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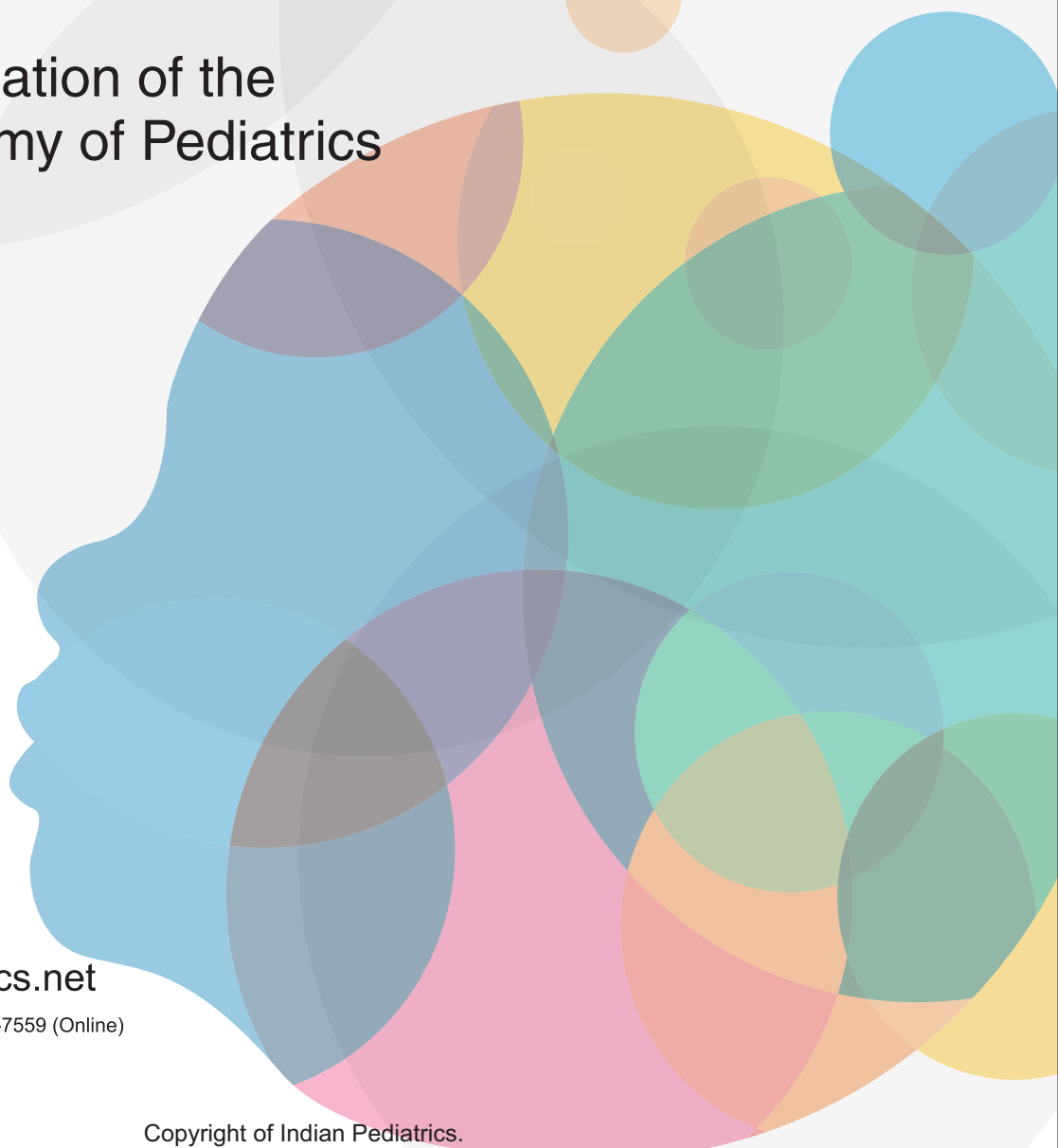

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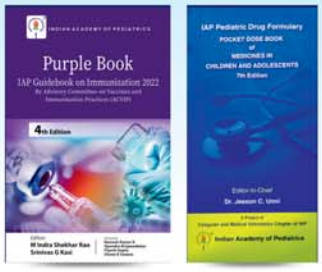

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PRESIDENT'S PAGE

Championing the Cause of Rare Blood Disorders in Children

GV Basavaraja

National President, Indian Academy of Pediatrics, 2024
president@iapindia.org

Dear IAPians,

As we celebrate the World Thalassemia Day on May 8, let us turn our attention to the commonly overlooked realm of rare blood disorders. While these conditions may not always command the spotlight of regulatory bodies due to the perceived lack of significant economic impact, as pediatricians we do understand that for the children afflicted by these conditions and their families, these disorders are a lifelong challenge.

Thalassemia, an uncommon hemoglobinopathy, profoundly impacts the lives of those affected by this blood disorder. Dependence on recurrent blood transfusions for survival is only one of the several challenges faced by individuals with thalassemia. A lack of awareness among families further exacerbates this problem as it leads to erratic medical visits. The consequences of this neglect manifest as symptoms of chronic fatigue, abnormal physical features, and enlargement of the liver and spleen. Additionally, the very treatment meant to sustain life - transfusions carry their own set of risks, including transfusion reactions and the risk of transmitting infections like hepatitis B and HIV. However, the most ominous threat that looms over these patients remains iron overload which wreaks havoc on vital organs like the liver and heart, stunts growth, causes hypogonadism and a host of complications including hormonal imbalances and diabetes [1]. Unfortunately, not all patients are able to access the chelators needed to tackle the iron overload due to issues of availability and also because these are not available free of cost at all centres. Despite the existence of hematopoietic stem cell transplantation, the potentially curative treatment, such interventions remain elusive for most patients as they are costly and available at select centres. There is a need for garnering more awareness for blood donation initiatives and increasing the access to comprehensive care for those living with thalassemia.

On April 17, we also celebrated the World Hemophilia Day and we must continue our efforts to increase awareness about this rare clotting disorder. Although, we have transitioned from our reliance on blood components like cryoprecipitate and fresh frozen plasma to the use of recombinant factors not only for treating hemophilia but also for prophylaxis, the access to these treatments is not uniform across all states in India [2]. Sadly, individuals with hemophilia continue to face the spectre of protracted and excessive bleeding triggered by even minor injuries, and in some cases, spontaneously. Joint hematomas, a frequent complication, not only inflict agonizing pain but also carry the potential for permanent disability if left untreated [3]. Intracranial bleeds remain the most dreaded complication, underscoring the urgency for raising awareness about this condition.

On the bright side, with the declaration of the Rights of Persons with Disabilities Act, 2016, blood disorders including thalassemia, hemophilia and sickle cell anemia were recognised as a benchmark disabilities [4]. This lifted off the veil covering the face of these blood disorders. In 2024, the Director General of Health Services (DGHS) has directed all hospitals to maintain disease-specific transition registries and organise joint clinics for transition of patients suffering from chronic diseases including thalassemia and hemophilia, to an adult care team in the same hospital for uninterrupted comprehensive treatment [5]. These developments have given us direction and motivation to strive for better care for these patients as we offer them the hope of increased quality survival. Together, through education, advocacy, and compassionate care, we can work towards a future where no child's life is defined or diminished by the burden of these conditions.

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INVITED COMMENTARY

The Changing Landscape of Brain Infections in India

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Acute onset of fever with alteration in consciousness with or without seizures is an important cause of hospital admissions among children in large parts of India. Such a presentation is mainly caused by invasion of the brain by an infectious agent – virus, bacteria, protozoa, rickettsiae, mycoplasma etc., but also by a host of non-infectious brain inflammations, infectious encephalopathies and other functional (such as toxic or metabolic encephalopathy) and structural brain disorders if associated with fever due to another cause [1]. In 2006, the World Health Organization (WHO) coined the term 'acute encephalitis syndrome' (AES) for the purpose of surveillance of Japanese encephalitis (JE) which was an important cause [2]. AES is a symptom complex, the etiology of which varies with region.

The most important cause of AES in India over almost 4-5 decades (1970s to 2024) has been JE. Since the first large epidemic reported from Bankura in West Bengal in 1973 [3], there have been repeated annual epidemics and outbreaks in monsoon and post-monsoon season in southern and eastern states, extending upto Gorakhpur division in eastern Uttar Pradesh (UP). It may be mentioned here that JE is a severe viral encephalitis with a fulminant clinical course, high risk of mortality and permanent neurological sequelae, and unfortunately, with no specific antiviral treatment available so far. The year 2005 saw a severe epidemic in UP, after which the Government of India imported the Chinese live attenuated vaccine (SA-14-14-2 strain) and administered it in campaign mode to children aged 1-15 years in affected districts [4]. JE vaccine was later included in the National Immunization Schedule in 181 JE endemic districts of India in 2011. In fact, after poliomyelitis, JE control took centre stage as an international priority for preventing death and disability in affected regions. International agencies and governments rolled out evidence-based public health measures to control JE. Since around 2015, the prevalence of JE as a cause of AES in UP did come down to less than 10% [4].

Since the early 2000's an illness with fever, encephalopathy, rash, low platelets, bleeding manifestations, mildly raised liver enzymes and a peculiar non pitting edema is being seen and reported from various parts of the country - dengue with encephalopathy (DE) [5]. Dengue infection has also been proven to invade the brain as an infectious encephalitis [6]. It was proposed that a neurotropic strain of the virus was in circulation.

In UP, although JE incidence as a cause of AES came down but AES itself did not decrease. This was baffling for some years, until it was realised that scrub typhus meningoencephalitis (STM) had replaced JE as the dominant cause in the eastern districts [7]. There were increasing reports of scrub typhus (ST) from various parts of the country – both North and South. The ecological conditions for spread of ST exist over large parts of our country. For some reason, STM is a common manifestation of ST infection in India. Fortunately, STM is a milder illness than JE and responds well to antimicrobials – tetracyclines and azithromycin. State governments issued directives to treat acutely febrile children in Gorakhpur division with empirical doxycycline at primary health centres [8]. Minocycline has the added advantage of having neuroprotective properties and achieving much higher levels in the brain [9].

India has also witnessed localized outbreaks of acute encephalopathy in Saharanpur [10] and later in Muzaffarpur, Bihar [11] which upon investigation were held to be toxic in origin. West Nile virus and Chandipura virus are both prevalent in India but their contribution to AES is not clear. The latter was implicated as the cause of 'Epidemic brain attack' reported from Andhra Pradesh in 2003. India remains endemic for rabies. Primary amebic meningoencephalitis due to Naegleria infection acquired by swimming in freshwater ponds occurs sporadically. Nipah virus is another agent associated with outbreaks of severe encephalitis in Kerela and West Bengal [12].

Misra and Kalita have differentiated two clinical syndromes of encephalitis prevalent in northern India – pure neurological illness (exemplified by Herpes simplex encephalitis, rabies and JE) and others with systemic manifestations also – rash, thrombocytopenia, bleeding,

liver function derangement (dengue, STM, cerebral malaria, leptospirosis etc) [13]. This approach may prove useful in the initial work up and treatment in other parts of the country as well.

Establishing an etiological diagnosis of AES is a difficult task even in affluent settings. This is illustrated by the California Encephalitis Project conducted in USA around the turn of the century, in which confirmed diagnosis was possible in only 16% [14]. Virological investigations are complex, expensive and require a sophisticated infrastructure. Many non-infectious illnesses can mimic brain infections. Timing of sample collection is important. These difficulties can be precluded to some extent by using the multiplex polymerase chain reaction (PCR) technology wherein several pathogens can be tested in a single test. PCR for a panel of agents relevant to the region can be designed. Another strategy applicable to resource constrained settings is to develop 'clinical prediction rules' for important pathogens.

The article by Rebecca et al in the current issue of *Indian Pediatrics* reports a 5-year (2015-19) retrospective data review from a tertiary hospital in Tamil Nadu [15]. Clinical, laboratory and radiological profiles were related to outcome. Many non-infectious disorders including poisoning, toxin or drug related, tumours and vascular causes of AES were excluded. Etiological diagnosis was established by a comprehensive array of tests – blood and CSF cultures for bacteria, serology, PCR, latex agglutination, viral isolation etc. Definitive etiological diagnosis was established in as high as 56.4% children, with a wide variety of agents involved. The study also reveals the AES patterns in southern India from where recent comprehensive data is scarce. STM (11.2%) and DE (9%) were the most common etiologies. Apparently, not a single patient over this 5-year period received a diagnosis of JE, although it is not clear as to how many were tested for JE and what test was used. Another study from South India found JE in 4% [16]. A large-scale, systematic surveillance study in 3 northern/eastern states (UP, Bihar and Assam) was conducted over 4 years (2014-17) in patients presenting with AES, using an algorithmic approach. The overall yield increased 3.1 times to 33.2%; the most commonly identified etiologies being STM (18.5%), JE (17.7%) and DE (5.2%) [17]. Comparison of these northern versus southern data suggests that JE is declining faster in southern states than the north and east. In conclusion, AES remains a challenge to physicians in India. Infectious and non-infectious etiologies have to be considered and the pattern of infection may change with region and time.

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INVITED COMMENTARY

Can Infant Pulmonary Function Tests be Used as a Screening Tool for Diagnosis of Airway Anomalies in Infants?

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Infant pulmonary function tests (IPFTs) have been performed by specialist centres for more than 40 years. The commonly used IPFTs have been tidal breathing flow volume loops (TBFVL), rapid thoracoabdominal compression (RTC), raised volume RTC (RVRTC), infant plethysmography, multibreath washout and forced oscillation. Although IPFTs have been a great research tool for pediatric pulmonologists, they have limited clinical utility at present. A large international survey showed significant variability in practice on IPFT for clinical purposes and decision making [1]. Centres performing more studies were more likely to do so for clinical purposes.

Some European and North American centres have been using IPFTs (usually RVRTC plus multibreath washout) for clinical monitoring of patients with cystic fibrosis and occasionally for infant interstitial lung diseases. There are sparse data on the utility of IPFTs in phenotyping severe bronchopulmonary dysplasia [2]; follow up of newborns receiving antenatal steroids [3], vascular airway compression [4], and diagnosis or follow up of infants with airway anomalies [5].

In the current issue of *Indian Pediatrics*, Pathania and colleagues [6] publish an exploratory study on IPFTs (Tidal Breathing Flow Volume Loops, TBFVL) in 53 children aged 0-2 years with airway anomalies and compared with controls using Exhalyzer D equipment (Eco Medics, Duernten, Switzerland) and Spiroware-1 software. They correlated TBFVL visual patterns with findings of flexible bronchoscopy. They included infants with isolated laryngomalacia (n = 28), laryngomalacia with additional airway anomalies (n = 24; most of them with associated tracheomalacia, bronchomalacia, or tracheobronchomalacia) and isolated pharyngomalacia (n = 1). Notably, there were no children with other congenital common airway anomalies leading to stridor like vocal cord palsy, isolated subglottic stenosis and vascular airway compression, etc that were included. Infants who were sick or having nasofacial anomalies were excluded due to obvious practical reasons.

The authors describe association between bronchoscopy diagnoses and characteristic TBFVL visual patterns. Isolated laryngomalacia was associated with normal expiratory limb and fluttered inspiratory limb (pattern 3) or a flattened expiratory limb with fluttered inspiratory limb (combined pattern 3 and 4). Those with associated bronchomalacia had a concavity in expiratory loops (pattern 5) and those with associated tracheomalacia had a flattened expiratory limb (pattern 2). There was some overlap amongst various patterns. The authors intended to perform six-month follow-up TBFVL in all subjects, but were only able to present these data in 14 children as their study was interrupted by the COVID pandemic. These limited follow-up data are not presented in detail, but it appears that some children had improvement both in TBFVL visual pattern and clinical assessment. The authors suggest that different graphic patterns in TBFVL may correspond to airway obstruction at a particular site (at the larynx or below the larynx), but are not yet able to identify more specific diagnoses.

The authors are to be congratulated for presenting a relatively large volume of data and attempting to correlate this to bronchoscopy findings of airway obstruction. Their group has a track record for publishing data in this field, including a report of normative data on IPFT in a prospective birth cohort study [7]. However, we feel that as of now TBFVL cannot replace bronchoscopy in the initial investigation of children with suspected upper airway abnormalities.

This study is exploratory with subjective outcomes wherein the authors have classified children according to visual patterns of the TBFVL, but as yet have not provided

standardized criteria for how these visual patterns can be defined and clearly categorized. For the purpose of the study these patterns were characterized by three observers, with discussion and consensus in the case of disagreement, but there is no report of the interobserver variability or any attempt at post-operative validation of these categorizations by a 4th or 5th observer. We know from studies in multiple other fields (e.g. scoring of chest CT abnormalities) that visual pattern recognition often has high variability and poor repeatability [7]. The authors present the results of standard TBFVL parameters, and from this it appears that there are group differences in time to reach peak tidal expiratory flow as a proportion of total expiratory time (tPTEF/tE) between their previously tested controls and children with laryngomalacia and additional lower airway abnormality. However, they have not related this or other objective TBFVL parameters to their visual pattern categorization.

It also appears that there is imperfect concordance between bronchoscopy diagnoses and TBFVL visual patterns emphasizing the need to calculate positive or negative predictive values for the analysis. TBFVL visual patterns also cannot reliably distinguish isolated laryngomalacia from laryngomalacia combined with other lower airway disorders, or tracheomalacia from bronchomalacia.

It must be recognized that IPFT is a highly specialized investigation that requires specific equipment, and a great deal of investigator training and experience. It can only be safely performed in infants with relatively mild symptoms, and is not an option for infants in borderline respiratory failure. These investigations have been available for many decades, but are still only rarely used even in resource rich settings. In contrast, flexible bronchoscopy is widely available, and is a relatively safe procedure provided correct guidelines are followed. A trained bronchoscopist will not have difficulty in correctly identifying and categorizing most of the lower airway abnormalities.

In conclusion, the authors should be congratulated for this novel work which has undoubtedly contributed to the IPFT literature. We hope that they and others are able to take this further with objective classification of different TBFVL visual patterns, assessments of repeatability and interobserver variability, and further investigation of how these correspond to clinical and bronchoscopy findings. We agree with their suggestion that serial IPFT may have future value in assessing whether airway abnormalities are improving. However, at this time we caution against implementing the use of TBFVL visual patterns as a clinical tool.

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ORIGINAL ARTICLE

Acute Encephalitis Syndrome in Children and Adolescents: A Five-Year Descriptive Study From South India

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ABSTRACT

Objective: Acute encephalitis syndrome (AES) in children results in significant neurocognitive deficits or mortality. It is pertinent to study the AES patterns periodically to identify the changes in the etiological trends and outcomes. Our objective was to find the etiological agents of AES, mode of diagnosis, treatment given, and outcomes.

Methods: We reviewed the electronic records of children aged 1 month to 15 years who were admitted with AES in our centre from January 2015 to December 2019. We analyzed the the clinical, laboratory, and radiological profile of these children and adolescents in relation to their outcome. Poor outcome was defined as death, discharge against medical advice with neurological deficits, or Glasgow Outcome Score Extended (GOS-E) d≤ 5 at the time of discharge.

Results: Among 250 patients admitted with AES during the study period, a definitive etiological diagnosis was established in 56.4% of children (30.4% viral, 22% bacterial). Scrub typhus (11.2%) and dengue (9%) were the two most common underlying illnesses. Serology helped in clinching the diagnosis in 30% of children. A surge in AES cases in the post-monsoon season was observed in our cohort. Third-generation cephalosporin drugs (85.7%) and acyclovir (77.7%) were the most commonly used empiric antimicrobial drugs. About one-third of children (n = 80) had a poor outcome. GCS ≤ 8 at presentation and requirement for invasive ventilation were found to be significant predictors of poor outcome.

Conclusion: A definitive diagnosis was obtained in about half of the children with AES. Viral (30.4%) and rickettsial infections (22%) were the common etiologies identified. Poor outcome was observed in 32 % of patients.

Keywords: *Acute encephalitis syndrome, Children, Glasgow Outcome Score - Extended*

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INTRODUCTION

Acute Encephalitis Syndrome (AES) is defined by the World Health Organization (WHO) as "a syndrome in a person of any age, at any time of year, with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures)". Other clinical symptoms include increased irritability, somnolence, or abnormal behaviour unexplained by a usual febrile illness [1]. Encephalitis involves inflammation of the cerebral cortex, which may be due to infection or immune-mediated. The etiologies of AES are numerous and the Japanese encephalitis (JE) virus has been reported as the single most important virus causing AES (5-35%) in India. The common bacterial agents are *Orientia tsutsugamushi*, which causes scrub typhus, and *Streptococcus pneumoniae*. In the majority of AES cases, the etiology remains unknown [2].

Though AES is not a common problem among children, the presentation is acute and often associated with poor outcomes contributing to significant morbidity and mortality [3]. The mortality rate in children with AES in India has reduced considerably after the widespread use of JE vaccination, adequate vector control measures, and improvements in the field of health and sanitation [4]. The case fatality rate in JE-related AES was 11.2%, compared to 30-40% in the previous decades [5] . Several studies have shown that the long-term neurological sequelae in children with AES may be as high as 60-80% [6,7].

Identifying AES in children and timely management is pertinent to help prevent catastrophic sequelae. Hence, our

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study objectives were to identify the etiological agents, diagnostic methods, treatment options, and outcomes of children and adolescents with AES admitted in a tertiary care hospital over 5 years.

