer, S. ferritin and serum fibrinogen were normal. More data is required to know if inflammation and hypercoagulable states more commonly occur with alveolar disease in contrast to small airways involvement as seen in these three cases. The limitation of our workup lies in not testing for viral co-infection which may have triggered the exacerbation as well.

Literature on pediatric asthma and COVID-19 is sparse and limited to case reports highlighting mild disease mostly not requiring hospitalizations and ICU care [1,6]. One of the mainstays of aerosol therapy in acute wheezing episodes is nebulizations. However, it also amplifies the risk of infection transmission by stimulating a cough reflex, as well as generating a high volume of respiratory aerosols that may be propelled over a longer distance thus infecting bystander hosts. An added disadvantage being an increased risk of deposition of virus in the lower lung [7], nebulizations in COVID-19 remains the least suitable preference. Poor response to a metered dose inhaler/spacer, a child who is uncooperative or unable to follow the directions required for metered dose inhaler use and medication shortage remain the only possible indications of using nebulizers in these children. The Global initiative for asthma guidelines suggest that asthma exacerbations due to COVID-19 should be treated with corticosteroids as appropriate [8]. However, there is no research on the choice of corticosteroid. No adverse effects attributable to the use of steroids were noted in these children.

Though rare, COVID-19 infection in children may trigger a viral-induced wheeze that requires distinguishing from other viral and asthma triggers. Severe illness requiring substantial respiratory support may occur in these circumstances. Identifying similar presentations and reporting may help also to resolve the therapeutic dilemmas.

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Neurological Manifestations of COVID-19 in Children

Coronavirus disease 2019 (COVID-19) in children is mostly an asymptomatic or mildly symptomatic infection [1]. We seldom suspect COVID-19 in children with non-respiratory complaints, more so with isolated neurological manifestations. we present our experience of treating three children of COVID-19 who presented with only neurological symptoms.

A 2-year-old previously healthy boy who had one day fever, three watery stools and pain abdomen, presented with febrile status epilepticus, hypotensive shock and hypoxia. A diagnosis of acute febrile encephalopathy was entertained and he was started on fluid resuscitation. He was shifted to critical care unit where he was mechanically ventilated in view of poor respiratory efforts with encephalopathy and received ceftriaxone, vancomycin and acyclovir. Reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) on a nasopharyngeal swab was positive and his antibody testing in serum was negative. His cerebrospinal fluid (CSF) analysis was in normal limits with negative RT-PCR for SARS-CoV-2. He fulfilled the criteria for multisystem inflammation syndrome MIS-C in children and was treated with intravenous immunoglobulin (IVIG) 2 grams/kg along with remdesivir. His fever and requirement for inotrope support persisted, and intravenous methylprednisolone (10 mg/kg/day) was given for 3 days. His general condition improved, he did not have any further seizures, and was extubated after 48 hours. He was switched over to oral prednisolone for 2 weeks and low dose aspirin for 6 weeks, and was doing well on follow-up six weeks later.

A 15-month-old previously healthy boy presented with simple febrile seizures. On day two, he developed a maculopapular rash over the extremities with bilateral non-purulent conjunctival congestion, periorbital puffiness and cheilitis. He had persistent high-grade fever of >103ºF even on the fifth day and was referred for further management. His father had confirmed SARS-CoV-2 infection one month back. He fulfilled the criteria for MIS-C with Kawasaki disease phenotype, and was treated with intravenous immunoglobulin (2 g/kg), aspirin and steroids, as in the previous child. He was well on follow-up four weeks later.

An 8-month-old boy was brought with complaints of high-grade fever of 103ºF for one day, followed by first episode of generalized tonic-clonic seizure lasting for more than 20 minutes on day one of illness. He was given intravenous midazolam followed by intravenous levetiracetam as the seizure episode was prolonged. There was a history of contact with confirmed SARS-CoV-2 in a close relative. His RT-PCR for SARS-CoV-2 in nasopharyngeal swab was positive**.** As the child did not have any encephalopathy or meningeal signs and no further episodes of seizures, CSF analysis and neuroimaging were deferred. He became afebrile from day three of illness. He was discharged on oral levetiracetam with a diagnosis of febrile status epilepticus, and is well on 2-weeks follow up.