METHODS

We reviewed the electronic medical records of children aged one month to 15 years admitted between January 2015 to December 2019 to the Department of Pediatrics or Pediatric Neurology at Christian Medical College, Vellore, India, with a diagnosis of AES as per the WHO definition [1]. We used search terms: "encephalitis", "cerebritis", "encephalopathy", "meningoencephalitis" to identify children fulfilling the case definition of AES. We excluded children with brain tumours, epilepsy, brain/ vascular malformations, intracranial bleeding, poisoning, toxin- or drug-related encephalopathy, underlying systemic disorders causing encephalopathy such as uremic or hepatic encephalopathy, steroid psychosis, hypothyroidism (myxoedema coma), neurometabolic disorders and rheumatological disorders such as CNS lupus and vasculitis.

Data were extracted onto a case record form to capture the demographic, clinical, laboratory, treatment, and outcome details. Aseptic meningitis was defined as the presence of clinical signs and symptoms of meningitis, with sterile cerebrospinal fluid (CSF) bacterial cultures and CSF pleocytosis of more than five cells/mm^3 [8]. Pyogenic meningitis was defined as the presence of meningitis with a positive CSF bacterial culture, or the presence of bacterial antigens detected on latex agglutination test. The outcome was assessed in terms of mortality and neurological status at the time of discharge and a follow-up after six months. It was grouped into three categories: complete recovery, discharged against medical advice (DAMA) or dead. Good outcome was defined as complete recovery, discharged against medical advice (DAMA) without any deficits or Glasgow Outcome Score Extended (GOS-E) > 5 (child can get back to normal life with/ without minimal difficulty). Poor outcome was defined as death, DAMA with neurological deficits, or GOS-E <5 (child will be restricted to home or further debilitated) at the time of discharge. Neurological deficit was defined as disorders of the central and peripheral nervous system, which can cause functional or intellectual disability [9]

Statistical analysis: Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS version 22.0, Chicago, IL). Descriptive statistics were used for the representation of frequency, mean, and standard deviation (SD). Data not following normal distribution were represented as median and interquartile range (IQR). Categorical variables between the two groups were compared with the χ^2 test and Fisher's exact test, whereas continuous variables were compared using the Kruskal–Wallis or Mann–Whitney U test. Factors such as age, undernourishment, immunosuppression, Glasgow Coma Scale (GCS) on admission, duration of mechanical ventilation and etiology of AES were analysed by logistic regression for their effect on outcomes. *P* value < 0.05 was considered significant.

RESULTS

Out of 1224 electronic data of children shortlisted using the key search terms, 250 children fulfilled the AES diagnostic criteria during the 5-year study period and were included for analysis.

Children with AES were admitted from various states across India; Tamil Nadu (*n* = 160, 64%), Andhra Pradesh (*n* = 71, 28.4%), West Bengal (*n* = 6, 2.4%), Karnataka (*n* = 3, 1.2%), Odisha (*n* = 3, 1.2%), Jharkhand (*n* = 3, 1.2%), Kerala (*n* = 2, 0.8%), Chhattisgarh (*n* = 1, 0.4%), Assam (*n* = 1, 0.4%) and Meghalaya (*n* = 1, 0.4%). There was significantly a greater number of AES cases per month in the postmonsoon period, between October to February (range: 23-33/month), compared to the other months (range: 15-23/month) (*P* = 0.014). The seasonal pattern of AES with common etiological agents in our cohort is shown in **Fig. 1**.

There were 37 infants (14.8%), 92 (36.8%) between 1-5 years, and the rest 121 (48.4%) aged 6-15 years. The proportion of children with good neurological outcome was 19 (51.3%) in less than 1 year, 63 (68.4%) in 1-5 years and 83 (68.5%) in 6-15 years of age. The common presentating symptoms included fever (100%), seizures (74.7%), altered sensorium (74.3%), vomiting (56.6%), headache (34.7%), and altered behaviour (23.8%).

The etiology of children with AES was determined using multiple modalities. CSF analyses were available in 187 (74.8%) children. Aseptic meningitis was seen in

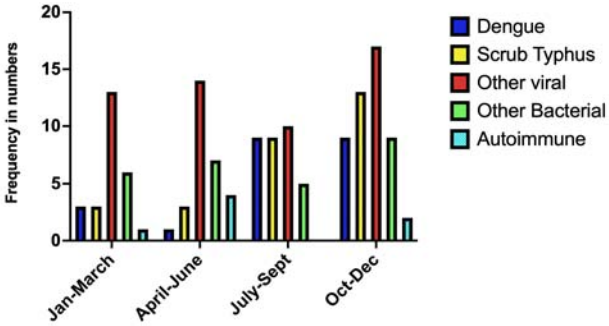

Fig. 1 Seasonal variation in etiological agents causing acute encephalitis syndrome among children

Table I Tests for Etological Diagnosis in Acute Encephalitis Syndrome

Etological Agent	*Diagnostic Modality*	*Diagnostic Yield n (%)*
Bacterial		55 (22)
Rickettsioses	Scrub typhus (IgM+ Weil Felix OX K)	28 (11.2)
	Spotted fever (IgM+ Weil Felix OX 2/OX 19)	5 (2)
S. pneumoniae	CSF Latex agglutination and blood culture	5 (2)
Salmonella (*Salmonella typhi* and C2)	Blood culture	2 (0.8)
	Widal test (Paratyphoid and typhoid- 1 each)	2 (0.8)
Klebsiella spp.	Blood culture	4 (1.6)
Enterococcus	CSF culture	1 (0.4)
	Blood culture	1 (0.4)
H. influenzae type B	CSF culture	1 (0.4)
	Blood culture	1 (0.4)
Neisseria meningitidis	Blood culture	1 (0.4)
Mycoplasma pneumoniae	Cold agglutinin	1 (0.4)
Staphylococcus aureus	Blood culture	1 (0.4)
Acinetobacter spp.	Blood culture	1 (0.4)
Nonfermenting gram-negative bacilli (NFGNB)	CSF culture	1 (0.4)
Viral		75 (30)
Dengue	Serology	22 (9)
Epstein Barr virus	CSF PCR	11 (4.4)
	Serology	1 (0.4)
Herpes Simplex virus	CSF PCR	9 (3.6)
	Serology	1 (0.4)
Influenza A virus	Nasopharyngeal swab	7 (3)
Mumps virus	Serology	6 (2.4)
Varicella Zoster virus	CSF PCR	4 (1.6)
	Blood PCR	1 (0.4)
Influenza B virus	Nasopharyngeal swab	4 (1.6)
Cytomegalovirus	CSF PCR	3 (1.2)
Enterovirus	CSF PCR	1 (0.4)
	Nasopharyngeal swab	1 (0.4)
Measles virus	Serology	1 (0.4)
Parainfluenza virus	Nasopharyngeal swab	1 (0.4)
Boca virus	Nasopharyngeal swab	1 (0.4)
Chikungunya virus	Serology	1 (0.4)
Fungal		
Candida	Blood culture	1 (0.4)
Parasite		
Cysticercosis	CSF Antigen	1 (0.4)
Autoimmune		
Anti-NMDA receptor	CSF/Serum antibodies	8 (3.2)
None		110 (44)

CSF Cerebrospinal fluid, NMDA N-methyl-D-aspartic acid, PCR Polymerase chain reaction

49.2% and pyogenic meningitis in 1.2%. CSF latex agglutination or viral PCR was positive in 34 (16%) of these children. Other diagnostic methods used were serology, which aided in diagnosing 30% of cases, for dengue, scrub typhus, other rickettsial infections, measles, mumps, Epstein Barr virus, Herpes simplex virus (HSV), spotted fever rickettsioses, chikungunya, and cysticercal antibody. Nasopharyngeal (NP) swabs for multiple viruses were sent in 40 children and was positive in 17 (42.5%) cases.

Definitive etiological diagnosis was established in 56.4% of these children (30.4% viral, 22 % bacterial). The two most common etiologies identified in our cohort were scrub typhus (11.2%) and dengue (9%). Description of the etiological profile in children and adolescents with AES including the diagnostic modalities is presented in **Table I**. Amongst infants, HSV was the most common etiological agent identified along with dengue (13.5%).

MRI of the brain was performed in 108 (43.2%) children; white matter hyper-intensities were the most common finding observed in 88 children (81.4%). EEG was performed in 126 (50.4%) children and was normal in 72 cases (50.4%). Only one out of the 10 children with HSV-related AES had periodic lateralised epileptiform discharges (PLEDs).

Antimicrobial therapy was administered to all patients. All children with rickettsioses (13.2%) had received doxycycline and had a good outcome at discharge. Other treatment modalities used were anti-edema drugs, immunomodulation with steroids or IVIG, anti-seizure medications, and general supportive care.. The majority of children in our study recovered without any deficits (n = 133, 53.2%), 36 (14.4%) were DAMA and 36 (14.4%) died. Good outcomes were seen in 68% (170) and bad outcomes in 32% (n = 80) of children. Among the two most common etiologies, the good outcome was seen in all children who had scrub typhus (n = 28), whereas in children with dengue, almost half (n = 10, 45%) had a bad outcome. Factors such as age, immunosuppression, GCS on admission , invasive ventilation and etiology of AES were analysed for their effect on outcome in children with AES. On univariate and multivariate analysis, GCS ≤ 8 on admission [OR 3.38 (95%CI 1.54,7.43), P = 0.002] and need for invasive ventilation [OR 17.48 (95%CI 8.1, 37.8), P < 0.0001] were significant predictors of poor outcomes (**Table II**).

DISCUSSION

Our study showed that a definitive etiological diagnosis was established in 56.4% of children with AES, with viral etiology being the most common (30.4 %). This was found to be higher than most other Indian studies, where more than 50% of children with AES had no identifiable etiology [10]. The California Encephalitis Project identified the etiology of AES in only 16% of cases and viral etiology was the most common (11%) [11]. **Table III** presents the yield of diagnostic tests from other Indian studies on AES [10,12,13,18-24]. Scrub typhus (11.2%) and dengue (9%) were the most common causes of AES in our study, which was similar to a prospective study conducted in the three high burden states of Uttar Pradesh, Assam and West Bengal, where scrub typhus was identified in 10.5% and dengue in 5% of AES cases [12].

Among the various host factors, infants were identified to be the most vulnerable population. This finding is in contrast to a study reported from Assam, where children aged 5-12 years were found to be at risk for AES [13]. An Australian multicentre prospective cohort study also showed that AES was more common in younger children (median age of 1.7 years) [14]. There was an increase in the number of AES patients during the postmonsoon season which was similar to a surveillance study done in Uttar Pradesh, where there was an increase in AES cases during the monsoons [15]. This seasonality can be used to prepare the health care services to be geared towards handling the increased number of AES cases. Since dengue and scrub typhus are the most common causes of AES, public education and preventive measures can be instituted to decrease AES cases.

MRI brain showing non-specific white matter hyper-intensities was the most common finding in our study (81.5 %). An Israeli retrospective study showed that neuro-

Table II Predictors of Poor Outcome in Children With Acute Encephalitis Syndrome

Parameter	*OR (95% CI)*	*P value*	*Adjusted OR*	*95% CI*	*P value*
Age	0.97 (0.92, 1.03)	0.32	-	-	-
Immunosuppression	1.47 (0.45, 4.78)	0.52	-	-	-
GCS ≤ 8	11 (5.6, 21.43)	< 0.0001	3.38	1.54-7.43	0.002
Invasive Ventilation	26.9 (12.9, 55.9)	< 0.0001	17.48	8.1-37.8	< 0.0001
Aetiology of AES	1.04 (0.95, 1.14)	0.38	-	-	-

CI Confidence interval, GCS Glasgow coma score, OR Odds ratio

Table III Diagnostic Yield in Various Studies From India on Acute Encephalitis Syndrome

Authors	*States represented*	*Study period*	*Sample size*	*Age group*	*Diagnosis*
Damodar et al [18]	Karnataka	2019-2022	376	1 mo -18 y	23%
Kakoti et al [13]	Assam	2019-2020	140	1 mo -12 y	37.9%
Tandale et al [10]	Maharashtra, Telangana	2018-2020	278	All ages	41.4%
Murhekar et al [19]	Uttar Pradesh	2016	407	All ages	65.4%
Tandale et al [20]	Maharashtra	2015-2016	280	< 15 y	22.1%
Goel et al [21]	Delhi	2015	50	1 mo -12 y	22%
Vasanthapuram et al [12]	Uttar Pradesh, West Bengal, Assam	2014-2017	10,107	All ages	49.2%
Medhi et al [22]	Assam	2012-2014	1707	All ages	46.8%
Tripathy et al [23]	Orissa	2012-2013	834	6 mo - 5 y	16.3%
Beig et al [24]	Uttar Pradesh	2004-2006	87	6 mo -12 y	21.8%

imaging was abnormal in 39% of children with AES at presentation [16]. Although PLEDs are considered specific for HSV, out of 10 children who had HSV-related AES only one had PLED. An etiology was established in 17.5% of our cases based on CSF analysis and 30.1% based on serological tests.

Considering the therapeutic response to doxycycline in rickettsiosis, it would be prudent to add empiric treatment for the same with doxycycline and/or azithromycin, especially during the peak season, till a definite alternate diagnosis is established. In a recent study in adults with scrub typhus infection [17] combination therapy with doxycycline and azithromycin, was more effective in preventing morality/ complications than either of the drugs used alone.

Our study has several limitations. Being a retrospective study, a structured etiological diagnostic algorithm was not followed in all cases and it is possible that etiological diagnosis would have been missed in a few cases. Children who were discharged against medical advice were not followed up and their final outcome was not ascertained. MRI brain scans were not done in 56.8% of children, which is a major limitation, considering the importance of neuroimaging in AES. Being a tertiary hospital-based study, the findings of this study cannot be extrapolated to general population. However, the findings of this study are important and add knowledge to this condition with high morbidity and mortality which is not well studied among children.

In conclusion, a definite etiological diagnosis for AES was obtained in a majority (56.4%) of the children in our study. Dengue and scrub typhus were the most common etiological agents of AES. Unfavorable outcome was seen in 32% of children, with low GCS ≤ 8 at presentation and the need for mechanical ventilation being the significant predictors.

Ethics clearance: Institutional Ethics Committee, No. 13145, dated July 08, 2020.

Contributors: WR, BR, MT, AMA, SY, EJ, SK: Concept and design of the study; WR, BR, MT, AJ: Critical writing/ intellectual content. All authors are equally contributed in literature review and final approval of the manuscript.

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WHAT THIS STUDY ADDS?

- Scrub typhus and dengue are the commonest cause of acute encephalitis syndrome in our study.
- Serological tests can aid in establishing the diagnosis in a third of cases with AES.
- Good outcome was seen in 68% children in our study.

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ORIGINAL ARTICLE

Infant Pulmonary Function Tests in Children with Airway Anomalies and Correlation with Bronchoscopy Findings

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ABSTRACT

Objectives: To evaluate the role infant pulmonary function tests (Tidal Breathing Flow Volume Loops, TBFVL) in children with airway anomalies and to correlate the TBFVL so obtained with bronchoscopy findings.

Methods: In this prospective cohort study, we enrolled children aged 0-2 years with airway anomalies and performed TBFVL and bronchoscopy. The primary outcome measure was graphic pattern of TBFVL in laryngomalacia. Secondary outcome measures were types of TBFVL results in various airway anomalies and controls.

Results: Out of 53 children enrolled, 28 (52.3%) had laryngomalacia. Pattern 3 (fluttering of inspiratory limb) was commonest TBFVL pattern in laryngomalacia. Among TBFVL parameters, the ratio of inspiratory time to expiratory time (Ti/Te) and tPTEF/tE was significantly high in children with isolated laryngomalacia compared to controls. At six months of follow-up, TBFVL pattern 1 (normal) became the commonest pattern.

Conclusion: A particular type of airway anomaly may have a characteristic graphic pattern in TBFVL and TBFVL pattern may indicate improvement in airway anomalies in follow-up.

Keywords: *Fluttering pattern, Laryngomalacia, Tracheomalacia, Tidal Breathing Flow Volume Loop*

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INTRODUCTION

Airway anomalies are not uncommon in children below two years of age and usually present with noisy breathing (stridor and/or wheezing). The exact incidence is unknown; however, studies have revealed an estimated 1 in 2,100 children. For the diagnosis of airway anomalies, bronchoscopy is the gold standard [1]. Infant pulmonary function tests (IPFT) are being explored for their clinical utility, specifically in diagnosing airway abnormalities. A review by Godfrey et al concluded that IPFT has potential clinical use in diagnosing and monitoring airway malacias [2].

A study by Majid et al evaluated the role of tidal breathing flow volume loop (TBFVL) in patients with tracheomalacia [3]. However, there is a need to generate more data as not many studies determine the clinical role of IPFT in airway anomalies. We conducted this study to assess the IPFT in children with suspected airway anomalies and to correlate the TBFVL so obtained with bronchoscopy findings.

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METHODS

We performed a prospective cohort study in the Department of Pediatrics of a tertiary care institute in Delhi, India, from July 2018 to April 2020 in children aged upto 2 years with physician suspected airway anomalies. The study was approved by Institutional Ethics Committee. Written informed consent was taken from the parents/guardians.

We suspected airway anomalies in infants with either persistent (more than two weeks) inspiratory or biphasic (both inspiratory and expiratory) stridor or in those with persistent (more than two weeks) barking or brassy cough, unexplained wheezing that was not responding to inhaled steroids for 4-8 weeks despite proper compliance and technique, or, in those with choking while feeding without significant developmental delay. We excluded children with hypoxia (SpO2 < 92%), hemodynamic instability, nasofacial deformities, tracheostomy and pulmonary bleed. We recorded a detailed history, physical examination and baseline data of all enrolled children. All enrolled infants underwent IPFT and bronchoscopy. The two investigations were done within a week of each other.

The person performing the IPFT was not aware of bronchoscopy findings, if bronchoscopy was done earlier. IPFT was performed during sleep or light sedation using triclofos single oral dose (50 mg/kg). TBFVL was performed in the pulmonary function test laboratory with EXHALYZER-D equipment (Eco Medics, Duernten, Switzerland) having Spiroware-1 software. IPFT included TBFVL. IPFT parameters evaluated were tidal volume (TV), inspiratory time (Ti), expiratory time (Te), Ti/Te, respiratory rate, peak tidal inspiratory flow (PTIF), peak tidal expiratory flow (PTEF), PTEF/PTIF, time to PTIF, time to PTEF, time to peak tidal expiratory flow/total time to expiration (tPTEF/tE), and the ratio of mid-tidal expiratory flow to mid-tidal inspiratory flow (MTEF/MTIF). We used normative data for a similar number of age (±1 month), gender and birth weight-matched healthy infants from the birth cohort study database from our department for reference [4]. We categorized the IPFT curve into five patterns as shown in **Fig. 1**, modified from the study by Filippone et al [5].

IPFT were reported by three observers blindly, and in case of discrepancy, the final diagnosis was made by discussion. Bronchoscopy was performed as per unit protocol under conscious sedation. Three observers independently reported abnormalities and severity after seeing the saved bronchoscopy video. Patterns and parameters of IPFT were compared with findings of bronchoscopy.

Enrolled children were followed-up for upto six months and a repeat IPFT was conducted. Bronchoscopy was not repeated at six months follow-up. The primary outcome measure was a graphic pattern of TBFVL in children with laryngomalacia. Secondary outcome measures were bronchoscopic diagnosis of various airway anomalies, graphic patterns in children with airway anomalies other than laryngomalacia, measurement of TBFVL parameters and measurement of change in TBFVL graphic patterns and parameters at six months follow up. We did not perform any intervention other than supportive care in the study.

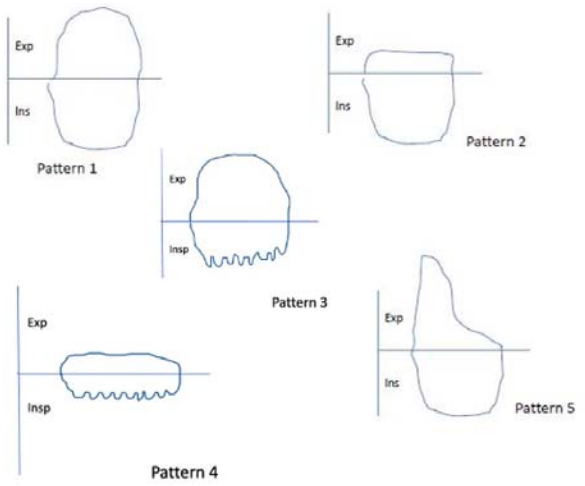

Fig. 1 Patterns of Infant Pulmonary Function Tests

The sample size was not calculated as ours was an exploratory study. We included all consecutive eligible children below 2 years of age during the study period.

Statistical analysis: The data was recorded in an Excel sheet, and statistical analyses were done using STATA software version 12. The pattern of IPFT loops and type of airway anomalies observed were presented using descriptive statistics. TBFVL parameters were compared among historical controls and those infants with various bronchoscopy airway anomalies using Student t test if data were normally distributed or Mann Whitney test if data had non-normal distribution. ANOVA test was used to compare differences between two or more means. Changes in TBFVL graphic patterns and parameters were analyzed after six months by paired t test.

RESULTS

A total of 88 children with suspected airway anomalies were screened. We included 53 infants for whom both bronchoscopy and IPFT were performed. The flow of patients is given in **Fig. 2**. The demographic and clinical characteristics of included participants are shown in **Table I**.