With increasing numbers of SARS-CoV-2 infections, non-respiratory manifestations are being reported across all age groups. The reason hypothesized is the distribution of angiotensin-converting enzyme 2 receptors (ACE-2R) or unexplained immune mechanism. ACE-2R are also present on the endothelial cells in the cerebral vasculature. Neurological manifestations in COVID-19 can be due to virus breaching the blood-brain barrier and entering the brain either trans-neuronally via the olfactory mucosa that has a relatively high expression of the ACE2 receptors, which then through olfactory nerve, crosses the cribriform plate or via hematogenous route [1] or as sepsis-induced coagulopathy leading to cerebral infarction [2] or immune-mediated neurological syndrome or can travel retrogradely via axonal transport to the brain from the gut or lungs. Few autopsy studies have demonstrated the presence of the virus in capillary endothelial cells of the frontal lobe of the brain [3]. The virus can also reach the brain by trojan horse mechanism via infected leukocytes migration across the blood brain barrier [4].

Seizures, encephalopathy, agitation, diffuse upper motor neuron signs, encephalitis, acute necrotizing encephalopathy, stroke, anosmia, ageusia, and Guillain-Barré syndrome have all been reported in adults with COVID-19 [5]. Encephalopathy (diffuse brain dysfunction) and encephalitis (acute, diffuse, inflammatory condition of the brain) are a major devastating presentation. Intense inflammatory response against the virus, triggers cytokine storm causing subsequent hypoxic and metabolic insults resulting in multiple organ failure including diffuse brain dysfunction. Altered consciousness is the hallmark clinical feature of encephalopathy. Individuals with encephalopathy/encephalitis are either severely or critically ill

and have a poor prognosis [4]. In a case series of four children under 18 years of age who presented with severe COVID-19 infection, the neurological symptoms included encephalopathy, headache, brainstem, cerebellar signs, muscle weakness, and reduced reflexes. MRI brain had signal changes in the splenium of the corpus callosum in all four patients and T2-hyperintense lesions associated with restricted diffusion were seen in three children [6]. In a recent multi-centric retrospective study which analyzed the MRI findings in adults with severe COVID 19 infection, signal abnormalities located in the medial temporal lobe, non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion with variable enhancement, associated with hemorrhagic lesions, and (c) Extensive and isolated white matter microhemorrhages were the most common findings. The presence of hemorrhage was frequent, and the detection is of clinical importance as it was associated with worse respiratory, neurological, and biological status [7].

Internationally accepted case definitions for MIS-C are still evolving. In our case series, all were confirmed cases of COVID-19, of which the first two children had neurological manifestations of acute febrile encephalopathy and febrile seizure with features of MIS-C while the third child presented as febrile status epilepticus. One child with MIS-C had fulfilled the criteria for incomplete Kawasaki phenotype (fever >5 days, rash, bilateral non-purulent conjunctival congestion, cheilitis) according to AHA guidelines. Many MIS-C cases present as Kawasaki disease shock syndrome with Kawasaki-like clinical symptoms, cardiac impairment and shock [9].

There were a few limitations in our observations. Imaging studies and CSF analysis were not done in all. We speculate that COVID-19 being a respiratory virus, other systemic manifestations especially neurological presentations may go unrecognized. In this pandemic situation, any child with primary neurologic symptoms and fever, with mild or absent respiratory symptoms, it could either be a part of MIS-C or a self-limiting finding of pediatric COVID-19 infection.

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SARS-CoV- 2 Encephalitis in an Adolescent Girl

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus can affect both the central and peripheral nervous system, and SARS neurological manifestations have also been rarely reported in children. We herein report COVID-19 encephalitis in a 13-year-old girl, who presented with status epilepticus and altered sensorium and had complete resolution of neurological symptoms in 48 hours.

A 13-year-old girl presented with fever for 2 days associated with headache and an episode of generalized tonic clonic seizures on day 2 of fever lasting for more than 30 minutes. She was treated with intravenous lorazepam and phenytoin sodium and in view of persistence of seizures and altered sensorium, she was referred to our center for further care. There was no history of cough, vomiting, head trauma, rash or drug ingestion. She was first born to non-consanguineous parents and developmentally normal for age. There was no past or family history of seizures. On examination at admission, she was febrile (100°F), irritable and had altered sensorium. She had brisk deep tendon reflexes with an extensor plantar response. There were no signs of meningeal irritation. Her pupils were equal and reacting to light. There was no papilledema or focal neurological deficits. Cardiopulmonary and abdomen examination were normal. Her investigations revealed normal white cell counts and negative CRP. Her serum electrolytes including calcium and magnesium, liver function tests were normal. MRI

brain was normal. Cerebrospinal fluid (CSF) analysis showed 200 white blood cells/mm^3 all lymphocytes with protein, 86 mg/dL, sugar, 77 mg/dL (corresponding blood sugar:126 mg/dL). CSF gram stain, AFB stain, bacterial culture and Xpert gene TB were negative. CSF biofire film array multiplex PCR was negative for viruses (CMV, HSV, entero and varicella). Nasopharyngeal aspirate for SARS-CoV-2 by qualitative RT-PCR was positive (cycle threshold: 27.26). Computed tomography (CT) chest showed patchy peripheral ground glass opacities involving the posterior segment of the right upper lobe and lateral segment of right middle lobe (COVID score 5/40). However, RT-PCR in CSF sample was negative for SARS -CoV-2 virus. Her EEG was normal. She was treated with levetiracetam and ceftriaxone. Within 48 hours of admission, she became afebrile, her sensorium improved and had no recurrence of seizures and ceftriaxone was stopped once CSF and blood cultures were reported sterile and was discharged home in a normal neurological state.

COVID-19 viral encephalitis was probably first reported by McAbee*, et al*. [1] in a 11-year- old male child whose nasopharyngeal swab was positive for COVID-19, whereas CSF was negative and the boy recovered without any specific treatment in six days. SARS-CoV-2 from the nose reaches CSF either by olfactory ensheathing cells, olfactory receptor neuron or by disrupting the respiratory epithelium then enters the blood stream and then enters brain through disrupted blood brain barrier, either caused by inflammation or by using angiotensin converting enzyme-2 (ACE-2) receptors present in the blood brain barrier endothelial cells, thereby resulting in viral proliferation, neuronal injury and damage [2]. Virus induced immunologic response also leads to swelling of the brain resulting in increasing cerebrospinal fluid pressure thereby resulting in alteration in consciousness. Abdel-Mannan, *et al*. [3] from UK had reported four children aged 8-15 years who had new onset encephalopathy and proximal muscle weakness. All of them were positive for SARS-CoV-2 virus in nasopharyngeal samples, and CSF (done only in 2 children) was negative for COVID-19 [3]. Neurologic improvement was seen in all of them. Acute splenial lesions were seen in four children [4] whereas, in our case, we could not identify any changes in the splenium of the corpus callosum. The neurological manifestations reported in COVID 19 are protean [4]. CSF pleocytosis (>5 WBC with predominant lymphocytes) that is characteristically seen in viral encephalitis, was seen in this girl. RT-PCR assays of the CSF samples being negative for SARS-CoV-2 in patients with neurological manifestations has not only been described in children [1,3] but even in adult patients and this dependes on the severity of the systemic illness, the neurotropic properties of the virus, and immune-mediated inflammatory mechanisms [5,6]. It has been earlier reported that RT-PCR of nasopharyngeal specimen for SARS-CoV-2 appears to be a useful investigation for confirmation of COVID-19 even in children with neurological presentation and children have a favorable outcome [7], as seen in our cases.