The median age of children was six months, ranging from 3 weeks to 20 months. Most were boys, and 92% were born at term gestation. The commonest symptom was noisy breathing in 44 (83%) children. The median age of appearance of noisy breathing was one month. Stridor was present in 24 (45%) children commonly noticed at the end of the 2nd week of life. Bronchoscopy was performed in 53 children; 28 (52.8%) had isolated laryngomalacia. The details of bronchoscopy findings are shown in **Table II**. The graphic patterns of TBFVL are shown in **Table III**. Pattern 3 (normal expiratory limb and fluttered inspiratory limb) was the most common pattern in children with isolated laryngomalacia. In 21 out of 28 isolated laryngomalacia cases, the graphic pattern was consistent with a fluttered inspiratory limb (pattern 3 plus pattern 4).

Forty per cent of children with bronchomalacia had an early expiratory peak with the concave expiratory limb. Tracheomalacia was present in 13 children (in seven associated with laryngomalacia and in six associated with laryngomalacia and bronchomalacia), and six out of these had flattened expiratory limb (three had pattern 2; three had pattern 4). One child with pharyngomalacia had a

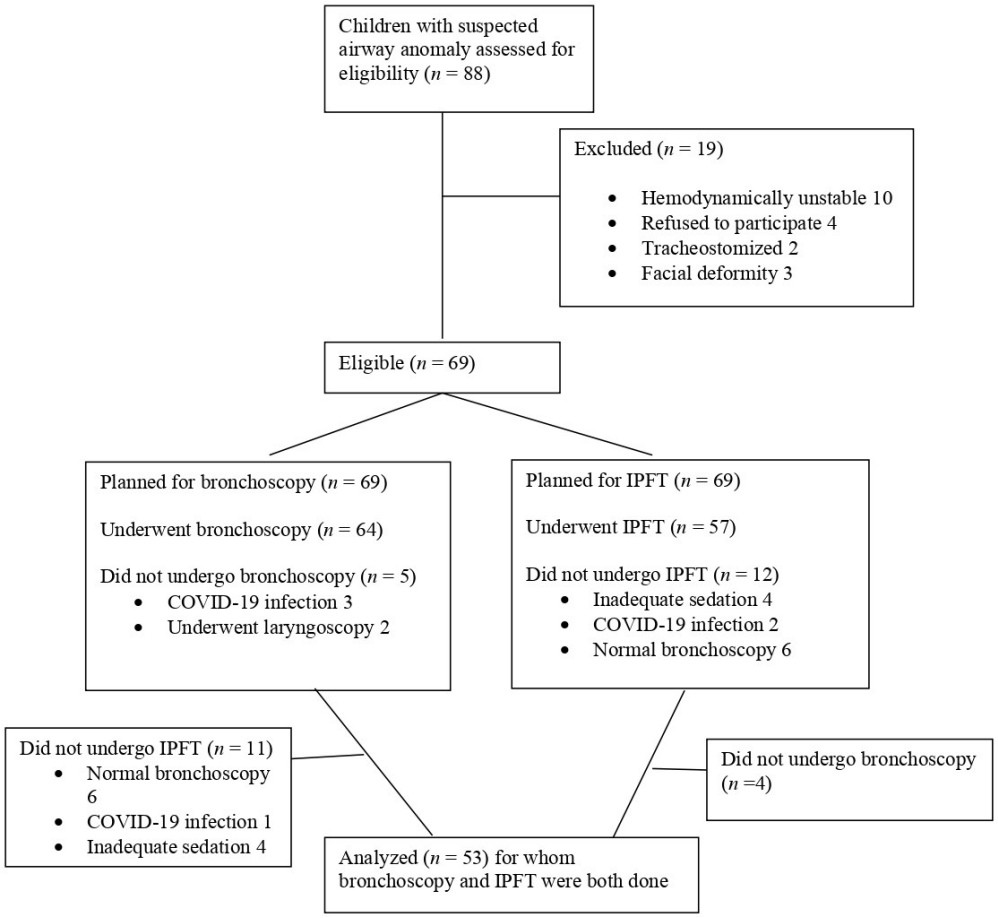

Fig.1 Flow of participants in the study

normal IPFT pattern (pattern 1). Out of four children with subglottic stenosis, three had a flattened expiratory limb. The representative patterns are shown in **Web Fig. 1**.

The TBFVL parameters in children with laryngomalacia and other airway anomalies compared to controls are shown in **Table IV.** There was a significantly high ratio of inspiration to expiration time in children with isolated laryngomalacia. The remaining TBFVL parameters were similar in children with isolated laryngomalacia and controls.

We could follow 14 children six months after diagnosis. The TBFVL Patterns 1, 2, 3, 4 and 5 were present in 3 (21.4%), 2 (14.3%), 4 (28.6%), 2 (14.3%), and 3 (21.4%) respectively at baseline. At six months follow up, TBFVL patterns 1, 2, 3, 4, and 5 were seen in 4 (28.6%), 2 (14.3%), 3 (21.4 %), 3 (21.4.3%), and 2 (14.3%) respectively. At baseline, pattern 3 was most common, followed by pattern 4. At six months of follow-up, pattern 1 (normal) was most common, followed by patterns 3 and 4. Out of these 14 patients, 4 had the same TBFVL pattern in follow up and TBFVL pattern had become normal in 2 patients and they also improved clinically.

Web Table I shows TBFVL parameters at baseline and after six months. There was no difference in TBFVL parameters except expiratory time, which significantly increased in follow-up.

DISCUSSION

In this study, we evaluated the IPFTs in 53 children with airway anomalies and corelated with bronchoscopy findings. Isolated laryngomalacia (n = 28) was the most common airway anomaly, followed by laryngo-tracheomalacia (n = 7), laryngotracheobronchomalacia (n = 6), and laryngomalacia with subglottic stenosis (n = 4). Among patients with isolated laryngomalacia, pattern 3 was most commonly observed followed by pattern 4.

In our study, isolated laryngomalacia was found in 28 (52.8%), and laryngomalacia was associated with other airway anomalies in 24 (45.3%) children, which is

Table I Demographic and Clinical Characteristics of the Study Population (*n* = 53)

Patient characteristics	*Value*
Age (mo)[a]	6 (3, 9)
Male Gender[b]	38 (71.7)
Delivered at term gestation[b]	49 (92.4)
Birth weight (kg)[a]	2.6 (1.7, 3.5)
Weight for age *z*-score at enrolment[a]	-2.82 (-3, -1.95)
Length for age *z*-score at enrolment[a]	-2.32 (-3.24, -1.46)
Clinical features at presentation[b]	
Noisy breathing	44 (83)
Stridor	24 (45.3)
Wheeze	7 (13.2)
Cough	21 (39.6)
Barking cough	8 (15.1)
Breathlessness	4 (7.55)
Feeding difficulty	22 (41.5)
Occasional choking while feeding	16 (30.2)
Recurrent lower respiratory tract infection	19 (35.8)
Examination at presentation[b]	
Inspiratory stridor at rest	9 (16.9)
Retrognathia	3 (5.6)
Pallor	3 (5.6)
Down facies	2 (3.8)
Pectus excavatum	1 (1.8)
High arch palate	1 (1.8)
Hemangioma face	1 (1.8)
Club foot	1 (1.8)
Respiratory system examination[b]	
Tachypnea	11 (20.7)
Chest retraction	7 (13.2)
Audible wheeze	2 (3.8)
Chest Auscultation	
Normal	36 (67.9)
Generalized rhonchi	9 (16.9)
Crepitations	3 (5.6)
Biphasic rhonchi	5 (9.4)

Values presented as [a]median (IQR), [b]n (%)

Table II Airway Anomalies Diagnosed by Bronchoscopy (*n* = 53)

Type of anomaly	*n (%)*
Isolated laryngomalacia	28 (52.8)
Laryngotracheomalcia	7 (13.2)
Laryngotracheobronchomalacia	6 (11.32)
Laryngomalacia and subglottic stenosis	4 (7.55)
Laryngomalacia and Bronchomalacia	3 (5.66)
Laryngomalacia and grade 1 laryngeal cleft	1 (1.89)
Pharyngomalacia	1 (1.89)
Laryngomalacia and pharyngomalacia	1 (1.89)
Laryngomalacia and vallecular cyst	1 (1.89)
Laryngomalacia and tracheal diverticulum/ blind pit	1 (1.89)

comparable with other studies [6,7]. Filippone et al studied TBFVL patterns in 113 children and reported that pattern 3 was always associated with laryngomalacia (100% sensitive) [5]. In our study, 21 children with isolated laryngomalacia had fluttered inspiratory limb; 13 had an only inspiratory flutter (pattern 3), and eight had associated expiratory flattening (pattern 4). Out of 24 cases of laryngomalacia 24 were associated with other airway anomalies; 12 (50%) had inspiratory fluttering, 5 of these had only inspiratory fluttering (pattern 3), and the remaining 7 had inspiratory fluttering with expiratory flattening (pattern 4). The slight discrepancy in pattern 3 (fluttered inspiratory limb) for isolated laryngomalacia in our study may be explained by that we performed TBFVL in a few children after bronchoscopy on the same day. In our study, 18 children had obstruction between glottis and bifurcation of the trachea (7 had laryngotracheomalacia, 6 had laryngotracheobronchomalacia, 4 had laryngomalacia with subglottic stenosis, and 1 had laryngomalacia with tracheal diverticulum). Of these 18 children, nine (50%) had expiratory flattening (4 had isolated expiratory flattening, and 5 had expiratory flattening and inspiratory fluttering). In our study, the Ti/Te ratio was significantly higher in children with isolated laryngomalacia compared to controls. The possible explanation for these findings may be prolonged inspiratory time in cases of isolated laryngomalacia. We found significantly high PTEF/tE in laryngomalacia plus subglottic stenosis compared to controls that was different from a study by Filippone et al [5]. The possible explanation for this difference may be that study by Filippone et al [5] had a variety of diagnosis in pattern 2, and only four cases out of 46 had associated laryngomalacia, whereas in our study, all four patients in this category had laryngomalacia plus subglottic stenosis.

Filippone et al [5] performed follow-up TBFVL in 12 cases of airway obstruction between glottis and carina after surgical or medical intervention (five had subglottic hemangioma, one had postintubation tracheal stenosis, five had secondary tracheomalacia) and found improvement in the expiratory limb from pattern 2 (flattened expiratory limb) to pattern 1 (normal pattern) and increase in expiratory flow rates [8]. We followed up 14 children (mostly laryngomalacia) without any specific intervention. We found a significant improvement in the pattern of

Table III Tidal Breath Flow-Volume Loop Graphic Patterns in Children With Different Airway abnormalities Detected on Bronchoscopy

Bronchoscopy diagnosis	*Pattern 1*	*Pattern 2*	*Pattern 3*	*Pattern 4*	*Pattern 5*
Isolated laryngomalacia (*n* = 28)	3 (10.7)	3 (10.7)	13 (46.4)	8 (28.6)	1 (3.6)
Pharyngomalacia (*n* = 1)	1 (100)	-	-	-	-
Laryngomalacia and pharyngomalacia (*n* = 1)	-	-	1 (100)	-	-
Laryngotracheomalcia (*n* = 7)	-	1 (14.2)	2 (28.6)	2 (28.6)	2 (28.6)
Laryngotracheobronchomalacia (*n* = 6)	1 (16.6)	2 (33.3)	0	1 (16.6)	2 (33.3)
Laryngomalacia and subglottic stenosis (*n* = 4)	0	1 (25)	1 (25)	2 (50)	0
Laryngomalacia and Bronchomalacia (*n*= 3)	0	1 (33.3)	0	0	2 (66.7)
Laryngomalacia and others (*n* = 3)	-	-	1 (33.3)	2 (66.7)	0

Pattern1 Normal TBFVL graphic curve, Pattern 2 Normal inspiratory limb and flattened expiratory limb of TBFVL curve, Pattern 3 Normal expiratory limb and fluttered inspiratory limb of TBFVL curve, Pattern 4 Inspiratory limb fluttered and expiratory limb flattened, Pattern 5 Early expiratory peak with the concave expiratory limb

TBFVL towards normal pattern, though we could not find a difference in TBFVL parameters, likely due to a small number of follow up cases. Moore et al evaluated 21 children at a median (range) age of 9.4 (7.6 - 14.3) mo who were diagnosed with tracheobronchomalacia during infancy and reported persistence of symptoms and abnormal pulmonary functions [8].

Based on our study and reviewing the literature, it may be said that graphic patterns in TBFVL may be suggestive of airway obstruction at a particular site (larynx or below the larynx). Using TBFVL as initial screening test for airway anomalies may obviate the need for invasive bronchoscopy procedures in many infants with airway anomalies. Although, TBFVL pattern will usually suggest a site of obstruction, not a specific diagnosis. Airway anomalies frequently occur in combination, and TBFVL patterns may be combined. As seen in our study, these may be challenging to interpret, where about 50% of cases had combined airway anomalies. Although Pattern 3 on TBFVL may be almost diagnostic of laryngomalacia, other patterns may warrant the need for bronchoscopy as well. Thus, findings of TBFVL must be interpreted in context and history and physical examination findings.

Table IV Tidal Breathing Flow Volume Loop Parameters in Various Types of Airway Anomalies

TBFVL parameter	*LM (n=28)*	*LM + TM (n = 7)*	*LM + TM + BM (n = 6)*	*LM + SS (n = 4)*	*LM + Others[a] (n = 4)*	*Miscella-neous[b] (n = 4)*	*Controls (n = 53)*	*P value*
Tidal volume(mL)	43.7 (20.5)	35.8 (18.8)	38.2 (12.4)	34.7 (13.8)	53.0 (28.2)	62.2 (36.8)	33.7 (22.5)	0.700
Tidal volume (mL/kg)	8.0 (2.7)	7.10 (0.96)	8.48 (4.04)	8.33 (1.3)	7.18 (1.17)	8.13 (2.82)	7.65 (2.81)	0.440
Insp time (sec)	0.69 (0.21)	0.54 0.18)	0.53 (0.18)	0.52 (0.13)	0.75 (0.14)	0.66 (0.11)	0.60(0.14)	0.214
Exp time (sec)	0.77 (0.28)	0.6 (0.25)	0.59 (0.19)	0.78 (0.41)	1.09 (0.28)	0.97 (0.31)	0.76 (0.26)	0.723
Ti/Te	96.9 (31)	92.9 (31)	94.3 (13.7)	77.8 (17.8)	59.5 (43.9)	76.8 (30.5)	76.3 (21.2)	0.064[c]
Resp rate/min	44.7(14.6)	46.3(14.6)	57.9(16.3)	52.5(14.4)	33.2(5.3)	39.3(12.2)	50.2(10.4)	0.076
PTIF	0.10 (0.04)	0.09 (0.04)	0.12 (0.06)	0.11 (0.04)	0.18 (0.16)	0.15 (0.06)	0.08 (0.05)	0.089
PTEF	0.09 (0.03)	0.07 (0.04)	0.13 (0.03)	0.09 (0.05)	0.08 (0.03)	0.13 (0.06)	0.07 (0.04)	0.179
Time to PTIF	0.30 (0.13)	0.34(0.13)	0.25 (0.13)	0.34 (0.14)	0.35 (0.18)	0.36 (0.15)	0.30 (0.09)	0.794
Time to PTEF	0.19 (0.10)	0.16 (0.05)	0.19 (0.10)	0.32 (0.22)	0.15 (0.03)	0.17 (0.09)	0.21 (0.11)	0.941
tPTEF/t E	30.0 (14.3)	23.6 (14.3)	34.6 (14.8)	41.9 (15.5)	14.8 (6.1)	18.8 (8.3)	30.6 (13.3)	0.024
MTEF/MTIF	103.2 (42.6)	80.2 (42.6)	106.7 (38.8)	74.7 (22)	68.6 (22.7)	85.4 (42)	95.1 (16)	0.112

Values expressed as mean (SD). LM Laryngomalacia; TM Tracheomalacia; BM Bronchomalacia; SS Subglottic stenosis; MTEF Mid tidal expiratory flow; MTIF Mid tidal inspiratory flow; PTIF Peak tidal inspiratory flow; PTEF Peak tidal expiratory flow; tPTEF/tE Time to peak tidal expiratory flow/total time to expiration; TBFVL Tidal Breathing Flow Volume Loop. [a]Others (Vallecular cyst 1, Laryngeal cleft 1, Tracheal diverticulum 2), [b]Miscellaneous (Pharyngomalacia 1, Pharyngomalacia + LM 1, LM + bronchomalacia 1). [c]P value for comparison of Ti/Te for laryngomalacia versus controls is 0.005.

WHAT THIS STUDY ADDS?

- Where-ever available, IPFT based on TBFVL can be used as a screening tool to detect airway anomalies in infants.
- TBFVL pattern and parameters may suggest airway obstruction at a particular site (larynx or below the larynx).

Our study is one of the few studies that evaluated IPFT in children with airway anomalies with a reasonable number of participants. It is also possibly one of the few studies wherein children with airway anomalies were followed up with repeat IPFT. IPFT parameters were compared with a similar number of controls, matched with birth weight, sex and age. The IPFT was performed successfully in most children with mild sedation or during sleep. Reporting of IPFT patterns and bronchoscopy findings was done by three persons independently to decrease observer bias. Also, the reporting IPFT and bronchoscopy were done without knowing the results of other procedures.

Unfortunately, follow up of all participants could not be completed due to the COVID pandemic. Also, a uniform sequence of first doing IPFT and then doing bronchoscopy could not be done in all patients as there are fixed days for bronchoscopy in our institute. Controls were taken from a birth cohort, and we did not perform bronchoscopy on them (gold standard to diagnose airway anomaly). We could not do IPFT of children who had normal bronchoscopy.

We concluded that graphic patterns in TBFVL may suggest the site of airway obstruction. Where-ever the facility of TBFVL is available, it may be used as a screening test for airway anomalies, and invasive bronchoscopy procedures may be avoided for screening. Abnormal patterns observed in TBFVL may be confirmed with bronchoscopy as per the clinician's judgement.

Contributors: AP: Conception of work, acquisition, analysis and interpretation of data, and drafting of the work. KRJ, RL, SKK, JS: Conception of work, interpretation of data, and revising of the work. All authors have approved the final version and are accountable for the accuracy of the work. KRJ will act as guarantor of the manuscript.

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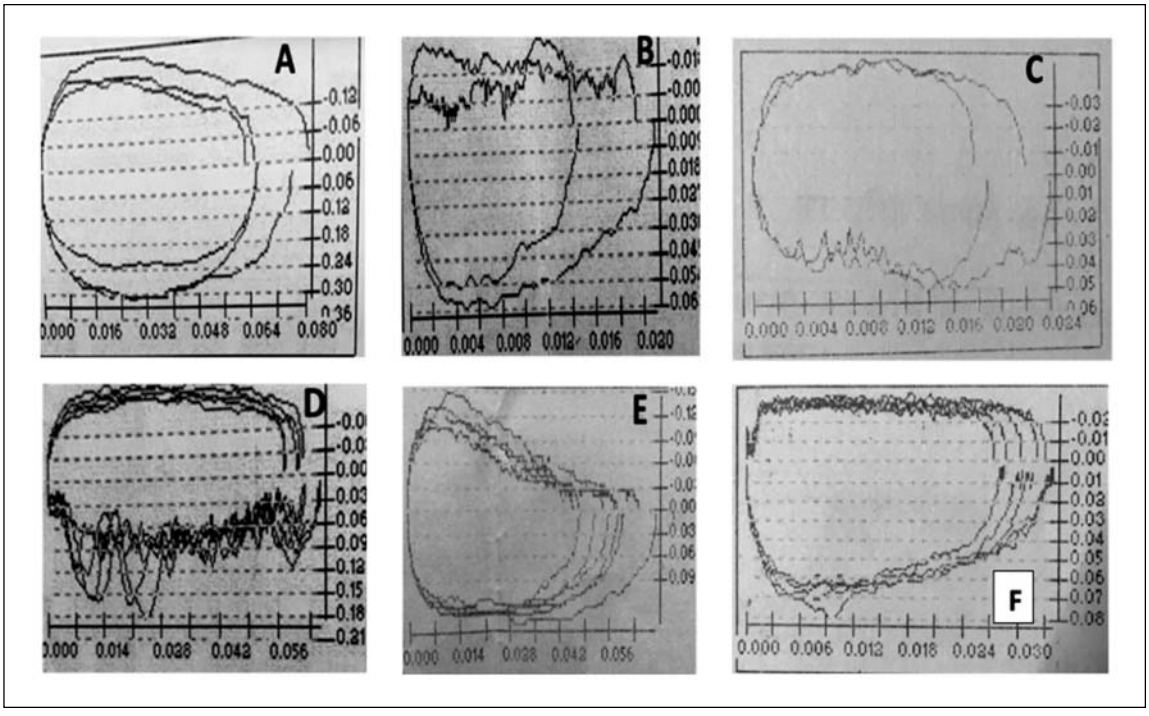
Web Table I Tidal Breathing Flow Volume Loop Parameters in Children With Airway Anomalies at Baseline and Follow up (*n* = 14)

TBFVL parameter	*Baseline*	*At six months of follow up*	*P value*
Tidal volume (mL)[a]	45 (30, 59.4)	55.5 (34,72)	0.187
Inspiratory time (s)[b]	0.62 (0.20)	0.68 (0.19)	0.236
Expiratory time (s)[b]	0.70 (0.24)	0.83 (0.29)	0.026
Ti/Te[b]	93.3 (21.1)	88.51 (20.57)	0.525
Respiratory rate (breath/min)[b]	45.6 (13.60)	44.6 (13.90)	0.688
PTIF (L/min)[a]	0.11 (0.061, 0.15)	0.13 (0.09, 0.17)	0.533
PTEF (L/min)[b]	0.11 (0.04)	0.12 (0.04)	0.135
Time to PTIF[b]	0.31 (0.11)	0.34 (0.11)	0.485
Time to PTEF[a]	0.16 (0.12, 0.19)	0.16 (0.14, 0.27)	0.593
tPTEF /tE[b]	26.2 (6.90)	27.2 (9.10)	0.734
MTEF/MTIF[b]	99.6 (30.40)	92.0 (22.30)	0.495

Values expressed as [a]median (IQR) or [b]mean (SD). MTEF Mid tidal expiratory flow, MTIF Mid tidal inspiratory flow, PTIF Peak tidal inspiratory flow, PTEF Peak tidal expiratory flow, TBFVL Tidal Breathing Flow Volume Loop, Te Expiratory time, tE total time to expiration, Ti Inspiratory time, tPTEF Time to peak tidal expiratory flow



Web Fig. 1 Representative images of each type of IPFT pattern and subglottic stenosis, A Pattern 1 Normal, B Pattern 2 Normal inspiratory limb and flattened expiratory limb; C Pattern 3 Normal expiratory limb and fluttered inspiratory limb, D Pattern 4 Inspiratory limb fluttered and expiratory limb flattened, E Pattern 5 Early expiratory peak with the concave expiratory limb, F Subglottic stenosis

ORIGINAL ARTICLE

Anthropometric Growth Reference for Indian Children and Adolescents

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ABSTRACT

Objective: We aimed to develop anthropometric growth references for Indian children and adolescents, based on available 'healthy' child data from multiple national surveys

Methodology: Data on 'healthy' children, defined by comparable WHO's Multicentre Growth Reference Study (MGRS) selection criteria, were extracted from four Indian surveys over the last 2 decades, *viz*, NFHS-3, 4, and 5 and Comprehensive National Nutrition Survey (CNNS). Reference distributions of height-for-age for children up to 19 years, weight-for-age for children up to 9y, weight-for-height for children less than 5 years and BMI for age for children between 5-19 y were estimated by GAMLSS with Box-Cox Power Exponential (BCPE) family. The national prevalence of growth faltering was also estimated by the NFHS-5 and CNNS data.