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Platelet Normalized Serum Vascular Endothelial Growth Factor Levels in Progressive Pediatric Solid Malignancies

We read with interest the recently published article by Pramanik, *et al.* [1]. The study reported inconsistent trends in serum vascular endothelial growth factor (VEGF) and thrombospondin-1 (TSP-1) in 108 patients with progressive pediatric solid tumors who received metronomic chemotherapy or placebo [1]. While higher baseline serum VEGF levels predicted inferior overall survival, authors found that responders with metronomic chemotherapy had significantly lower VEGF levels at baseline compared with non-responders. Further, there was no association of serial VEGF levels with response to metronomic chemotherapy.

Of note, VEGF is released from the α granules on platelet activation during sample collection and therefore, serum levels are considered as an inaccurate indicator of actual measurement of circulating VEGF [2]. Patients with disseminated cancer may have a higher platelet count and carry even higher VEGF per platelets compared with general population [3]. Thus, plasma is preferred over serum to measure VEGF because collecting blood in citrate tubes avoids platelet activation and therefore preventing the spurious high VEGF levels released from platelets [4]. Since the authors used serum to measure VEGF levels in pediatric patients with solid tumors in the study, the results must be interpreted with caution [1]. However, serum VEGF levels normalized to patient's platelet count provides serum VEGF/platelet, which can neutralize the effect of VEGF released from platelets while withdrawing blood [5]. Therefore, the authors may consider analyzing the data after calculating serum VEGF/platelet for all measurements in individual patients, if data on platelet count is available. It will be interesting to see if a consistent pattern is then noticed between serum VEGF/platelet with the response to metronomic chemotherapy and survival outcomes.

Further, the authors described the effect of baseline serum VEGF levels with overall survival in overall population as well as responders in patients randomized to metronomic chemotherapy arm [1]. While this finding is interesting, it is an exploratory subgroup finding in a small number of patients, which can be interpreted as hypothesis generating at best and therefore, should be interpreted with utmost caution.

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AUTHORS' REPLY

We appreciate the comments and suggestions by the reader. Available literature shows that there is a controversy regarding the best blood compartment and the best test to measure VEGF in cancer patients. VEGF in cancer patients is the sum total of platelet derived VEGF as well as other sources like neo-angiogenesis in the tumor tissue. One of the studies showed that the best discrimination between healthy volunteers and cancer patients was observed in platelet poor plasma (PPP). As generating plasma induces platelet activation with consequent VEGF release from platelets, citrate-theophylline-adenosine-dipyridamole plasma was suggested by some authors to evaluate VEGF [1]. Serum VEGF is more practical because VEGF levels in citrated plasma are low and lie close to the limits of ELISA sensitivity. Some studies have shown that a standardized measurement of serum VEGF, normalized by the patient's platelet count, which gives a value of serum VEGF per platelet, can be a useful parameter [2].

We had our baseline platelet counts for all the patients but the corresponding platelet counts for subsequent follow up (A2 and A3) assessments were not available for all patients [3]. Hence, we restricted our analysis to baseline values only. On applying pair wise correlation to the baseline platelet count and serum VEGF, we found an insignificant correlation; r=0.16 (P=0.09) (***Fig.* 1a**). Baseline serum VEGF showed a significant positive correlation with baseline VEGF per platelet (r=0.81, P<0.0001) (***Fig.* 1b**). As the serum VEGF and VEGF/per platelet correlate significantly, both are likely to follow similar trends; this implies that we are likely to have similar observations, whether we use serum VEGF or VEGF/platelet.

Similar observations were reported by Vermeulen, *et al*. [4]; they commented that in view of the lack of a strong association

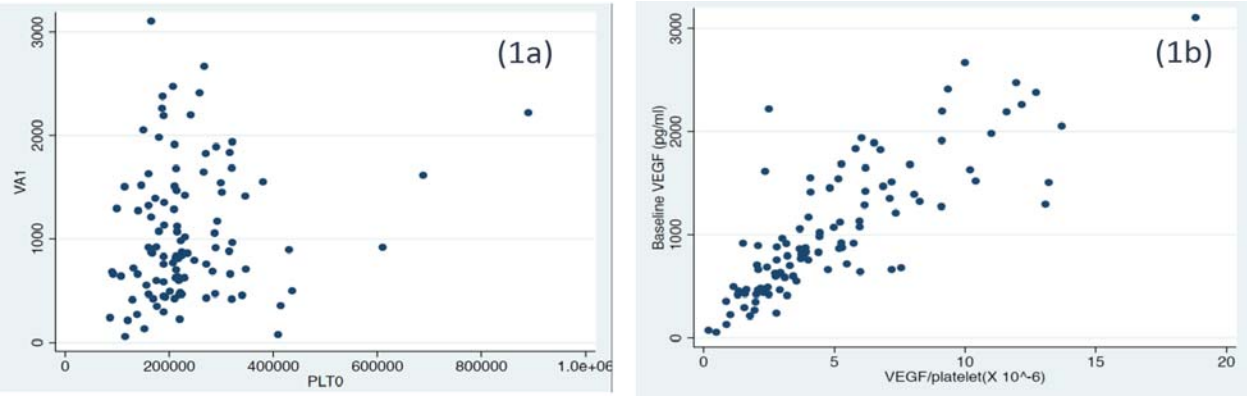

Fig. 1 *Scatter plots showing correlation between (a) baseline VEGF and baseline platelet counts, and (b) baseline VEGF and baseline VEGF per platelet.*

between serum VEGF and platelet count, and the association of serum VEGF with the degree of stimulation of endothelial cell proliferation in vitro, measuring serum VEGF might be more suitable in cancer patients than measuring plasma VEGF. Also, it has been postulated that at least part of the VEGF in platelets represents that endocytosed from the plasma due to their scavenging effect [4]. So, measuring the entire collection (serum VEGF) may not be less appropriate.

Further, most previous studies on metronomic chemotherapy had measured serum VEGF and we intended to be consistent and comparable to them [5,6]. Hence, our conclusion remains the same that VEGF is not a reliable biomarker for metronomic chemotherapy, but the best test for VEGF still remains an illusion.

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Psychosocial Wellness During the COVID- 19 Pandemic: Building an ARCH

The COVID-19 pandemic is associated with significant morbidity and mortality. However, little attention has been devoted to psychological factors, emotional distress and social disruption in children. It is believed that the disease, multiplied by forced quarantine and nationwide lockdowns can induce acute panic, anxiety, obsessive behaviors, paranoia, depression and post-traumatic stress disorder (PTSD) [1]. The pandemic is likely to be followed by a 'second pandemic' of mental health crises [2]. This necessitates a comprehensive public health response with innovations for providing mental health care, while maintaining social distancing.

To support and protect psychosocial well-being of children, we propose the ARCH model for mental health workers, parents and teachers. ARCH is an acronym for Adapt and attempt, Resilience, Collaboration and care, and Humor and humility.

In an uncertain and evolving situation, children may be encouraged to adapt to the current scenario and attempt solutions in a new normal, rather than wait for familiar comfort zones. Options for physical activities have been drastically reduced. Children tend to spend their excessive free time on television or mobile phone [3]. Introducing positive adaptation skills is essential. Children need to feel safe, secure, and positive about

their present and future. Caregivers can help by focusing children's attention on stories about how people come together, find creative solutions to difficult problems, and over-come adversity during the epidemic [4]. Caregivers need to ensure against promoting negative adaptation skills.

Since failure may be a likely outcome due to unprecedented challenges, resilience needs to be fostered. This entails 'listening' and being emotionally available to the child. Letting children express their concerns, and participating in their activities are key initiatives. Children should be given an idea of what realistically to expect rather than painting rosy but ostensibly false pictures of the situation. Queries from children need to be answered with simple concrete explanations appropriate to their level of cognitive development. Being honest and supporting them with their challenges help build resilience in the situation.