Results: The distributions of the new proposed Indian growth references are consistently lower than the WHO global standard, except in the first 6 months of age. Based on these references, growth faltering in Indian children and adolescents reduced > 50% in comparison with the WHO standard.

Conclusion: The study findings revealed that the WHO one-standard-fits-all approach may lead to inflated estimates of under nutrition in India and could be a driver of misdirected policy and public health expenditure in the Indian context. However, these findings need validation through prospective and focussed studies for more robust evidence base.

Keywords: *Anthropometry, Body Mass Index (BMI)-for-age, Growth reference, Stature-for-age, Weight-for-age, Weight-for-height*

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INTRODUCTION

The prevalence of undernutrition among under-five Indian children, as measured through the WHO Child Growth Standards, remains high in the latest National Family Health Survey (NFHS-5, 2019-21) with 35.5% of children being stunted, 32.1% underweight and 19.2% wasted [1]. Another national survey, the Comprehensive National Nutrition Survey (CNNS 2016–18) also reported a prevalence of 35% stunting, 33% underweight and 17% wasting in a similar population [2]. These reports present a negligible decline from the 38.4% stunting, 35.7% underweight and 21% wasting reported in NFHS-4 (2014-15) [3], NFHS-3 (2004-05) [4]. This static level of growth faltering questions the impact of existing national programs aimed to prevent under nutrition in young children [5]. However, the apparent lack of adequate response could also be due to the use of the one-size-fits-all WHO Child Growth Standards to diagnose growth faltering in the Indian context.

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The WHO Growth Standards for under 5-year-old children were presented in the Multicentre Growth Reference Study (MGRS), 2006, which described these as how children should grow when their needs are met [6]. Longitudinal and cross-sectional data from six countries (Brazil, Ghana, India, Oman, Norway and USA), from participants who had no economic, environmental or biological risk factors for growth, who were singleton, delivered at term gestation, with no significant morbidity, and with non-smoking mothers who agreed to follow infant feeding recommendations. Affluent neighbour-hoods were purposively selected for Ghana and India. Growth references for school going children and adolescents (5-19 years) were developed by the WHO using the same data (derived from US children and adolescents) that was used for the construction of the original National Center for Health Statistics (NCHS) charts [6]. This involved the pooling of three data sets; Health Examination Survey (HES) Cycle II and Cycle III, and Health and Nutrition Examination Survey (HANES) Cycle I [7]. No information was given regarding their feeding.

In the Indian context, there has been recent advocacy for the use of local growth standards. The national representativeness of the small homogenous affluent neighbourhoods in South Delhi in the Indian site in the WHO study (0-5 years) has been questioned. Further justification stems from the analyses of national survey datasets, utilizing inclusion criteria similar to MGRS by WHO, which demonstrate a significant deviation of mean z-scores by WHO standards from zero for all the three indices: Height-for-age *z*-score (HAZ), weight-for-age *z*-score (WAZ) and weight-for-height *z*-score (WHZ) in under-five children (-0.52 to -0.79) in a subset of healthy Indian children [8]. In effect, using the WHO standard instead of these contextual references almost doubled the estimated growth failure in India [8]. From a clinical perspective, the use of WHO growth standards has also been shown to result in disease misclassification, including pathological short stature [9,10], macrocephaly and microcephaly [11], screening of fetal growth restriction for predicting future morbidity [12] and diagnosing cardiometabolic risk factors [13,14]. The WHO growth references for 5-19 years were developed from a potentially obesogenic environment (USA). Thus, there is a need for nationally representative standard for 5-19 years, preferably as a single (continuous), representative and contemporary Indian growth standard spanning from birth to 19 years for use in clinical practice [15].

We therefore aimed to develop anthropometric growth references for Indian children from birth to 19 years of age using predefined criteria to select participants at low risk of growth constraint from contemporary data of nationally representative surveys. These were compared against the global WHO anthropometric growth standards. In addition, based on the newly constructed growth references, we developed a simple software application to permit the immediate calculation of various indices of child growth from birth to 19 years. We prefer to use the term growth reference instead of standard, especially since these analyses emanate from retrospective datasets, and need further validation from robust, prospective studies.

METHODS

This study used multiple national cross sectional survey data sets, from each of which subsets of healthy children were extracted. Selection was based on uniform criteria for socio-demographic variables, so as to replicate those used in the WHO-MGRS survey to the extent feasible.

The Comprehensive National Nutritional Survey (CNNS, 2016-18) was the first ever nationally representative nutrition survey of Indian children and adolescents [2]. The CNNS survey reported data from preschool children (0-4-year-old), school-age children (5-9-year-old), and adolescents (10-19-year-old) in all the 30 geographical states of India by multistage sampling. Children and adolescents with physical deformity, cognitive disabilities, chronic illness, acute febrile or infectious illness, acute injury, ongoing fever, and pregnancy were excluded. Data of 31,058 children for under-5-year-old, 36,775 for 5-9-year-old and 34,154 for adolescents with valid anthropometric measurements were used for selection of healthy subset for analysis across the age groups.

The National Family Health Surveys (NFHS) [1,3,4] are large-scale, multi-round surveys conducted in a randomly selected representative sample of households across India. Multistage random sampling, with a consistent sampling strategy is used. The survey provides state and national information for India. Data on under-5 children from NFHS-5 (2019-21), NFHS-4 (2015-16) and NFHS-3 (2005-06) were accessed [1,3,4]. The NFHS-5, NFHS-4 and NFHS-3 collected anthropometric measurements and sociodemographic information from 2,32,920, 2,59,627 and 1,24,385 children of age below 5years, respectively, from across India.

The 'healthy child' selection criteria for children aged 1-4 years replicated to the extent feasible, those used by the 2006 WHO MGRS for Indian site [16]. Accordingly, a healthy child should *a*) live in an urban locality; *b*) belong to the highest two quintiles of socio-economic status (SES) as defined by respective surveys; *c*) have a non-smoking mother with education that was graduate or above; *d*) be exclusively breastfed for the first 4 months; *e*) be partially breastfed for 12 months; and *f*) be without infection, including any fever and diarrhea, in the two weeks prior to the survey. When applied to all under-5 children in the four selected national surveys, 13,204 under-5 children were selected in the analytical sample; 1,821 from NFHS-3, 4,531 from NFHS-4, 4,918 from NFHS-5 and 1,934 from CNNS (**Fig. 1**).

Healthy 5- to 19-year-old children and adolescents were selected from CNNS, based on the criteria that the child should: *a*) live in an urban locality; *b*) belong to richer and richest SES as defined by CNNS; *c*) be non-anemic; *d*) not use tobacco; *e*) have serum albumin concentration $\frac{24}{12}$ 3.5 g/dL; hemoglobin A1c (HbA1c) concentration $\frac{c}{\lambda}$ 6% and serum C-Reactive Protein level $\frac{c}{\lambda}$ 5 mg/dL. Thus, 6,659 healthy children were extracted of which 3,583 were between 5-9 years while 3,077 were between 10-19 years.

Statistical methods: Prior to analysis, children in the lower and upper 5% (below 5th and above 95th percentile) of the respective *z*-scores were excluded to avoid excess variability due to unobserved factors. Homogeneity in the

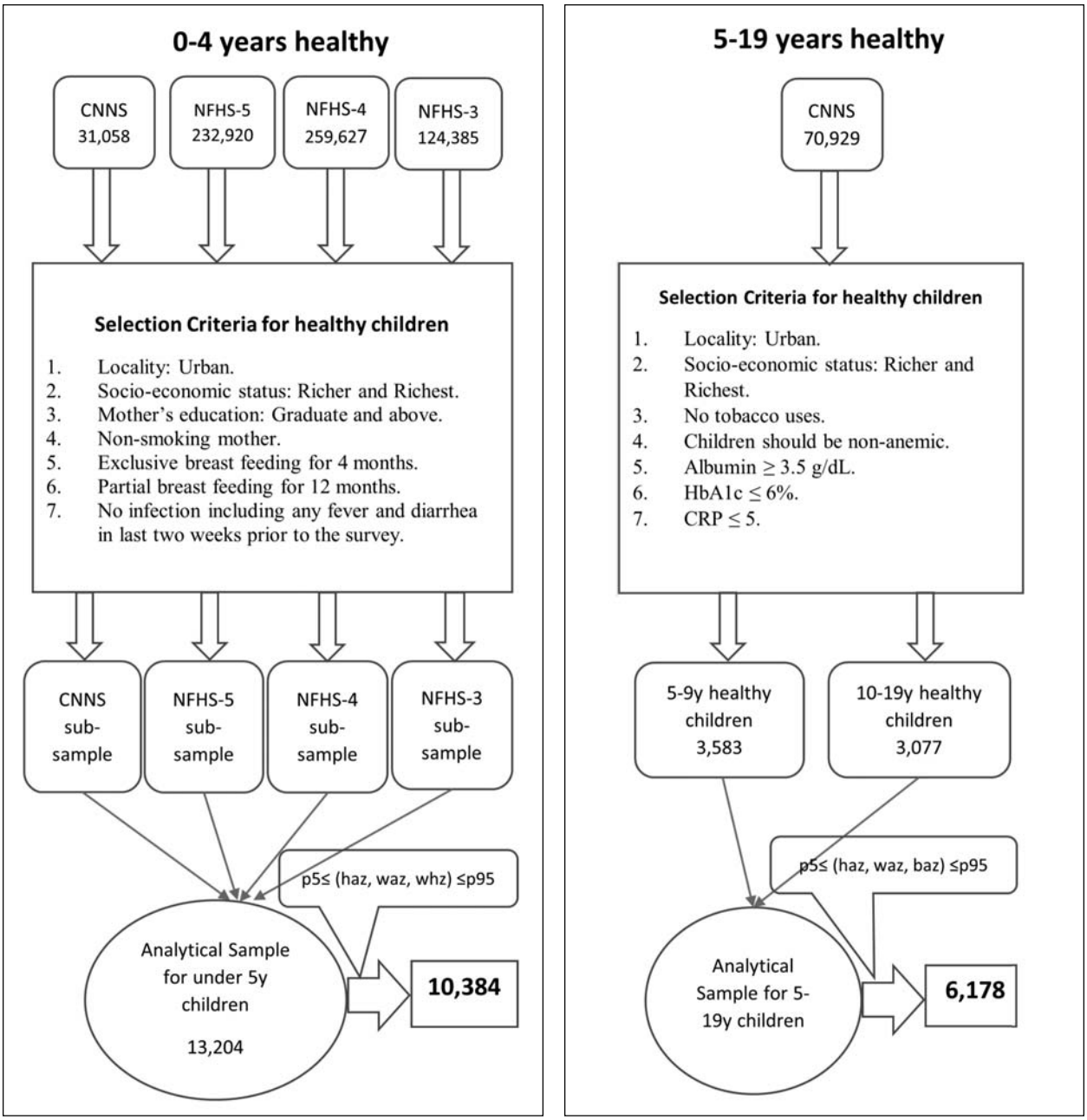

Fig. 1 Steps involved in the selection of the analytical sample (p5 5th percentile, p95 95th percentile)

mean and variance of under-five growth metrics has been demonstrated across all the four surveys using the same extracted healthy subset [8] hence, these data were combined. A similar strategy was used for older children. If significant differences from 0 for these growth standards were found, growth reference were derived from the analytical sample described above, using the standard generalized additive model for location, scale and shape (GAMLSS) [17]. This method was used by WHO to develop their growth standards.

For 0 to 4-year-old children, the analytical sample data were used to derive the required parameters for the HAZ, WAZ and WHZ using GAMLSS with Box-Cox Power Exponential (BCPE) family. The GAMLSS technique can model the temporal growth with highly asymmetric data and can define age-specific distribution by location, scale, and shape (skewness and kurtosis) parameters without assuming any parametric probability distribution.

A penalized cubic smoothing function was used which estimated degrees of freedom by a least generalized cross

validation score. Therefore, no degrees of freedom were required to be specified. Further, as a penalized spline was used, power transformation of age was not considered, because the number of knots and position are learned by the data in penalized splines. Observing that the kurtosis parameter (τ) of BCPE family was close to 2, we restricted (τ) = 2 for three references. Similarly, the skewness parameter or Box-Cox power parameter (ν) for HAZ reference was fixed at 1 but allowed to vary over age for WAZ and WHZ parameters. The goodness of fit of the model was examined by Q-Q normal plot of the z-scores that plotted sample quantiles against theoretical quantiles of normal distribution. To assess the fitting within subintervals of age ranges, a worm plot of *z*-scores was used. If most of the dots fell on the diagonal line (45^o angle) for Q-Q normal plot or in between the two dotted lines for each subgroup in worm plot, it was considered to be a good fit. With final models, BCPE parameters (μ, σ, ν, τ = 2) of HAZ, WAZ and WHZ references were estimated for each month of age until 5 years, separately. Further, age-specific HAZ, WAZ and WHZ were computed and compared within subsets of analytical sample by upper one and upper two deciles of Wealth Index with entire analytical sample as part of sensitivity analysis for choice of upper four deciles of Wealth Index as the cut-off.

The prevalence of stunting, underweight and wasting or thinness across age and sex groups of Indian children and adolescents was estimated in the NFHS-5 (for under-5) and the CNNS (for 5- to 19-year-old children) using the derived references. The values so obtained were compared with corresponding prevalence data obtained using the WHO Child Growth Standards. Non-overlapping 95% confidence intervals of the estimate of prevalence between the study references and the WHO standards was considered as statistically significant difference. Further, the occurrence of double burden of malnutrition (DBM), as the prevalence of a significant proportion of overweight or obese (WHZ > 2.0 or BAZ > 2.0) along with underweight (WHZ < -2.0 or BAZ < -2.0) children was also examined with the use of both standards. The statistical software R version 4.2.1 (R Core Team, 2022, Vienna, Austria) was used for data analysis. The accepted false positive error for all statistical tests was set at 5%.

RESULTS

For 0-4-year-old children: After excluding data corresponding to the upper and lower 5% of HAZ, WAZ and WHZ, 10,384 (CNNS: 1,585; NFHS-3: 1,561; NFHS-4: 3,622; NFHS-5: 3,616) valid data for under-five children (5377 boys, 5007 girls) were obtained. All growth metrics indicated substantial deviation from the standard normal distribution are shown in **Table I**. Age and sex of children in the analytical sample are reported in **Web Fig 1**. Location (M), scale (S) and shape (L) parameters for new reference HAZ (0 to 59 months), reference WAZ (0 to 59 months) and reference WHZ (50 to 120 cm), estimated by GAMLSS are reported in **Web Tables I-III**, respectively. Reference centile curves for HAZ, WAZ and WHZ for boys and girls are shown in **Fig. 2**. The overall fitting of the model to the data was found to be satisfactory. The 2.5th, 50th and 95.5th centile curves were estimated and compared between presently derived Indian reference and WHO Child Growth Standards in **Fig. 3**.

For 5-19-year-old children: After excluding data using the process described *vide supra*, data of 6,178 children were available from CNNS; 3,299 (1745 boys, 1554 girls) were in the 5 to 9 years age group while 2,879 (1458 boys, 1421 girls) were in the 10 to 19 years age group. Age (months) specific frequency distribution is reported in **Web Fig 1** and growth metrics indicating a substantial deviation from the standard normal distribution are shown in **Table I**.

Data estimated by GAMLSS are reported in **Web Tables I, II** and **IV**. The reference centile curves for HAZ, WAZ and BAZ are reported in **Fig. 4**. The goodness fit measure indicated satisfactory fit of the model to the data. Like in the under-five-year-old children, the centiles of the presently derived Indian references for children aged 5 to 19 years were also consistently lower than the existing WHO references for each respective metric (**Fig. 3**).

The prevalence of stunting (15% vs 35%), underweight (17% vs 32%) and wasting (11% vs 19%) among children aged under-five were significantly reduced when the references for growth were applied to the NFHS-5 data, in comparison to the WHO Growth

Table I Distribution of z-scores for Different Anthropometric Growth Metrics Derived Against WHO Global Standards for Indian Children and Adolescents

	Estimated z-score	
Variable	*Mean (95% CI)*	*SD (95% CI)*
0-4 y children		
HAZ	-0.69 (-0.71, -0.66)	1.16 (1.14,1.17)
WAZ	-0.75 (-0.76, -0.73)	0.93 (0.91, 0.94)
WHZ	-0.53 (-0.55, -0.51)	1.07 (1.06, 1.08)
5-19 y children		
HAZ	-0.78 (-0.8, -0.76)	1.01 (1, 1.03)
WAZ	-0.8 (-0.83, -0.77)	1.14 (1.12, 1.16)
BAZ	-0.71 (-0.74, -0.69)	1.19 (1.17, 1.22)

HAZ Height-for-age z-score, WAZ Weight-for-age z-score, WHZ Weight-for-height z-score

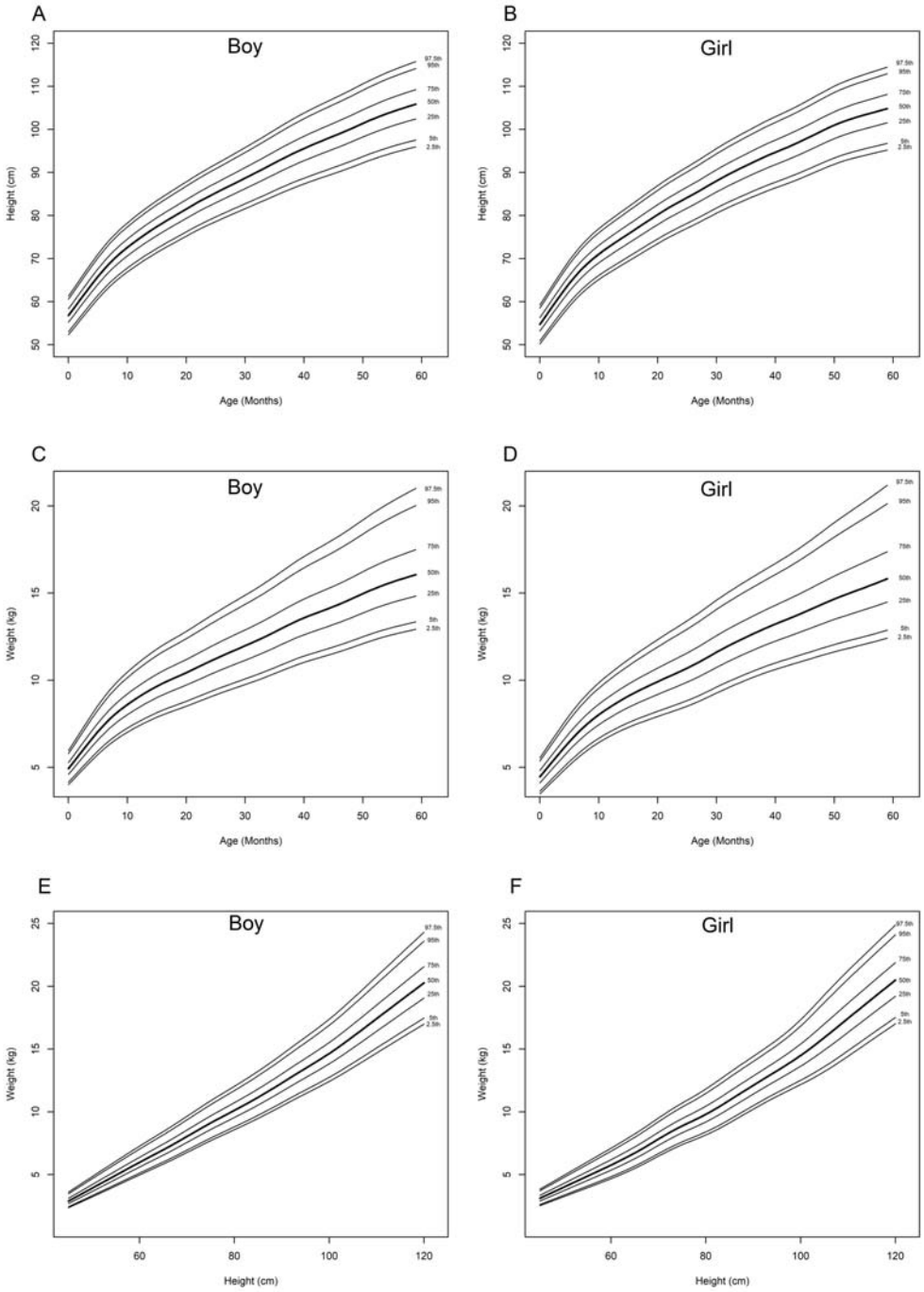

Fig. 2 Centiles of reference growth of height-for-age, weight-for-age, and weight-for-height in Indian children aged 0-4y

Standards. The prevalence of stunting in the CNNS data for children aged 5 to 19 years (6% vs 21%), 10- to 14-year-olds (7% vs 25%) and 15- to 19-year-olds (5% vs 29%) was also significantly reduced when India-specific height standard was compared to the WHO height standards. A similar pattern was observed for thinness based on BMI standards (**Table II**).

The prevalence of overweight, as measured by WHZ > 2 for under-five-year-old children and BMI-for-age Z scores (BAZ) > 2 for children and adolescents aged above 5 years, using the present Indian reference, were comparable with the prevalence of overweight derived using the WHO standard (4.4% vs 3.4% for age <5y; 2.8% vs 2.1% for 5-19y; 1.6% vs 1.3% for 10-14y and 0.8% vs

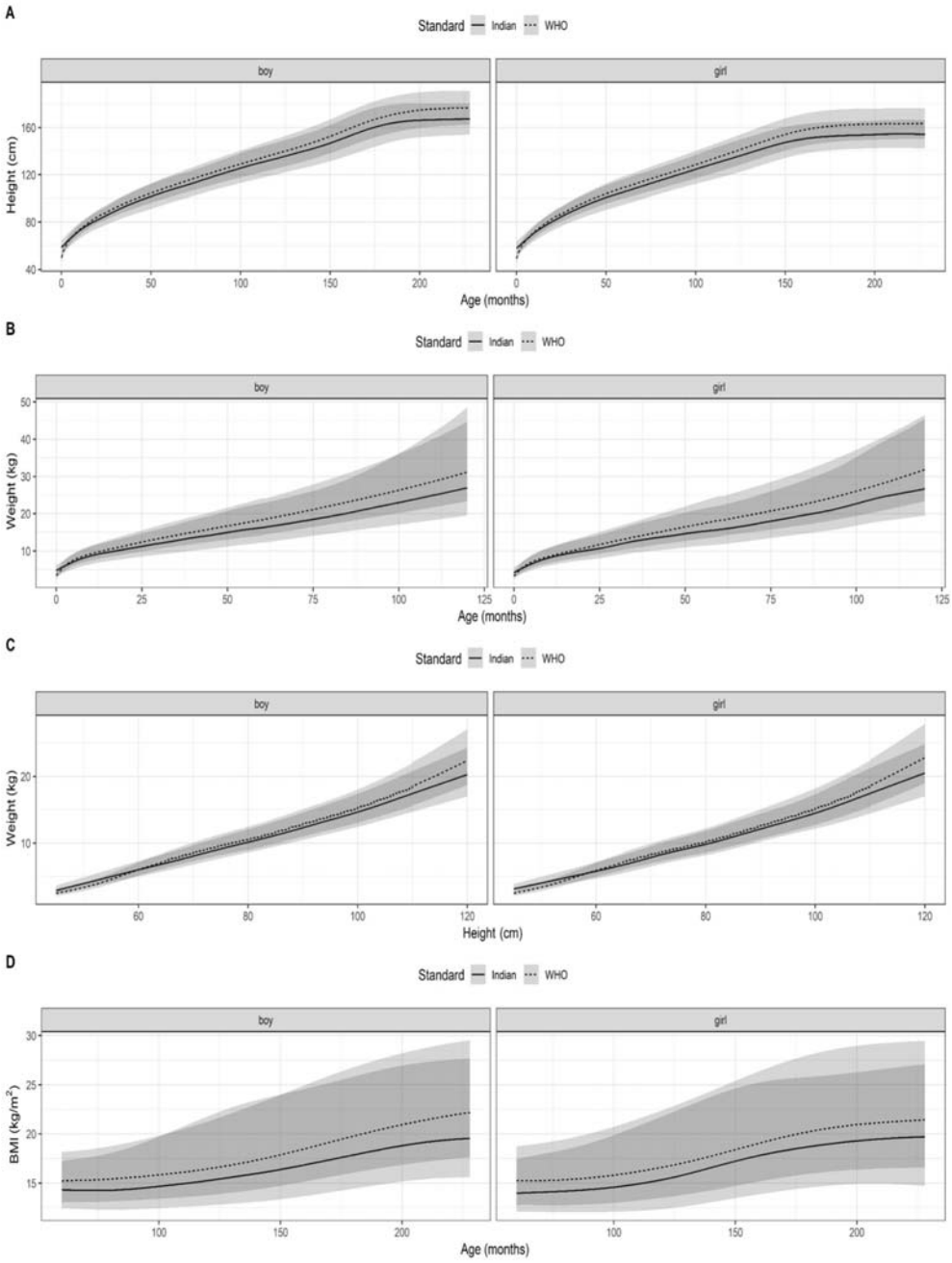

Fig. 3 Comparison of the present Indian growth reference against WHO growth standards and references (median with band of 2.5th and 97.5th percentiles). A Height-for-age; B Weight-for-age; C Weight-for-height; D BMI-for-age

0.1% for 15-19y respectively, **Table III**). However, the risk of being overweight (as measured by WHZ >1 for under-five children or BAZ >1 children and adolescents aged >5y) was higher using the present Indian reference in comparison with the WHO standard (13.8% vs 9.0% for < 5 year; 12% vs 6.3% for 5 to 19 year; 12.7% vs 7.5% for 10 to 15 year and 11.9% vs 4.3% respectively) as seen in **Table II**.

A user friendly web application (*https://datatools.sjri.res.in/ZSC/*) was developed on Python and Streamlit to calculate z-score and risk of growth faltering [8].

DISCUSSION

This paper has constructed contextual, nationally representative, and contemporary growth curves which are continuous; unlike the WHO standard, with a discontinuity

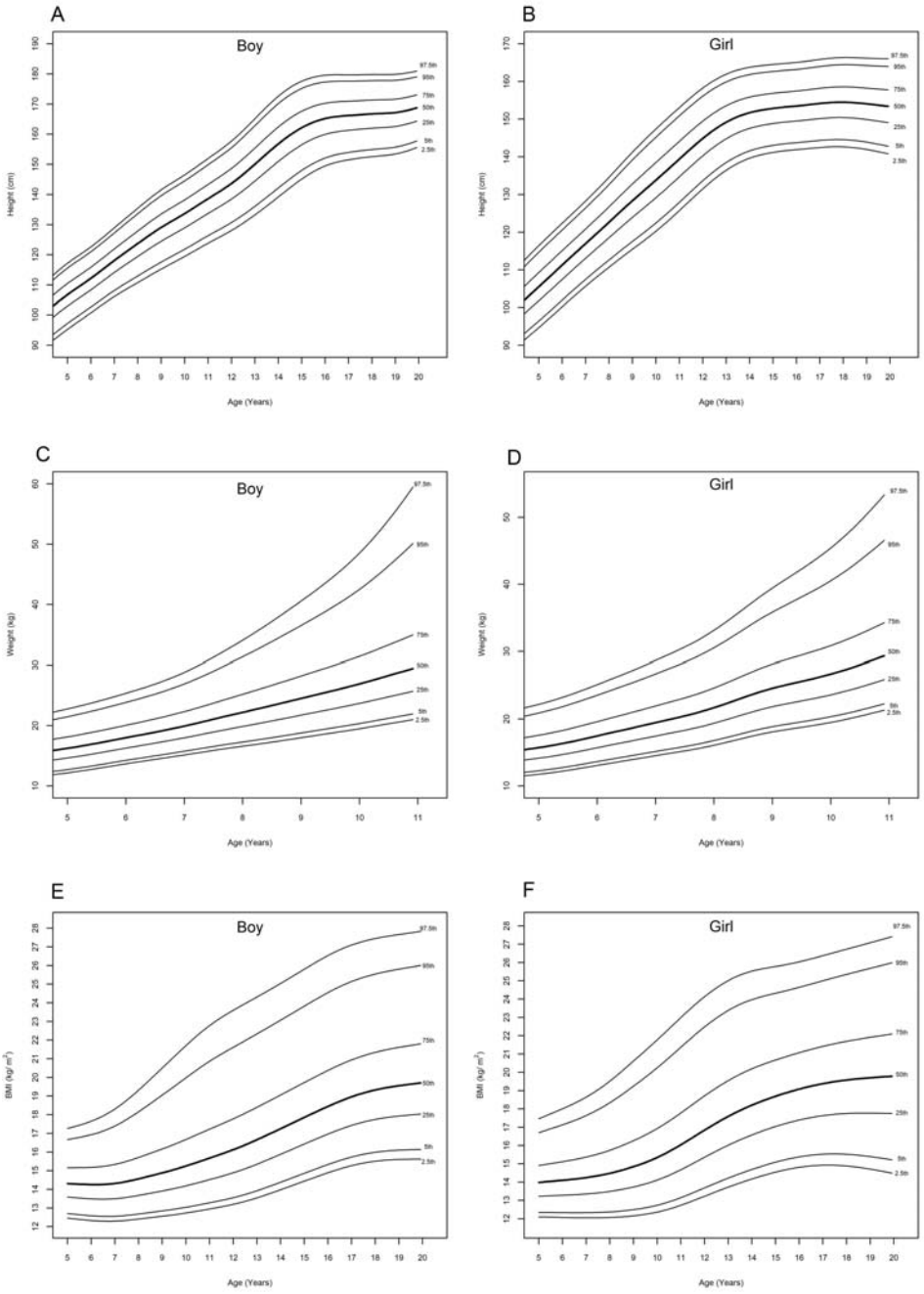

Fig. 4 Centiles of standard growth of height-for-age, weight-for-age, and BMI-for-age for Indian children aged 5-19 years

at 2 years and a different population after 5 years. The ideal approach to constructing growth references locally would be through a prospective, adequately powered and specifically focused study. Till such standards become available, we provide a reasonable alternative to fulfil the need for children aged 0-19 years. Following earlier reports [11] we reassessed the appropriateness of WHO Growth Standards using data on healthy children in India, and proceeded to develop India-specific anthropometric growth references across ages and for both genders of children and adolescents. This was possible because a healthy representative sample of under-5 year-old children could be selected from four different national surveys over the last 15 or so years, and similarly, a healthy sample of 5- to 19-year-old children could be selected from the CNNS, using similar criteria for health as used in the WHO MGRS

study [16] as used by WHO [7] along with additional biomedical parameters (**Fig. 1**) making the analytical data more robust. The present references were also developed by the same conventional GAMLSS [17] technique as was used by WHO [16].

The present references were consistently lower than the WHO growth standards (Fig.3). Thus, with these references, the estimates of growth faltering in Indian children and adolescents were reduced by ~40-80% across different metrices in comparison to those derived from WHO growth standards (**Table II**).

A caveat is that the present derived reference should only be applied for children aged 4 months and above, since in the healthy subsample of children had a limited representation of children upto 3 months of age. Therefore, the WHO Growth Standards should be recommended for infants upto 3 months of age.

A high prevalence of undernutrition is usually reported in low- and middle- income countries surveys when WHO Growth Standards are used [18]. However, several studies have critically examined the validity of the WHO Growth Standards for different populations, and a systematic review of the comparison of the use of regional growth references against the WHO Growth Standards has recommended the adoption of regional standards for growth [19]. While a method of creating synthetic growth reference charts by incorporating information from existing reference growth studies has also been suggested [20], there are no studies, to our knowledge, that have critically examined the appropriateness of the WHO standard, or the generation of contextual standards by using local healthy child populations defined by the stringent inclusion criteria that were used by WHO to develop the global standards.

Given that the NFHS-5 has shown an increase in the prevalence of overweight children from 9.9% to 13.8% compared to NFHS-4, it seems likely that the supplementary programs are having some effect on the right-hand tail of this distribution already. Using the present overweight cut-offs, the prevalence of overweight is much more, and this points to a serious emerging problem of double burden of malnutrition (DBM) in Indian children, which may be the tip of the iceberg, as an analysis of metabolic indicators of obesity in the CNNS showed that over 50% of adolescent children, whether normal weight, underweight or stunted, had at least one biomarker (high blood glucose, triglycerides or high blood

Table II Comparison of the Prevalence (95% CI) of Growth Faltering and Overweight or Obese Derived by WHO Standard and Indian Reference for Indian Children and Adolescents (Under 5y: NFHS-5 and Above 5y: CNNS)

Standard	Prevalence (%) with 95% CI			
	< 5y	5-9y	10-14y	15-19y
Stunting				
WHO	35.5 (35.2, 35.9)	20.8 (20.1, 21.5)	24.9 (23.9, 26.0)	28.9 (27.7, 30.2)
India	15.5 (15.3, 15.8)	6.2 (5.8, 6.6)	7.4 (6.8, 7.9)	5.5 (5.1, 6)
Underweight				
WHO	32.1 (31.8, 32.5)	30.5 (29.5, 31.4)		
India	16.9 (16.6, 17.1)	5.4 (5, 5.7)		
Wasting				
WHO	19.2 (18.9, 19.6)			
India	10.9 (10.6, 11.2)			
Thinness				
WHO		19.3 (18.6, 20.0)	22.9 (22.0, 23.8)	17.0 (16.2, 17.7)
India		5.3 (4.9, 5.7)	5.7 (5.2, 6.1)	3.2 (2.8, 3.5)
Overweight (WHZ >1) or Overweight (BAZ >1)				
WHO	9.0 (8.8, 9.2)	6.3 (5.7, 6.8)	7.5 (6.8, 8.2)	4.3 (3.9, 4.7)
India	13.8 (13.5, 14.0)	12.0 (11.2, 12.9)	12.7 (11.7, 13.6)	11.9 (11.0, 12.9)
Overweight (WHZ >2) or Obese (BAZ >2)				
WHO	3.4 (3.3, 3.5)	2.1 (1.9, 2.4)	1.3 (1.1, 1.5)	0.05 (0.01, 0.09)
India	4.4 (4.2, 4.6)	2.8 (2.5, 3.1)	1.6 (1.4, 1.8)	0.79 (0.59, 0.98)

WHO World Health Organization, BAZ Body mass index-for-age z-score, WHZ Weight-for-height z-score

WHAT THIS STUDY ADDS?

- The distribution of growth metrics among 'healthy' children and adolescents of India deviate significantly from the WHO growth standards.
- New growth references for Indian children and adolescents, based on 'healthy' participants were developed, which are nationally representative and could be more suitable for routine clinical use and for informing policy.
- Estimates of the prevalence of growth faltering among Indian children and adolescents reduced by approximately half using these references in comparison to WHO growth standards.

pressure) of excess nutrition [21]. This is because Indians are likely to have a greater adiposity for a given BAZ or WHZ [22], but this surprising finding is somewhat vindicated in the increased prevalence of anthropometric overweight in different age groups (13.8%, 12.0%, 11.7% and 11.9% for < 5 y, 5-19 y, 10-14 y and 15-19 y respectively) when the present standard is applied to the NFHS-5 and the CNNS populations. Further, the underestimation of possible risk of overweight (WHZ > 1; 14% vs 9%) diverts policy action away from the emerging epidemic of overnutrition and DBM in this age group.

A strength of this study is the use of data extracted from four different national surveys over different times and that the age-specific mean HAZ, WAZ and WHZ of the extracted analytical sample are consistent across the upper four deciles and the uppermost decile (**Web Fig. 2**) for under-5-year-old children. The 5-19 year data from the CNNS is recent, nationally representative and employed predefined criteria, including biochemistry, to select participants for analysis. The extreme measurements at both ends were also removed before analysis to avoid undue variability by unknown and unobserved factors, which are expected to partially account for the measurement error. The limitations are lack of adequate data for 0-3 months age, 'intersurveyor' variability in measurements, which is mostly random in largescale surveys, and some dissimilarity in selection criteria from the WHO MGRS due to non-availability of relevant data.

It could be argued that that the 'affluent neighbourhood' in South Delhi that were sampled for the WHO MGRS represented the most privileged and were therefore best suited for selecting children free from environmental constraints for child growth. However, we believe that environmental growth constraints among the richer families selected by us are broadly comparable, given the additional socio-demographic selection criteria. Further, these children are more representative of the national population.

The evidence presented here and from the systematic review [19], argues that the one-growth standard-fits-all approach for deriving population estimates of anthropometric growth faltering could be misleading. However, these findings need validation through prospective and focussed studies for developing a more robust evidence base. In the interim, Indian stakeholders could consider using the present growth references for routine clinical use and for informing policy after factoring for the potential barriers and logistic challenges.

Ethics clearance: The Institution Ethics Review board of St. John's Medical College provided waiver of review for this secondary data analysis. No. 164/2022, dated Aug 22, 2022.

Contributors: SG, TT, AVK: Conceptualised the study; RM, SG, AVK, TT: Wrote the first draft of the paper. HPS: Reviewed and edited the manuscript. RM, SG: Performed the statistical analysis. All authors have approved the final version of the manuscript. SG, TT: Had access to the data and have verified the data.

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Competing interest: None stated.

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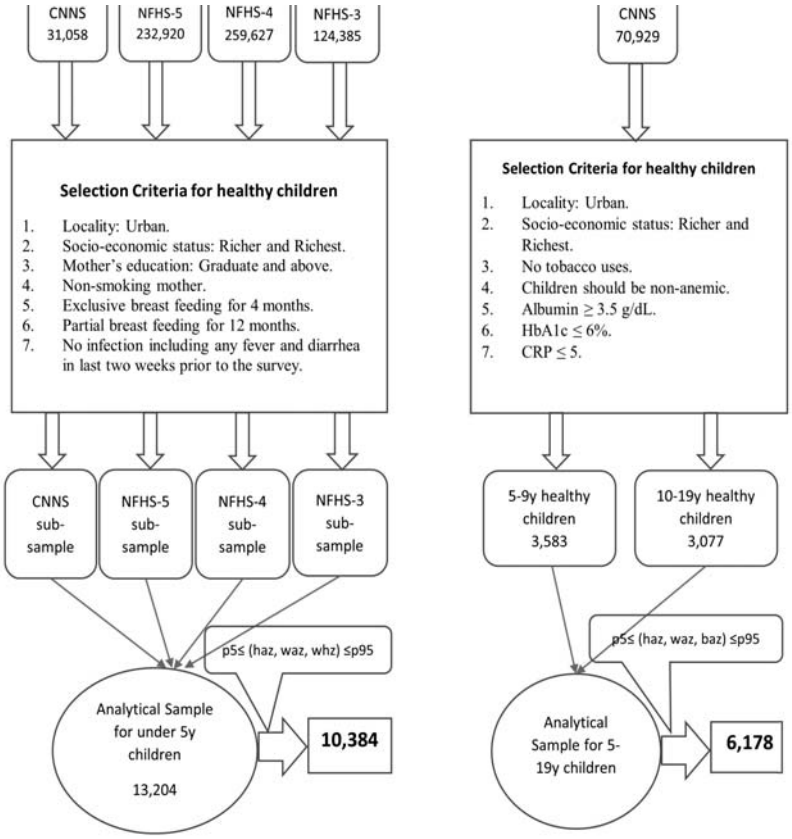
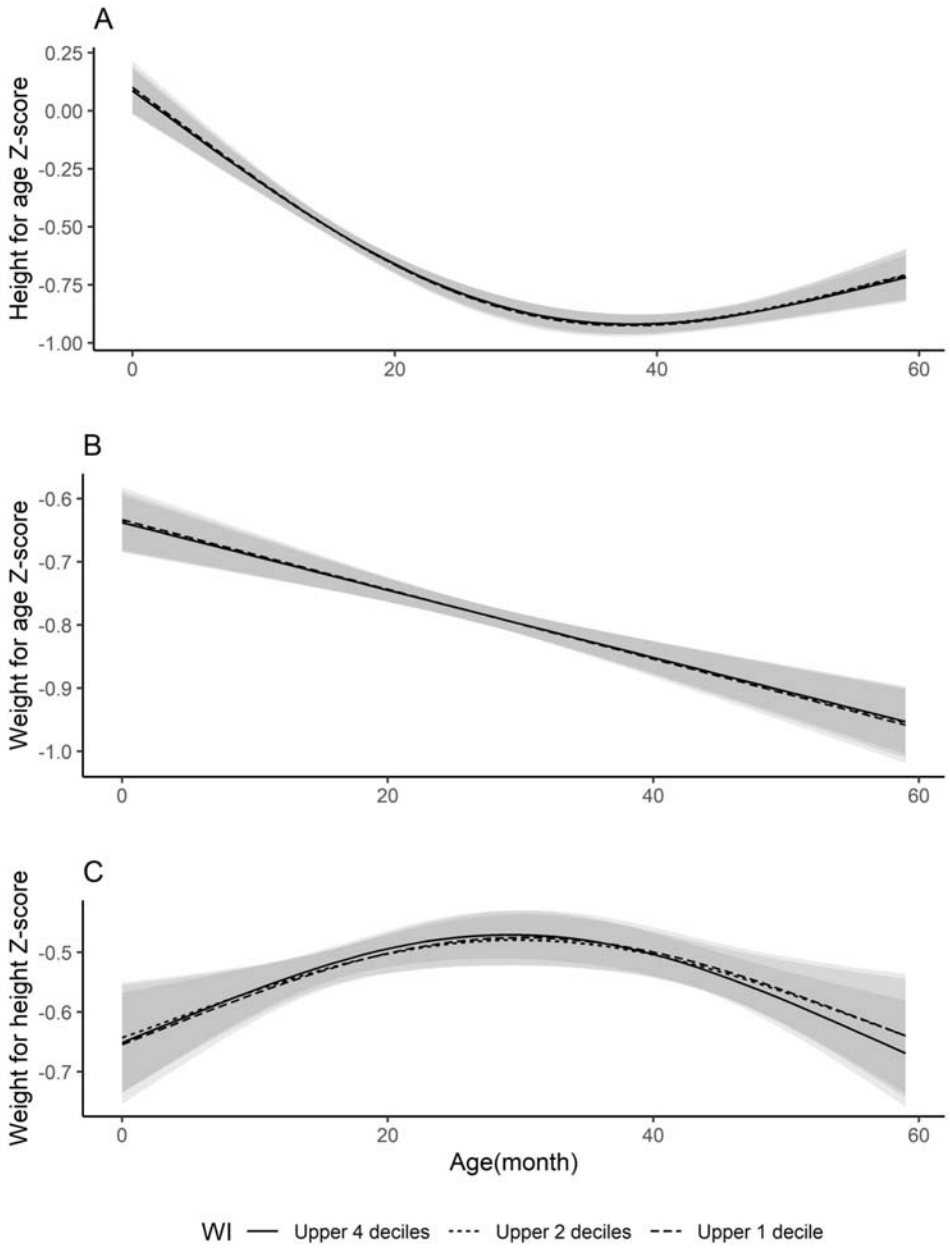


Web Fig. 1 The multiple bar diagrams depict age and sex wise available data



Web Fig. 2 Age-specific mean z-scores of HAZ, WAZ and WHZ of healthy under-five children across upper 4 deciles, upper 2 deciles and uppermost deciles of wealth

ORIGINAL ARTICLE

Nurse-Guided Maternal Interventional Package for Neonatal Stress – A Randomized Controlled Trial

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ABSTRACT

Objective: To assess the role of nurse-guided maternal interventional package for reducing stress behaviour among preterm neonates admitted in neonatal intensive care unit (NICU).