Collaboration and care are imperative in a prolonged crisis. Children need to be encouraged to reach out to parents, siblings, peers, school mates, teachers, and other caregivers to pool resources and ideas, and work together collaboratively to find creative solutions to everyday challenges under super-vision and guidance, while caring for each other's contributions [5].

Humor in daily life is vital for the child to withstand distress, and inculcating humility is imperative to help the child to maintain a sense of calm acceptance and balance.

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Integration in Medical Education: Need to Address the Misconceptions

I appreciate the efforts of the authors of the article on integration in medical education published recently in the journal [1]. Competency-based under graduate medical curriculum for Indian medical graduates has given elaborate guidelines on how integration can be achieved in various subjects [2]. Competency tables of this document have suggested for areas of integration according to subject-wise competencies.

Integrated teaching activity has not received expected success, though attempted widely. There are many misconceptions among the faculty about implementation of integrated teaching sessions. Integrated teaching has been organized as a series of lectures involving faculty from many departments. The extra efforts required for inter-departmental coordination has made the organization of activity irregular and episodic, lacking in sustainability. The lengthy structure of the resultant sessions has also not been able to arouse sufficient interest among the students.

Integrated teaching can be made more meaningful if these misconceptions are addressed. It has been rightly pointed out in the competency-based undergraduate curriculum document that there should be integration of concepts and not necessarily of teachers [2]. The faculty can identify the topics in their curriculum where integration with other disciplines can reduce redundancy, duplication and increase the relevance of learning for the students. The teachers from other departments may be consulted for planning of sessions and not for actual partici-pation in the sessions, unless deemed necessary. Integration of relevant concepts from other disciplines will help in enriching the routine teaching activity. The faculty from the parent discipline can perform this integration at their own level to make the learning experience for the student more meaningful and relevant.

Integration should be an integral part of routine teaching program of each department, rather than an independent activity. Integration should be used as an opportunity to enrich the departmental teaching activities without compromising the departmental learning objectives. Integrated teaching sessions should be short and brief, to be completed in the routine allotted time, avoiding too many objectives in one session. Multiple teaching methods such as case discussions, group activity and panel discussions can generate interest in students. Intensive coordinated action by teachers is required to make integrated teaching successful activity.

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Spinal Muscular Atrophy Type 1 With Exon 8 Deletion and Bilateral Optic Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease with incidence of 1 in 5-10,000 live births and is caused by homozygous deletion of exons 7 and 8 in the *SMN1* gene [1]. Isolated exon 8 deletion has been reported in only one case series [2]. It is characterized by symmetrical proximal weakness; although, extraocular muscles are typically spared, there are a few case reports of associated external ophthalmoplegia [3,4] and one case report with optic atrophy [5]. We report a boy with SMA type 1 with optic atrophy due to isolated deletion of exon 8 of the *SMN* gene.

A preterm, 34 week, male baby, with birthweight of 1700 g was born to a 24 year-old para 2 live 1 mother, by third degree consanguineous marriage. Baby was delivered by vaginal route, with delayed cry at birth, was born limp and apneic requiring positive pressure ventilation and chest compression. Mother had history of polyhydramnios with amniotic fluid index (AFI) of 29 cm in second trimester with decreased fetal movements. There was a history of sibling death of a male baby at 30 weeks of gestation born one and half years back. On examination, baby was alert with spontaneous eye opening, had long facies with bilateral temporal hollowing; pupils were mid-dilated and non-reacting to light. Tone was decreased in all limbs, power was 2/5 around hip joint and knee joint and 3/5 in bilateral elbow joints; contractures were present at elbow, ankle and foot. Tongue fasciculations were present and bilateral deep tendon reflexes were absent. Baby had bulbar palsy with bilateral optic disk pallor.