Methods: A randomized controlled trial was conducted among 100 mothers and their newborns delivered preterm and admitted consecutively in the NICU over 4 months. Mothers in the intervention group (n = 50) received education and demonstration regarding the use of maternal touch, facilitated tucking, kangaroo mother care (KMC), non-nutritive sucking (NNS), nesting and maternal voice alongwith a handout in local language for five consecutive days, while those in the control group (n = 50) received routine care including KMC and NNS for five consecutive days. Neonates were assessed before and five days after enrolment or intervention by using modified Infant Positioning Assessment Tool (IPAT), Neonatal Stress Scale and Preterm Neonate's Behaviour Assessment Scale.

Results: The mean (SD) score of positioning was significantly higher in the intervention group as compared to control group [9.62 (1.17) vs 6.58 (1.72), $P < 0.001$]. The median (IQR) score of stress was significantly lower in the intervention group compared to the control group [7 (7,10) vs 11(8,12.75), $P = 0.004$]. The mean (SD) scores for the autonomic and visceral subsystem behavioral response were significantly higher in the intervention group [5.28 (1.4) vs 3.25 (1.0), $P < 0.001$]. Mean (SD) attention interaction subsystem behavioral response score in the intervention group was significantly higher compared to the control group [2.96 (1.2) vs 1.85 (0.9), $P = 0.001$].

Conclusion: Mothers can be guided by nurses on neonatal stress behaviour and how to handle neonates in NICU, which significantly improves positioning and behavioral scores and reduces stress scores.

Keywords: *Behavioral response, Neonatal stress, Positioning, Preterm*

Trial Registration: Clinical Trial Registry-India CTRI/2022/07/043693 **Published online**: March 14, 2024; **PII**:S097475591600612

INTRODUCTION

Around 15 million infants are born prematurely every year, with an average preterm birth rate of 11% [1]. In 2020, 3.02 million preterm babies were born in India [2]. Premature birth poses significant stress for mothers and babies as they spend several months in the Neonatal Intensive Care Unit (NICU) due to severe morbidities. Unfortunately, the environment in the NICU is very different from the intrauterine life [3]. It has been seen that premature neonates may be exposed to approximately 134 stressful procedures during their first two weeks of life [4]. Light, noise, sound, interventions, routine handling by doctors and nurses (such as weighing, radiographs, skin breaking procedures etc.) are the major stressors that cause stress reaction in the preterm neonates [5].

Preterm neonates exhibit stress behaviours alongside autonomic, motor, attention and state systems. Increased heart rate, facial grimacing, fussing, limb extension, hyperalert, arousal, covering eyes, finger splay etc. are some of the stress behaviours that occur following exposure to a stressful event [6]. Stress in the neonatal period can lead to cognitive impairments, poor motor skills, learning disabilities, psychosocial issues, lack of social control, and impulsive behaviour later in life [7].

Controlling of NICU environment, family-centred care and appropriate handling can reduce the stress and improve longterm outcomes. Developmentally Supportive Care (DSC) is one of the models for interventions that are used to promote the behavioral organization of neonates, reduce stress, protect the sleep rhythms, enhance the

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physiological stability and promote the growth and maturation [8].

Nurses have an important role as main caregivers, although they cannot take the role of family, they can assist mothers by educating them in giving consistent and comforting care for their newborns. The family is seen as the sentinel entity in nurturing a preterm neonate so development care focus should be directed at the family, especially the mothers [9]. There is emerging evidence that mother-infant interaction plays a crucial role in controlling the infant stress behaviour as well as moulding the infant behaviour and physiology [10]. We planned this intervention trial wherein the impact of nurse-guided education of mothers delivering preterm neonates was assessed in terms of estimates of neonatal stress in NICU.

METHODS

A randomized controlled trial was conducted in the level III NICU of tertiary centre in North India over four months' duration, from August to November 2022. Prior approval was obtained from Institutional Ethics Committee for conduct of the study.

Preterm neonates (born before 37 weeks of gestation) and their mothers were included in the study after obtaining written informed consent from mothers. Babies on high frequency ventilation, persistent pulmonary hypertension and those born to sick mothers were excluded. Preterm neonates admitted consecutively in the NICU were randomized to either the intervention arm or the control arm. Randomization was done through computer generated random numbers and allocation concealment was guaranteed by the use of sequentially numbered, opaque and sealed envelopes. It was done by an independent person not involved in the conduct of the study.

After baseline assessment, mothers in the intervention group were trained with the nurse-guided interventional package for 5 days to reduce neonatal stress behaviours. The package included education, information and demonstrations regarding handling of the baby and the role of maternal touch, maternal voice, facilitated tucking, nesting, kangaroo mother care (KMC) and non-nutritive sucking (NNS). After the nurse gave the demonstration to the mother, a return demonstration for the same was taken from the mother and her doubts, if any, were cleared. Daily reinforcement was done and mothers were and motivated to perform the interventions. Positioning was performed 3-4 times, KMC was done at least 4 hours/day and, NNS was practiced 3-4 times/day. The preterm neonates in the control group were given routine care alongwith KMC and NNS for 5 days and reassessed. To avoid contamination, babies in the two groups were kept in separate cubicles in the NICU.

The tools used for data collection included the modified sociodemographic scale by Kuppuswamy [11], clinical profile, modified Infant Positioning Assessment Tool (IPAT) [12], Neonatal Stress Scale [13] and Preterm's Neonate Behavioral Assessment Scale [14]. The IPAT is a validated and reliable tool which is used to evaluate the posture of premature infants in six areas of the body i.e. head, neck, shoulders, hands, hips/pelvis, and knees/ankles/feet with cumulative scores ranging from 0-12. A score of 12 is the ideal cumulative score, 9-11 is an acceptable cumulative score and score of 8 indicates need for repositioning. Neonatal Stress Scale is a self-structured tool consisting of 24 components which cover four domains i.e. autonomic, motor, attention and state, to assess neonatal stress. A score of 0-8 represents mild stress, a score of 9-16 represents moderate stress and a score of 17-24 represent severe stress. Preterm's Neonate Behavioral Assessment Scale has two subsystems: autonomic/visceral subsystem and the state regulation and attention-interaction subsystem. The total score of autonomic/visceral subsystem ranges from 0-8; score of 5-8 represents normal behavioral response, 2-4 represents suspected abnormal behavioral response, and score ≤ 1 indicates definite abnormal behavioral response. The total score of state regulation and attention-interaction subsystem ranges from 0-6; score of 4-6, 2-3, and ≤1 represent normal, suspected abnormal and abnormal behavioral response, respectively. All babies were assessed for positioning, stress and behavioral response at enrolment and 5 days after intervention or enrolment in the intervention and control groups, respectively.

Sample size of 98 neonates, 49 per group, was calculated using Open Epi Menu App by considering the mean (SD) difference of Stress Behaviour Score of 5.46 [15] at 80% power and 95% CI.

Statistical analysis: Data was entered in SPSS software. Descriptive statistics were used for baseline characteristics. *Chi*-square test, Bowker's McNemar's, and was used to compare continuous data between the two groups. Unpaired *t*- test, Paired *t*-test, or Wilcoxon sign ranked test were used for intragroup comparison. Mann Whitney U test was used for skewed numerical data comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 105 preterm neonates were assessed for eligibility; of these, 100 eligible neonates were enrolled and randomized to the intervention ($n = 50$) and control group ($n = 50$). See **Fig. 1**. **Table I** shows the baseline characteristics of enrolled preterm neonates. Except one, all preterm neonates had respiratory distress. At

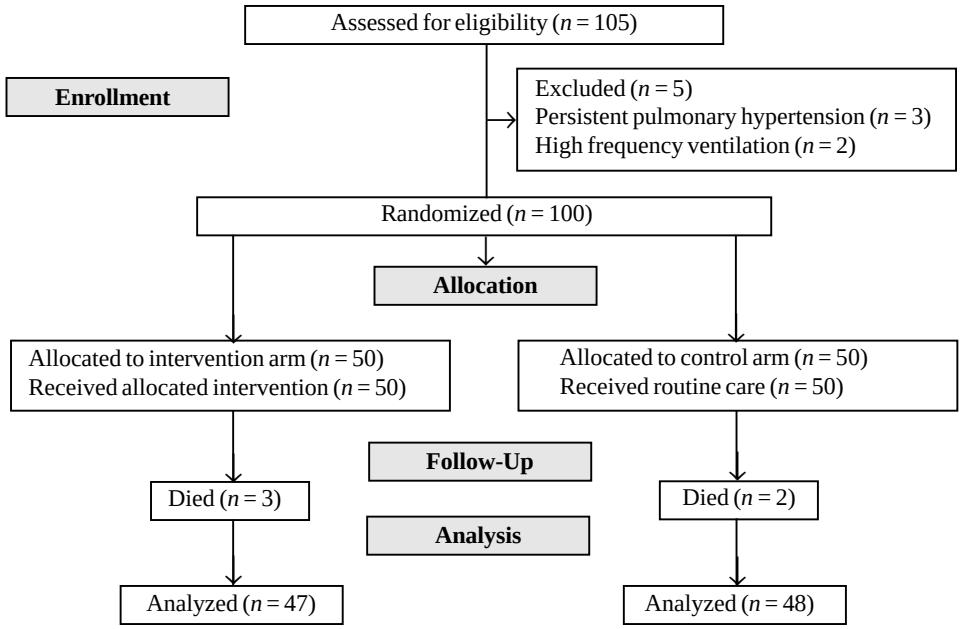

Fig. 1 Flow of study participants

Table I Baseline Characteristics of Enrolled Neonates

Variables	*Intervention group (n=50)*	*Control group (n=50)*
Gestational age (wks)[a]	30.1 (2.7)	30.7 (3.1)
Birth weight (g)[a]	1179.2 (365.1)	1339.7 (540.6)
Male	27 (54)	33 (66)
Appropriate for gestational age	29 (58)	33 (66)
Age at enrolment (d)[a]	7.1 (3.8)	6.4 (3.9)
Respiratory support (Nasal CPAP) at enrolment	33 (66)	31 (62)
Socioeconomic Class (as per Modified Kuppuswamy scale 2021)		
Upper	1 (2)	4 (8)
Upper middle	12 (24)	8 (16)
Lower middle	18 (36)	19 (38)
Upper lower	19 (38)	19 (38)
Maternal education		
No formal education	2 (4)	-
Primary	2 (4)	-
Middle	10 (20)	8 (16)
Matric	3 (6)	8 (16)
Inter/diploma	8 (16)	19 (38)
Graduate	20 (40)	11 (22)
Postgraduate	5 (10)	4 (8)

Data expressed as n (%) and [a]mean (SD), CPAP Continuous Positive Airway Pressure

enrolment, most of the neonates were receiving orogastric feeding; 84% (*n* = 42), and 72% (*n* = 36) neonates in the interventional and control group, respectively. Of these, 64% (*n* = 32) in the interventional group and 66% (*n* = 33) in the control group were receiving exclusive expressed breastmilk.

Table II shows a significant improvement in the level of stress and in positioning and behavioral response in the intervention group as compared to the control group after the intervention.

Table III shows the intergroup and intragroup comparison of scores of positioning and behavioral response in terms of autonomic, visceral subsystem and state-regulation, attention interaction subsystem and neonatal stress scores. Scores of positioning and behavioral response in terms of autonomic, visceral subsystem and state-regulation, attention interaction subsystem in the intervention group were significantly higher than the control group following intervention. There was also a significant improvement in the scores within the intervention group but no significant change was observed in control group.

There was a significant reduction in the median scores of stress after the intervention, compared to the control group. There was also significant improvement in the median scores within the intervention group but no significant change was observed within control group.

Table II Comparison of Positioning and Stress, Autonomic, Visceral and State Regulation Attention Interaction Subsystem

Variables	Preintervention		P value	Postintervention		Pvalue
	Intervention group (n = 50)	Control group (n = 50)		Intervention group (n = 47)	Control group (n = 48)	
Positioning[a]						
Ideal positioning (score 12)	0	0	1.00	4 (8.5)	0	< 0.001
Acceptable positioning (score 9-11)	5 (10.0)	4 (8.0)		41 (87.2)	7 (14.6)	
Need for repositioning (score < 8)	45 (90.0)	46 (92.0)		2 (4.3)	41 (85.4)	
Neonatal Stress Score[b]						
Mild (1-8)	1 (2.0)	2 (4.0)	0.78	30 (63.8)	16 (33.3)	0.004
Moderate (9-16)	45 (90.0)	43 (86.0)		17 (36.2)	30 (62.5)	
Severe (17-24)	4 (8.0)	5 (10.0)			2 (4.2)	
Domain 1: Autonomic and Visceral Subsystem[c]						
Normal behavioral response (5-8)	-	1 (2.0)	0.27	32 (68.1)	4 (8.3)	0.001
Suspected abnormal behavioral response (2-4)	38 (76.0)	32 (64.0)		13 (27.7)	36 (75.0)	
Definite abnormal behavioral response (≤ 1)	12 (24.0)	17 (34.0)		2 (4.3)	8 (16.7)	
Domain 2: State Regulation and Attention Interaction Subsystem[c]						
Normal behavioral response (4-6)	-	-		14 (29.8)	2 (4.2)	0.001
Suspected abnormal behavioral response (2-3)	29 (58.0)	25 (50.0)	0.55	24 (51.1)	24 (50.0)	
Definite abnormal behavioral response (≤ 1)	21 (42.0)	25 (50.0)		9 (19.1)	22 (45.8)	

Data expressed as n (%), [a]Modified Infant Positioning Assessment Tool, [b]Neonatal Stress Scale, [c]Preterm Neonate's Behavior Assessment Scale.

DISCUSSION

For the optimum development of a preterm, adequate and appropriate nurturing in the neonatal intensive care unit (NICU), that is attentive and responsive caregiving are necessary steps [16]. Appropriate nesting can be practiced in the NICU to achieve optimal position and is a standard developmentally supportive position which maximizes the stability of the neonate and promotes behavioral organization.

We observed a significant improvement in the positioning, neonatal stress and behavioral response in the neonates after the intervention. The improvement in positioning was reflected in the IPAT scores after the intervention which is consistent with the results of a study by Jeyabarathi et al who reported that following implementation of nesting among high risk newborns there was a significant improvement in positioning score [17].

The stress associated with the preterm birth is particularly more in the initial weeks after birth when maximum interventions are done and the neonate is sick. The preterm infants show signs of stress as reflected in the autonomic, motor and state attention subsystem. DSC interventions such as KMC, NNS, facilitated tucking,

Table III Scores of Positioning, Autonomic, Visceral Subsystem and State Regulation, Attention Subsystem and Neonatal Stress Scores

Variables	Intervention group	Control group	P value
Positioning			
Preintervention[a]	6.38 (1.67)	5.80 (1.72)	0.092
Postintervention[b]	9.62 (1.17)	6.58 (1.72)	< 0.001
P value	< 0.001	0.078	
Domain 1: Autonomic and Visceral Subsystem			
Preintervention[a]	2.68 (1.13)	2.26 (1.27)	0.09
Postintervention[b]	5.28 (1.49)	3.25 (1.07)	< 0.001
P value	< 0.001	0.237	
Domain 2: State Regulation and Attention Interaction Subsystem			
Preintervention[a]	1.86 (0.85)	1.64 (0.77)	0.18
Postintervention[b]	2.96 (1.23)	1.85 (0.94)	< 0.001
P value	< 0.001	0.14	
Neonatal Stress Score[c]			
Preintervention[a]	12 (10, 12.25)	11 (10, 14)	0.73
Postintervention[b]	7 (7, 10)	11 (8, 12.75)	< 0.001
P value	< 0.001	0.16	

[a]Preintervention n = 50 per group; [b]Postintervention n = 47 and n = 48 in the Intervention and Control groups respectively; Data expressed as mean (SD) or [c]median (IQR)

WHAT THIS STUDY ADDS?

- Involvement of mother in the care of the preterm neonates admitted in NICU not only reduces the stress related behaviours but also increases the mother-infant bonding by involvement of mother in positioning, nesting, KMC and NNS.

maternal touch and maternal voice help to minimize the stress and promote the growth and maturation of preterm neonates. Our study shows that the statistically significant reduction was achieved in the level of stress in preterm neonates after the implementation of intervention. The similar findings from Shin et al and Namzoo et al showed that mother's voice and lullaby practices improved the physiological parameters in the intervention groups [18,19]. Ibrahim et al showed a significant improvement in the behavioral organization in the preterm neonates who were nursed in the NICU in nesting position as compared to the group receiving routine NICU care with traditional positions without nesting [20].

Parental involvement especially that of mother in the DSC of neonates helps to minimize the stress among the preterm neonates and promotes optimum growth and development. This is supported by the findings of our study as well as that by Byers et al wherein the infants who had received developmentally supportive family-centred care showed lesser behavioral stress signs [9].

The strength of our study includes a randomized control design. The interventional package was found to be effective and could be taught to mother by the nurses. Limitations of our study include a small sample size due to limited time period and that it could not be blinded due to nature of the study.

We conclude that mothers can be trained by nurses regarding developmentally supportive care which can reduce stress and improve behavioral response in neonates admitted in NICU.

Ethics clearance: Institutional Ethics Committee, PGIMER Chandigarh with reference number IEC-INT/2022/MSc-118, dated Mar 4, 2022.

Trial Registration: Clinical Trial Registry-India CTRI/2022/07/043693.

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ORIGINAL ARTICLE

Physical Activity of School-Going Adolescents During the COVID-19 Pandemic: A Natural Experiment Study

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ABSTRACT

Objective: To assess the impact of the COVID-19 pandemic associated governmental restrictions on physical activity and sedentary behavior of school-going adolescents in India and its effect on nutrition and health status.

Methods: This was a before-after natural experiment study that recorded paired data of 449 (206 boys) school-going adolescents. COVID-19 related governmental measures (March 24, 2020 till February 2021) were taken as the natural experiment. The change in proportion of adolescents who met the recommended amount of physical activity guidelines and change in sedentary and dietary behaviors and body mass index (BMI) were compared.

Results: The proportion of adolescents performing adequate physical activity decreased from 33.9% to 30.7% (OR 1.2,95% CI 0.9,1.6) during the pandemic. Fruit intake increased by 8.1% during the pandemic while junk food intake decreased by 17% during the pandemic. Mean (SD) BMI z-scores increased from -0.7)1.4) to -0.5)1.3) ($P < 0.001$).

Conclusion: While there was a small decrease in the proportion of physically active adolescents during the pandemic, a shift towards healthier dietary habits was seen.

Keywords: *Accelerometer, Lifestyle behaviors, Junk food, MVPA, Natural Experiment, Sedentary*

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INTRODUCTION

The World Health Organization (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure [1]. Physical inactivity is among the leading causes of mortality worldwide [1]. Globally, 81% of adolescents aged 11-17 years were insufficiently physically active in 2016 [2]. Physical activity decreases as the age increases [3-5]. Physical activity may be expressed in terms of types (e.g. aerobic, strengthening, flexibility etc.), duration, frequency, and intensity [1,6]. On an absolute scale, light intensity activity refers to activity that is performed at greater than 1.5-2.9 times the intensity of rest, while moderate to vigorous intensity activity is one that is performed at greater than 3 times the intensity of rest [1]. WHO recommends an average 60 minutes/day of moderate to vigorous intensity physical activity (MVPA) in a week; and vigorous intensity physical activity such as those to strengthen muscles and bones at least 3 times in a week in children and adolescents [7]. 'Exercise' is a sub-category of physical activity and may be defined as 'physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective' [8].

Schools are an attractive platform to promote physical activity among adolescents. However, during the COVID-19 pandemic, about 1 billion children and adolescents were affected by school closures worldwide [9]. The school closure along with other measures such as home confinement led to many indirect consequences for adolescents such as sleep disturbances, mental disorders,

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social isolation and change in lifestyle behaviors such as physical activity, sedentary and dietary behaviors [10]. Preliminary evidence suggests a decreasing trend in physical activity levels coupled with an increase in screen time [11-14]. However, a multicountry study showed an increase in proportion of physically active adolescents from before to during pandemic in Colombia, Spain and Italy [15]. A systematic review of changes in physical activity around the world during COVID-19 pandemic showed an average decrease of 17 minutes/day of MVPA in children and adolescents aged 4-18 years [16]. A similar decrease in physical activity during the pandemic was also noted in Indian adolescents and youth [17,18].

School-based physical activity is likely to change during pandemics like COVID-19 [19]. The aim of the 'Impact of COVID-19 on the physical activity, sedentary and dietary behavior of school-going adolescents (ICPASA)' study was to assess the effect of COVID-19 associated governmental restrictions on the health of school-going adolescents. We compared the sedentary behavior, nutritional status and dietary behavior of adolescents before and during the COVID-19 pandemic.

METHODS

The study was a before-after, natural experiment study design wherein the baseline measurements were taken before the pandemic (September 2018 - February 2019) and follow-up measurements were done during the pandemic (October 2020 - March 2021). Governmental measures such as lockdown and school closures started in India on the March 24, 2020.

The study participants included adolescents enrolled in schools of Mohali, Punjab, India. The study was initially planned as a cluster randomized trial. COVID-19 related school closures, limited the interventional design and the pandemic related governmental measures were taken as a natural intervention. A total of 20 schools, 10 government (public) and 10 private schools, were randomly recruited for the study following permission from the Department of Education, Punjab. The details of school selection and recruitment were described earlier [20]. The study was approved by the Institute Ethics Committee and registered in a trial registration.

People were asked to stay at home to avoid exposure to the coronavirus and observe physical distancing when stepping out of the house for essential services. The school summer break came to an end in the first week of July after which both public and private schools gradually started online education while they were still closed.

Baseline measurements were conducted before the pandemic (2018-19). Schools that had a higher number of absentees on the day of data collection were revisited for the second time to maximize the response rate per school. Physical activity, sedentary and dietary behaviors were measured using a modified version of the Global School-Based Student Health Survey (GSHS) 2006 questionnaire which encompasses school-time MVPA, strengthening exercises and transport domain related physical activity (PA) [21]. Questions related to leisure-time PA were included from Baecke questionnaire [22], and those related to recess-time PA were included from Physical Activity Questionnaire for older Children (PAQ-C) [23] (**Web Table I**). Anthropometric measurements of height, weight and waist circumference were recorded. Body Mass Index (BMI) was manually calculated by the standard formula using height and weight measurements. The objective measures of physical activity using accelerometer ActiGraph GT3x-BT were recorded in a sub-sample. Students were given verbal instructions to wear ActiGraphs for 7 days mounted on the right side of the waist in front of the right hip at all times except while sleeping or performing water activities such as swimming and bathing. The raw data recorded in the Actigraph was converted into objective activity using the ActiLife6 software. Data was considered valid if the accelerometer was worn for at least 3 days a week (minimally two week days and 1 weekend day) and for at least 480 minutes in a day.

As per the government's guidelines a hybrid mode of both online and offline classes were adopted by most schools and schools were opened in a phased manner starting October 2020 when all schools that participated during baseline were approached for follow-up measurements. The same students who participated in baseline measurements (6th to 8th class) were included in follow-up measurements approximately two years later (8th to 10th class).

For the follow-up measurements, a few questions related to lifestyle behaviors were included in the modified GSHS 2006 questionnaire used during baseline data collection and was pretested in a similar population. See **Web Table II**. Data collection of self-report measures of physical activity, sedentary and dietary behavior which started in October 2020 was conducted via online questionnaire while the schools were still closed. Physical activity was measured objectively with an accelerometer and subjectively with a questionnaire. As regular classes resumed by January 2021, students who participated in baseline measurements and attended schools during the pandemic were approached for objective physical activity measures using ActiGraph and anthropometric measurements. Anthropometric measurements of height, weight and waist circumference were recorded. BMI was

calculated using the formula weight (kg) /height (m^2) and computed into BMI z-scores as per the 2007 WHO references [24]. ActiGraphs were selectively handed out to students whose ActiGraph measurements were recorded during baseline and who were present on the day of data collection. Data collection was done adhering to the latest guidelines issued by the government to prevent the spread of COVID-19.

The change in proportion of adolescents reaching the recommended level of physical activity using self-reported measures as per WHO guidelines was the primary outcome of the study. Secondary outcomes included lifestyle changes in adolescents in terms of physical activity and sedentary behaviors; dietary modifications, objective measures of physical activity (assessed in a subsample) and change in anthropometry (BMI and waist circumference) were assessed as indicators of under-nutrition and overweight/obesity.

Statistical analysis: IBM SPSS Statistics for Windows (version 28) was used for statistical analyses. The differences between paired proportions were assessed using the McNemar test and reported as odds ratio with 95% confidence interval (CI). The comparison of continuous variables was performed with paired-samples *t* tests for before-after differences and independent samples *t* test for between group differences. Two-sided *P* values < 0.05 were considered statistically significant. The 95% CI for odds ratio of paired observations was computed using an online calculator (*http://vassarstats.net/propcorr.html*).

RESULTS

A total of 1308 students were approached and 1086 students (83%) participated in the baseline measurements. The flow of the study participants is shown in **Fig. 1**. 20 schools participated at baseline while 18 schools participated in the follow-up measurements as two private schools dropped out included unwillingness to participate, not enough attendance, or other pandemic related priorities at the time. There were no statistically significant differences between the baseline characteristics of those adolescents who participated in the study versus who dropped out/ refused to participate after the initial recruitment (*data not shown*).

Table I shows the socio-demographic characteristics of 449 participants at baseline. **Table II** describes the adolescents' physical activity, sedentary and dietary behaviors recorded using the modified GSHS questionnaire. **Table III** shows paired data of anthropometric indices of 308 adolescents categorized by gender and school type. **Table IV** illustrates the results from objectively measured physical activity and sedentary time (n = 37) using ActiGraph wGT3x-BT. When adjusted for wear time, the time spent in light physical activity and counts per minute were lower during the pandemic than before.

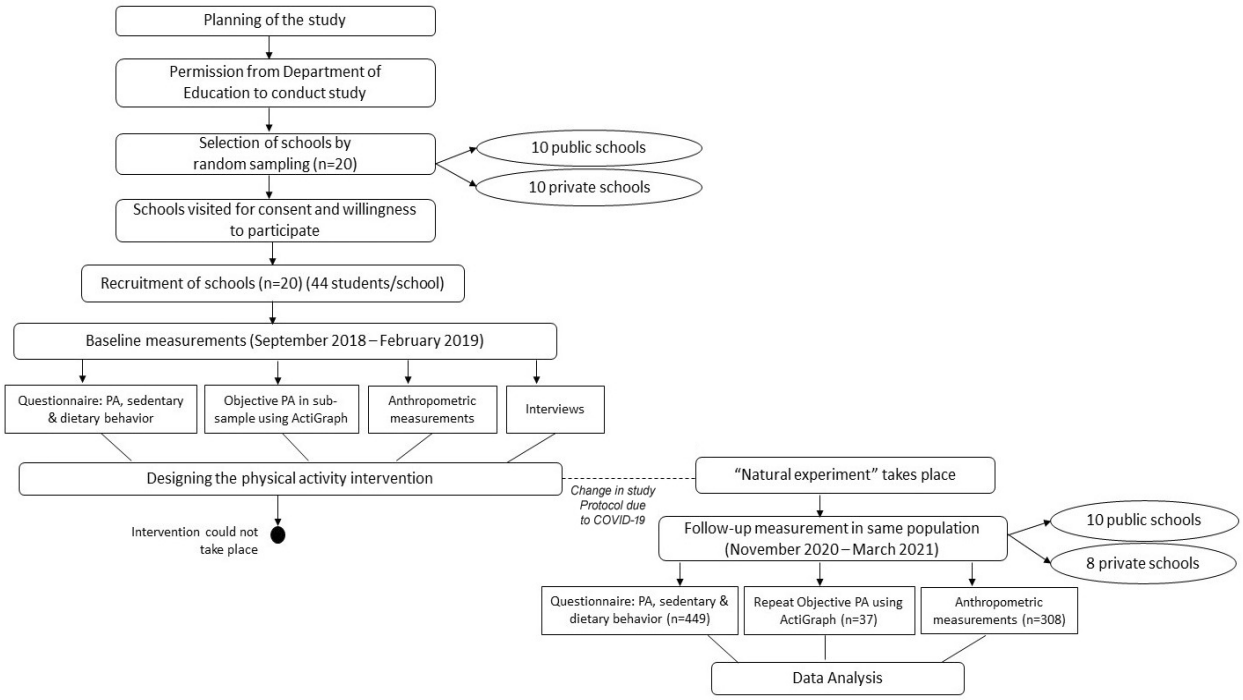

Fig.1 Criteria of School Selection and Recruitment

Table I Demographic Profile of Participants at Baseline (*n* = 449)

Characteristics	*Value*
Age[a], y	12.9 (1.2)
Boys	206 (45.9)
Government School	256 (57)
Private School	193 (43)
Parental Education	
• Maternal literacy[b]	263 (59.4)
• Paternal literacy[c]	335 (76.8)
Body mass index (BMI)[a], kg/m^2	17.9 (3.2)
Waist circumference[a], cm	62.8 (8.3)

Data expressed as [a]mean (SD) or n (%); Missing values [b]n = 6 and [c]n = 13

The follow-up survey on behavior and perceptions about the lifestyle during home confinement reported that 180 (40.8%) adolescents received physical activity related assignments from school such as doing yoga at home on a daily or weekly basis during school closures. Most adolescents reported spending less than two hours of screen-time for school assignments (*n* = 317, 71.0%) and screen-time for leisure (*n* = 349, 78.1%). While 167 (37.2%) adolescents reported to have gained weight, 163 (36.3%) did not perceive weight gain and 119 (26.5%) were unaware of change in weight.

DISCUSSION

The present study reports an increase in BMI and a decrease in physical activity of adolescents during the pandemic. The proportion of adolescents with adequate physical activity levels according to WHO guidelines in the current study was comparable to another study reporting Indian data [25]. There was a small, non-significant decrease in this proportion during the pandemic. There was a shift towards healthier dietary patterns during the pandemic with adolescents eating more fruits and less junk food. This is in contrast with studies from other countries that reported unhealthy dietary patterns during home confinement [15,26]. The healthier shift in the current study may have resulted from families preferring home-cooked food and opting for healthier snacking options like fruits. During this time, many small businesses including restaurants serving junk food were closed or completely shut down. Additionally, the general preference to avoid unhygienic practices that may be involved in preparation of junk food, including avoidance of contact with unknown persons, may have contributed to a significant decrease in its consumption.

The BMI and waist circumference as anthropometric indices of obesity increased significantly during the pandemic. This significant increase was also reflected within subgroups as per gender and school types. The gain in BMI*Z* score from underweight towards normal weight category may be result of consumption of more fruits and less junk food with a healthier behavior of adolescents during the pandemic.

There was limited data for accelerometry during the pandemic as fewer students attended schools. While the data reports an increase in wear time during the pandemic, the mean counts per minute (CPM) decreased significantly during this time. Data further reports a significant decrease in light PA, and no significant increase in moderate to vigorous physical activity (MVPA). This reduction in CPM may be explained with the type of PA performed by the adolescents. It is possible that adolescents were doing less light-intensity physical activity such as walking to school every day, or housework like buying groceries, or the house-work may have been divided among family members. Therefore, even though data measured in a sub-sample may have limited external validity, it still has some

Table II Comparison of Physical Activity, Sedentary Behavior, and Dietary Behavior (*n* = 443)

	Missing (n)	*Before COVID-19*	*During COVID-19*	*Odds ratio / Mean Difference[b] (95% CI)*	*P value*
Physically active[a]	6	150 (33.9)	136 (30.7)	1.2 (0.9, 1.6)	0.322
60 minutes daily PA, d/wk[b]	6	4.8 (2.4)	3.9 (2.8)	0.9 (0.6, 1.2)	0.121
Stretching exercises, d/wk[b]	4	4.0 (2.3)	3.2 (2.8)	0.9 (0.5, 1.2)	< 0.001
Leisure Time PA score[c]	21	9.9 (2.5)	9.8 (2.8)	0.1 (0.3, 0.4)	0.665
Sleeping for >8 h/d[a]	2	193 (43.2)	222 (49.7)	1.3 (1.0, 1.7)	0.059
Fruit at least once/d[a]	4	298 (67.0)	334 (75.1)	1.6 (1.2, 2.3)	0.004
Vegetable at least once/d[a]	3	416 (93.3)	399 (89.5)	1.7 (1.0, 2.8)	0.046
Junk food at least 3 d/wk[a]	2	240 (53.7)	164 (36.7)	2.2 (1.6, 3.0)	< 0.001

Data presented as [a]n (%) and [b]mean (SD); [c]Leisure time PA was divided into 3 categories of Play, walk and cycle (from Baecke questionnaire) and asked on a Likert scale ranging from 1=never to 5=very often. This score is the average of the sum of 3 scores. PA: Physical activity

WHAT THIS STUDY ADDS?

- The adolescents adopted healthier dietary practices but had decreased physical activity during the pandemics than before.

Table III Comparison of BMI z-Score by Gender and School

	n	*Before COVID-19*	*During COVID-19*	*Mean Diff (95% CI)*	*P value*
BMIZ score	308	- 0.7 (1.4)	- 0.5 (1.3)	0.2 (0.1, 0.3)	< 0.001
Gender					
Boys	143	- 0.8 (1.5)	- 0.7 (1.5)	0.1 (0.0, 0.2)	0.019
Girls	165	- 0.6 (1.3)	- 0.4 (1.1)	0.2 (0.1, 0.4)	< 0.001
School Type					
Government	195	- 1.0 (1.2)	- 0.8 (1.2)	0.2 (0.1, 0.3)	< 0.001
Private	113	- 0.3 (1.6)	- 0.1 (1.5)	0.2 (0.1, 0.4)	0.012

Data presented as mean (SD); BMIZ Body mass index z-score

Table IV Comparison of Physical Activity of Adolescents (as Measured by Accelerometry)

	Before COVID-19 (n=37)	*During COVID-19 (n=37)*	*Mean Diff (95% CI)*	*P value*
% wear time spent in MVPA	17.3 (7.2)	18.0 (6.5)	- 0.7 (- 3.0, 1.6)	0.547
% wear time spent in Light PA	9.0 (2.0)	8.1 (2.0)	1.0 (0.2, 1.8)	0.020
% wear time spent Sedentary	73.7 (8.9)	73.8(7.7)	- 0.1 (- 2.9, 2.7)	0.920
Counts per minute[a]	798.2 (297.5)	776.2 (278.4)	- 22.0 (64.7, 108.7)	< 0.001
MVPA ≥ 60 minutes[a]	24 (65.5)	21 (57.4)	1.7 (7.0, 0.4)	0.727

Data presented as mean (SD) or [a]n (%). MVPA Moderate to vigorous physical activity, PA Physical activity

internal validity as it highlights the changes in intensity and types of physical activity in adolescents during that time.

The study results need to be looked at with certain limitations. The response rate of online questionnaires was low despite frequent reminders. As the schools gradually started reopening, it became easier to reach out to adolescents who physically attended schools. However, many adolescents continued with online education as their parents did not consent to send their children to attend schools. A few families were displaced from their homes as businesses/non-essential services were shutting down, while a few adolescents had finished middle schools, and a few older adolescent boys had started working during the pandemic to support their families. This led to a high dropout rate of 59%. The sample included for the purpose of the study was representative of the total study population at baseline. Anthropometric measurements and accelerometry could only be done for students who attended schools. The included sample for accelerometry was not representative of the entire sample population. Therefore, the results of the objective data could not be used to further describe or supplement the results of the subjective data from the questionnaire.

The COVID-19 related governmental regulations had a varied impact in different countries on lifestyle behaviors like physical activity and dietary behaviors. These differences arise due to the cultural differences between countries, and the societal and environmental factors that influence the behavioral choices made by adolescents. Therefore, policies around physical activity, sedentary and dietary behaviors in future pandemics or natural disasters must address societal inequalities and should be culturally adaptable so that they do not alter the lifestyle of adolescents.

Ethical clearance: Institute Ethics Committee, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. No.: NK/4026/Study, dated Jan 17, 2018; Institute Ethics Committee, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. No. NK/6692/Study/525 dated Nov 05, 2020.

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data, refining, critical appraisal. All authors were involved in conception, developing the methodology and approved the final manuscript.

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Web Table I

Modified GSHS 2006 Questionnaire (For Baseline Assessment)

Study Questionnaire

Name of School: _____
School Code No: _____
Student ID: _____

1. How old are you?

A 11 years old or younger
B 12 years old
C 13 years old
D 14 years old
E 15 years old
F 16 years old or older

2. What is your sex?

A Male
B Female

3. In what class are you?

A Class 6
B Class 7
C Class 8
D Class 9
E Class 10
F Class 11

4. What is your family's monthly income?

5. Height

6. Weight

7. Waist Circumference

8. Date of Birth

Physical Activity Module

Physical activity is any activity that increases your heart rate and makes you get out of breath some of the time. Physical activity can be done in sports, playing with friends, or walking to school. Some examples of physical activity are running, fast walking, biking, dancing, or football.

ADD UP ALL THE TIME YOU SPEND IN PHYSICAL ACTIVITY EACH DAY. DO **NOT** INCLUDE YOUR PHYSICAL EDUCATION OR GYM CLASS

The next 2 questions ask about physical activity.

9. During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?

A. 0 day
B. 1 day
C. 2 days
D. 3 days
E. 4 days
F. 5 days
G. 6 days
H. 7 days

10. During a typical or usual week, on how many days are you physically active for a total of at least 60 minutes per day?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

The next 2 questions ask about physical education class and stretching exercises.

11. During this school year, on how many days did you go to physical education class each week?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days or more

12. During the past 7 days, on how many days did you do stretching or strengthening exercises, such as toe touches, knee bends, or push-ups?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

The next question asks about hours of sleep per day

13. Typically, how many hours do you sleep per day?

A Less than 4 hours
B 4 to 6 hours
C 6 to 8 hours
D 8 to 10 hours
E More than 10 hours

The next question asks about the time you spend mostly sitting when you are not in school or doing homework.

14. How much time do you spend during during a typical or usual day sitting and watching television, playing computer games, talking with friends, or doing other sitting activities, such as listening to music?

A Less than 1 hour per day
B 1 to 2 hours per day
C 3 to 4 hours per day
D 5 to 6 hours per day
E 7 to 8 hours per day
F More than 8 hours per day

The next 2 questions ask about going to and coming home from school.

15. During the past 7 days, on how many days did you walk or ride a bicycle to and from school?

16. During the past 7 days, how long did it usually take for you to get to and from school each day? ADD UP THE TIME YOU SPEND GOING TO AND COMING HOME FROM SCHOOL.

The next 2 questions ask about your total physical activity per day.

17. During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

18. During a typical or usual week, on how many days are you physically active for a total of at least 60 minutes per day?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

19. In the last 7 days, what did you normally do *at recess/lunch* (besides eating lunch)? (Check one only.)

A. Sat down (talking, reading, doing schoolwork).
B. Stood around or walked around.
C. Ran or played a little bit.
D. Ran around and played quite a bit.
E. Ran and played hard most of the time.

The next 3 questions ask about leisure time physical activity

20. During Leisure time, I play sport.

A Never
B Seldom
C Sometimes
D Often
E Very often

21. During leisure time, I walk.

A Never
B Seldom
C Sometimes
D Often
E Very often

22. During leisure time, I cycle.

A Never
B Seldom
C Sometimes
D Often
E Very often

Diet Module

The next 4 questions ask about foods you might eat and drinking and eating habits.

23. During the past 30 days, how many times per day did you usually eat fruit, such as apple, mango, banana, pineapple, papaya, jackfruit, guava, or

A I did not eat fruit during thepast 30 days
B Less than one time per day
C 1 time per day
D 2 times per day
E 3 times per day
F 4 times per day
G 5 or more times per day

24. During the past 30 days, how many

times per day did you usually eat vegetables, such as cauliflower, ladyfinger, pumpkin, brinjal, cabbage spinach, peas, tomato, cucumber, or beans?

A I did not eat vegetables during the past 30 days
B Less than one time per day
C 1 time per day
D 2 times per day
E 3 times per day
F 4 times per day
G 5 or more times per day

25. During the past 30 days, how many times per day did you usually drink carbonated soft drinks, such as Coke, Pepsi, Limca, or Fanta?