Baby was continued on mechanical ventilation and IV fluids and later was started on tube feeds. Baby had recurrent episodes of gastroesophageal reflux (GER). Investigations revealed serum creatine phosphokinase (total) of 150 IU/L, tandem mass pectrometry (TMS) and urine gas chromatography ass pectrometry (GCMS) were normal. Muscle biopsy showed maintained fascicular architecture with variation in fibre size with focal fat infiltration and occasional muscle fiber degeneration. No dystrophic, neurogenic, congenital myopathic, atrophic changes were seen. Gene analysis for *SMN1* gene revealed exon 8 deletion. Baby remained ventilated in hospital with multiple extubation failures, and died on day 57 of life.

In SMA, there is homozygous mutation or deletion of the *survival motor neuron 1* (*SMN1*) gene, located in the telomeric region of chromosome 5q13. *SMN2*, a gene that is similar to *SMN1* is located in the centromeric region, determines the severity of illness [6]. Genetic alteration to the *SMN1* gene is responsible for a reduction in survival motor neuron (SMN) protein. The *SMN2* gene only produces 25% of SMN protein and so does not completely compensate for the absence of *SMN1* [6]. The lack of the SMN protein causes degeneration of alpha motor neurons in the ventral horn of the spinal cord.

According to the age of onset and clinical severity SMA is divided into three subtypes (types 1-3). The hallmark of SMA type 1 is severe, progressive muscle weakness and hypotonia and present by 6 months of age, with 95% of patients having signs and symptoms by 3 months [5,6]. Optic atrophy is an unreported association of SMA, with the exception of one case report [5]. Present case had history of product of consanguineous marriage with previous sibling death with similar features, with antenatal ultrasound suggestive of polyhydramnios, with typical presentation of SMA and atypical presentation of extraocular muscle involvement with optic atrophy.

In conclusion, isolated exon 8 deletion of the *SMN* gene is a rarely reported and unusual mutation of SMA and optic atrophy is an unreported association.

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AUTHOR INDEX 2020

INDIAN PEDIATRICS

Volume 57, January-December, 2020

SUBJECT INDEX 2020

INDIAN ACADEMY OF PEDIATRICS
Kamdhenu Business Bay, 5th Floor, Plot No. 51, Sector 1,
(Near Juinagar Railway Station), Nerul,
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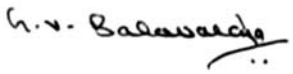
NOTICE FOR IAP ANNUAL GENERAL BODY MEETING

Notice is hereby given that the Annual General Body Meeting of the Indian Academy of Pediatrics for 2021 is scheduled to be held on 6th February 2021, from 06.30 pm onwards at CIAP Pedicon 2021 Hall A/B, Hotel Sahara Star, Mumbai to consider the following agenda.

Kindly make it convenient to attend the meeting.



Dr. G.V. Basavaraj
Hon. Secretary General, IAP 2020 & 2021

Place: Navi Mumbai
Date: 30th November, 2020

AGENDA

1. Confirmation of the minutes of the Annual General Body Meeting held on 10th January, 2020 at Indore.
2. Business arising out of the minutes.
3. Consideration and adoption of Annual Report of the Society.
4. Consideration and adoption of the audited Statement of Accounts for the year ended 31st March, 2020 and the Budget for the year 2021-2022.
5. Appointment of Auditors and fixing their remuneration for 2021-22.
6. Appointment of Honorary Legal Advisor for 2021-22.
7. Consideration of matters related to IAP Election for 2022.
8. Matters related to Pedicon 2022.
9. Any other business, notice of which has been circulated with the agenda.
10. Any other business of which 30 days notice has been given to the Secretary General in writing.
11. Consideration of correspondence.
12. Any other business with the permission of the chair.

Note:

(1) If there is no quorum within half an hour of time fixed for the meeting, the meeting shall be adjourned to a later time on the same day and same place. No quorum is needed for the adjourned meeting.

(2) Kindly note that entry into the meeting hall will be permitted to only those members who give their Central IAP membership number and who bring their personal photo ID (such as Driving License with photo / PAN Card / Voter ID Card / Valid Passport / IAP Identity Card / Aadhar Card)

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Iron Deficiency Anaemia