A I did not drink carbonated soft drinks during the past 30 days
B Less than one time perday

26. During the past 7 days, on how many

A 0 days
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

days did you eat at a fast food restaurant, such as McDonalds, Pizza Hut, or at those serving quick meals (e.g. Samosas, patties, burgers, noodles, tikkis, or ice-creams)?

The next 2 questions ask about the benefits of healthy eating or eating more fruits and vegetables.

27. During this school year, were you taught in any of your classes the benefits of healthy eating?

A Yes
B No
C I do not know

28. During this school year, were you taught in any of your classes the benefits of eating more fruits and vegetables?

A Yes
B No
C I do not know

Web Table II Modified GSHS 2006 Questionnaire (For Follow-up Measurement)

ICPASA Study Questionnaire

Name of School: _____

School Roll No. _____

1. How old are you?

A 11 years old or younger
B 12 years old
C 13 years old
D 14 years old
E 15 years old
F 16 years old
G 17 years or older

2. What is your gender?

A Male
B Female

3. In what class are you?

A Class 6
B Class 7
C Class 8
D Class 9
E Class 10

4.What is your total monthly family income? ----------

A. Height ---
B. Weight
C. Waist Circumference
D. Date of Birth5(i) Mother's education
   a. Middle school
   b. High school
   c. College
   d. Did not attend school

5(ii)Father's education

   a. Middle school
   b. High school
   c. College
   d. Did not attend school

Physical Activity Module

Physical activity is any activity that increases your heart rate and makes you get out of breath some of the time. Physical activity can be done in sports, playing with friends, or walking to school. Some examples of physical activity are running, fast walking, biking, dancing, or football.

ADD UP ALL THE TIME YOU SPEND IN PHYSICAL ACTIVITY EACH DAY.

The next 3 questions ask about physical activity.

6. During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?

A. 0 day
B. 1 day
C. 2 days
D. 3 days
E. 4 days
F. 5 days
G. 6 days
H. 7 days

7. During a typical or usual week, on how many days are you physically active for a total of at least 60 minutes per day?

A. 0 day
B. 1 day
C. 2 days
D. 3 days
E. 4 days
F. 5 days
G. 6 days
H. 7 days

8. During the past 7 days, on how many days did you do stretching or strengthening exercises, such as toe touches, knee bends, or push-ups?

A 0 day
B 1 day
C 2 days
D 3 days
E 4 days
F 5 days
G 6 days
H 7 days

The next question asks about hours of sleep per day.

9. Typically, how many hours do you sleep per

A Less than 4 hours
B 4 to 6 hours
C 6 to 8 hours
D 8 to 10 hours
E More than 10 hours day?

The next questions ask about the time you spend mostly sitting when you are not in school or doing homework.

10. How much time do you spend during a typical or usual day sitting and watching television, playing computer games, talkingwith friends, or doing other sitting activities, such as listening to music?

A Less than 1 hour per day
B 1 to 2 hours per day
C 3 to 4 hours per day
D 5 to 6 hours per day
E 7 to 8 hours per day
F More than 8 hours per day

11. How much time do you spend in front of the screen (TV, laptop, using mobile phone) for home-work/school-work?

A Less than 1 hour per day
B 1 to 2 hours per day
C 3 to 4 hours per day

D More than 4 hours per day

12. How much time do you spend in front of the screen (TV, laptop, using mobile phone) for leisure activities?

A Less than 1 hour per day
B 1 to 2 hours per day
C 3 to 4 hours per day
D More than 4 hours per day

13. During school closures, how many times did you receive assignments from school related to physical activity, such as yoga/ walking/ aerobics etc.?

(a) Daily
(b) Weekly
(c) fortnightly (once in 15 days)
(d) Monthly
(e) Rarely
(e) Never

14. During Leisure time, I play sport

(a) Never
(b) Seldom (2-3 times/month)
(c) Sometimes (once a week)
(d) Often (2-3 times/week)
(e) Very often (4-5 times/week)

15. During leisure time, I walk

(a) Never
(b) Seldom (2-3 times/month)
(c) Sometimes (once a week)
(d) Often (2-3 times/week)
(e) Very often (4-5 times/week)

16. During leisure time, I cycle

(a) Never
(b) Seldom (2-3 times/month)
(c) Sometimes (once a week)
(d) Often (2-3 times/week)
(e) Very often (4-5 times/week)

Dietary habits

The next 4 questions ask about foods you might eat and drinking and eating habits1

7. During the past 30 days, how many times per day did you usually eat fruit, such as apple, mango, banana, pineapple, papaya, guava, or chikoo?

A. I did not eat fruit during the past30 days
B. Less than one time per day
C. 1 time per day
D. 2 times per day
E. 3 times per day
F. 4 times per day
G. 5 or more times per day

18. During the past 30 days, how many times per day did you usually eat vegetables, such as cauliflower, ladyfinger, pumpkin, brinjal, cabbage, spinach, peas, tomato, cucumber or beans?

A. I did not eat vegetables duringthe past 30 days
B. Less than one time per day
C. 1 time per day
D. 2 times per day
E. 3 times per day
F. 4 times per day
G. 5 or more times per day

19. During the past 30 days, how many times per day did you usually drink carbonated soft drinks, such as Coke, Pepsi, Limca, or Fanta, or sweetened juices like Real juice, Frooti, Tropicana juice etc.?

A. I did not drink carbonated softdrinks during the past 30 days
B. Less than one time per day
C. 1 time per day
D. 2 times per day
E. 3 times per day
F. 4 times per day
G. 5 or more times per day

20. During the past 7 days, on how many days did you eat or order at a fast food restaurant, such as McDonalds, Domino's, Burger King noodles/chinese, tikkis, or ice creams)?

A. 0 day
B. 1 day
C. 2 days
D. 3 days
E. 4 days
F. 5 days
G. 6 days
H. 7 days

The next 2 questions ask about the benefits of Healthy eating or eating more fruits and vegetables.

22. During this school year, were you taught in any of your classes the benefits of eating more fruits and vegetables?

A Yes
B No
C I do not know

23. Has your consumption of snacks and branded foods like chips, namkeen, soups (like Knorr and Maggie), Maggie noodles or frozen foods (like McCain) changed during school closures

A Yes
B No
C I do not know

24. Did you gain weight during the school closure?

A Yes
B No
C I do not know

ORIGINAL ARTICLE

Social, Emotional and Behavioral Problems in Children With Foreign Body Ingestion: A Case Control Study

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ABSTRACT

Objectives: To compare the social, emotional, and behavioral status between the patients aged 1 to 4 years with foreign body ingestion and healthy individuals.

Methods: A case control study was conducted in a tertiary level hospital over 32 months. Children, aged 1-4 years, admitted to the pediatric emergency department with foreign body ingestion were included as cases. Patients with known autism spectrum disorders, cerebral palsy and incomplete evaluation were excluded. A matched control group constituted healthy individuals. Both groups were evaluated with Aberrant Behavior Checklist (ABC) and Brief Infant-Toddler Social Emotional Assessment (BITSEA) scales. Logistic regression was performed to determine the predictors of foreign body ingestion.

Results: Cases and controls included 150 children each. All ABC subscale scores (mean irritability, hyperactivity/dissonance, lethargy/social withdrawal, stereotypical behavior, and inappropriate speech) and problem area scores of BITSEA were significantly higher in the cases ($P < 0.001$). Hyperactivity was significantly predictive of foreign body ingestion [OR (95% CI) 1.37 (1.21, 1.55), $P < 0.001$]

Conclusion: Younger children with foreign body ingestion screened significantly higher for behavioral and emotional problems compared to controls**.** Hyperactivity was an important predictor factor for foreign body aspiration.

Keywords: *Aberrant behavior checklist, Attention-deficit/hyperactivity disorder, Brief infant–toddler social emotional assessment*

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INTRODUCTION

Accidental drug or foreign body ingestion is mostly seen in early childhood and is a common cause of emergency admissions in children. Up to 75% of the total ingestions occur in children 5 years of age or younger, with higher risks of complications like perforation or obstruction, and mortality [1]. This is especially so in children between 6 months to 3 years as they are predisposed to exploring things with their mouths and fingers. Foreign body ingestion in older children occurs due to many factors, such as triggering situations, the physical and social environment, and the psychological, behavioral, and emotional state of the child [2,3].

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There is an increasing recognition of the importance of early detection and the role of intervention for infants and toddlers with significant social, emotional and behavioral problems [4]. Many authors have reported an association between foreign body ingestion and attention-deficit hyperactivity disorder (ADHD) in children [5-7], however, we were unable to find any data on children aged one to four years. The probable reason for this is that it is often difficult to make a diagnosis of ADHD in this age group. Behavioral and emotional difficulties are reported to be precursor symptoms of ADHD in younger children [8]. The objective of this study was to compare the social, emotional, and behavioral status of children aged 1 to 4 years presenting with foreign body ingestion with apparently healthy controls.

METHODS

This prospective case-control study was conducted in a tertiary level hospital situated in Turkey over 32 months

between January, 2019 and August, 2022. The study was approved by the institutional ethics committee. The cases included consecutive patients aged one to four years admitted to the pediatric emergency department (PED) with foreign body ingestion or accidental poisoning. All eligible children were enrolled in the study after obtaining written informed consent from the parents/legal guardians and after stabilization and appropriate treatment in PED. Patients with known autism spectrum disorder, cerebral palsy, or for whom the evaluation was incomplete, were excluded.

Based on a previous study [5] and considering the prevalence of ADHD in children with FB, the calculated sample size for a similar sample proportion with a 5% margin of error and 95% confidence level was 149. The control group composed of healthy children, matched for age, gender, and socio-economic status, without a history of foreign body ingestion who had presented to the hospital for post-discharge follow-up visits for other health conditions.

The parents were asked to fill out clinical and socio-demographic details regarding their children's age, gender, gestational age, birth weight, type of birth, neonatal intensive care unit (NICU) stay, and any past history of foreign body ingestion. Details of parents (age, health status, and working status, and consanguinity) and siblings, (number history of ingestion and the ingested materials) were also collected.

The Aberrant Behavior Checklist (ABC) and the Brief Infant-Toddler Social Emotional Assessment (BITSEA) scales were used to screen the children for their social, emotional, and behavioral status. These scales were administered to the parents of each case by the pediatrician and took around 40-60 minutes to complete. The ABC assesses the severity of problem behaviors and psychiatric symptoms in children and adolescents. It is a 58-item rating scale in which each item is rated on a 4-point Likert scale, with higher scores indicating more severe problems. ABC is scored on five subdomains: Irritability (15 items); Hyperactivity/Noncompliance (16 items); Lethargy/ Social Withdrawal (16 items); Stereotypic Behavior (7 items); and Inappropriate Speech (4 items) [9]. The BITSEA is a reliable and valid screening tool for behavioral and developmental problems in toddlers. The scale compromises two subscales and consists of 42 items in total; the BITSEA Problem subscale (BITSEA/P) that is comprised of 31 items and the BITSEA Competence subscale (BITSEA/C) which is comprised of 11 items. The response format for each item has three responses: "not true/rarely" (score 0), "sometimes true/sometimes" (score 1), and "very true/often" (score 2). Higher total scores on BITSEA/P indicate a higher level of behavioral and emotional problems [10]. Turkish translations have been validated earlier in children aged 12- to 42-months for BITSEA and 14- to 43-months for ABC [11,12].

Statistical analysis: SPSS for Windows Version 20.0 package program was used. The distribution of variables was assessed with histograms, Shapiro-Wilk test, and non-parametric tests (as applicable). The differences between groups were tested by independent-sample t-test or Chi-square test (for normal distribution). Mann-Whitney U-test was used for comparing variables in which non-parametric testing was indicated; five subscale scores of ABC and the two domains of BITSEA (problem and competence). Binary logistic regression analysis was performed to identify predictors of foreign body ingestion.

RESULTS

Three hundred participants (150 patients and 150 controls) were enrolled (**Fig. 1**). The median (IQR) age of cases was 30 (20-37) months and of the controls was 33 (26-37) months. The percentage of males was 56% in the cases and 55% in the controls. There were no significant differences between both groups with respect to the variables under study (**Table I**). The ingested foreign substances included 40 (27%) pills, 23 (15%) dishwash rinse aid, 20 (13%) coins, 13 (9%) oral suspensions of medicine, 10 (7%) batteries, 9 (6%) beads, 8 (5%) hair clips, 6 (4%) multipurpose cleaning solution and 21 (14%) others. Most cases (89.4%) were discharged from the emergency department after intervention, and the remaining needed longer duration of hospitalization till they made full recovery.

The scale-wise mean (SD) scores of ABC in cases versus *vs* controls were as follows: irritability [21.5 (7.5) *vs* 4.4 (5.1)]; hyperactivity/non-compliance [32.7 (8.8) *vs*

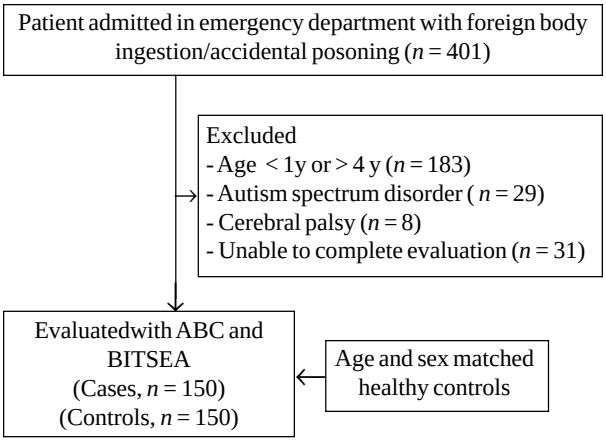

Fig. 1 Flow diagram of the study population

Table I Demographic Characteristics of the Study Participants

	Patients (*n = 150*)	*Control* (*n = 150*)	*P value*
Age (mo)[a]	30 (20, 37)	33 (26, 37)	0.285
Male gender[b]	85 (56)	82 (54.6)	0.727
Cesarean delivery[b]	86 (57)	78 (52)	0.571
Gestational age (wk)[c]	38.6 (1.35)	38.15 (2.38)	0.165
Birth weight (g)[c]	3317 (497)	3343 (675)	0.416
History of NICU stay[c]	34 (22.7)	33 (22)	0.946
Sibling number[b]			0.299
None	54 (36)	74 (50)	
1	66 (44)	50 (33)	
$^{24}_{12}2$	30 (20)	26 (17)	
Mother age (y)[c]	31.05 (5.93)	31.39 (5.06)	0.737
Father age (y)[c]	34.29 (5.98)	34.79 (4.65)	0.590
Consanguinity[b]	28 (18.7)	26 (17.3)	0.919
Working mother[b]	53 (35.3)	72 (48)	0.225
Working father[b]	145 (96.6)	144 (96)	0.865

Values expressed as [a]median (IQR), [b]*n* (%), or [c]mean (SD). *NICU: Neonatal intensive care unit.*

4.7 (5.2)]; lethargy/social withdrawal (4.41 (3.4) *vs* 1.39 (2.60)]; stereotypic behavior [4.24 (4.59) *vs* 0.24 (0.68)] and inappropriate speech [7.1 (2.6) *vs* 1.3 (1.9)]. These scores were significantly higher in the cases as compared to the controls across all domains ($P < 0.001$).

The mean (SD) score of BITSEA problem domain was significantly higher in the cases [27.3 (6.8)] compared to the controls [12.7 (7.5)] ($P < 0.001$). There was no significant difference between the groups in the competence domain; 17.3 (3.0) *vs* 17.7 (3.5) respectively ($P = 0.08$). The logistic regression analysis revealed that hyperactivity was the only variable that was significantly predictive of foreign body ingestion [OR (95% CI) 1.37 (1.21-1.55), $P < 0.001$] (**Table II**).

Table II Predictors of Foreign Body Ingestion (*n* = 150)

	Odds Ratio (95% CI)	*P Value*
Irritability	0.60 (0.81, 1.13)	0.60
Lethargy/Social withdrawal	1.15 (0.90, 1.48)	0.25
Stereotypic behavior	1.76 (0.97, 3.19)	0.06
Hyperactivity/Non-compliance	1.37 (1.21, 1.55)	< 0.001
Inappropriate speech	1.42 (0.93, 2.16)	0.10
Problem domain	0.97 (0.66, 15.66)	0.69
Competence domain	0.70 (0.58, 1.06)	0.11

DISCUSSION

Attention-deficit hyperactivity disorder is one of the most common neuropsychiatric disorders in school-aged children, and the estimated worldwide prevalence in children and adolescents is 3.4% and 5% [13]. Previous studies have shown an association between ADHD and foreign body ingestion in older children [5]. In most studies, Conners' Parent Rating Scales (CPRS) have been used to evaluate ADHD in symptomatic individuals between 3 and 17 years [6]. However, it is not suitable for younger children. Previous studies have shown that children and adolescents diagnosed with ADHD also have behavioral problems at a young age [14-16]. That is the reason we used the ABC and BITSEA scales in this study as a surrogate indicator of possible ADHD based on the hypothesis that children identified with behavioral problems during early childhood may be predictive of ADHD in the future. We found that the scores in the problem domain of BITSEA were significantly higher in patients with foreign body ingestion compared to healthy controls. In addition, hyperactivity was the most important predictor factor. Our finding suggests the possibility that patients presenting with foreign body ingestion may be indicative of ADHD later on. Buaermeister et al reported that the rate of ADHD in boys between the ages of 4 and 17 years was 2.3 times higher than in girls [17]. Hagos et al reported foreign bodies in the esophagus, ears, and nose in 72 children aged 11 months to 14 years, out of which two-thirds of them were boys [7]. The ingestion of foreign bodies in this study was also more commonly seen in boys.

Our study has certain limitations. Firstly, the children were assessed using a screening tool rather than a diagnostic instrument. However, as mentioned earlier it is difficult to diagnose ADHD in younger children who are more predisposed to foreign body ingestion. Secondly, the data was generated from a single center. Thirdly, we did not screen for Autism Spectrum Disorder (ASD), which can also manifest as hyperactivity in younger children and is associated with pica. The fact that all scales were performed by a single pediatrician strengthened the consistency.

There are many other studies that have demonstrated the association between self-inserted foreign bodies and ADHD [5,17-19]. However, all these studies were performed in patients aged over 3 years. Turgut et al investigated ADHD in children aged 3-17 years with foreign body ingestion using Conners' Parent Rating Scales-Revised (CPRS-R) in a case-control study [5]. In addition to the total CPRS-R score (17 *vs* 6), they reported a significantly higher prevalence of cognitive problems, oppositional behavior, hyperactivity, anxiety, perfec-

WHAT THIS STUDY ADDS?

- The domain-wise mean score of the Aberrant Behavior Checklist and the hyperactivity domain of BITSEA-P were significantly higher in children with foreign body ingestion and accidental poisoning compared to those without.
- Hyperactivity is associated with increased risk for foreign body ingestion in children aged 1 to 4 years.
- Patients with foreign body ingestion and accidental poisoning should be referred to trained professionals for behavioral and developmental screening, and in-depth evaluation by developmental pediatricians if warranted.

tionism, psychosomatic, social problems, and ADHD in the study group. Özcan et al also reported higher CPRS-R subscale scores in children aged 3 to 9 years with self-inserted foreign bodies compared to controls in a prospective case-control study [18]. Perera et al investigated the major features of ADHD in 34 children aged 3 to 10 years with self-inserted nasal and aural foreign bodies using CPRS and Strengths and Difficulties questionnaire (SDQ)–Parent Version [19]. They reported 14.3% ADHD in the study group. Although it was not possible to use a diagnostic tool for ADHD due to the younger age of our study group, we found higher ABC scores of hyperactivity and BITSEA-P domains suggesting of behavioral problems in the study group. In light of the results of this study, an adequately powered multicentric cohort study of children with foreign body insertion should be planned with initial screening using appropriate tools for assessing development, behavioral problems, and ASD. These children should be followed up and evaluated for ADHD using appropriate diagnostic tools once they become old enough.

Our study demonstrated that hyperactivity-behavioral symptoms may be more common in children under the age of four who swallow foreign bodies. On the basis of this we recommend that patients with foreign body ingestion and accidental poisoning should be referred to trained professionals for behavioral and developmental screening initially and an in-depth evaluation by a developmental pediatrician, if warranted.

Ethics clearance: IEC, Ankara Etlik City Hospital. No. E2018-171, dated Dec 10, 2018.

Contributors: BÖ: Data analysis; SBA, TÇY, NT: Conception/ design of the work, data acquisition, analysis and interpretation; RMY, MMG, ÝB: Drafting the work, revising it critically for important intellectual content; CDK, AG: Final approval of the version to be published; BÖ, NT: Ensuring accuracy of the questions/ study protocol, overall supervision; guarantor for the study. All authors contributed to the execution of the study and approved the final version.

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EVENTS

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ORIGINAL ARTICLE

Utility of Film Array Meningoencephalitis Panel in Children With Acute Encephalitis Syndrome: A Single Centre Experience from South India

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ABSTRACT

Objective: To describe the utility of film array meningoencephalitis (FAME) panel in the management of children with acute encephalitis syndrome (AES).

Methods: A retrospective audit was conducted between January 2017 to July 2022. We included children aged < 18 years with a diagnosis of AES for whom a CSF analysis study including FAME panel testing performed within 48 hours of admission was available. Electronic medical records were reviewed for details including demographic profile, clinical presentation, investigations and outcome.

Results: Out of 157 CSF samples sent for FAME panel testing, 49 were positive (31.4%.) Viral pathogens were identified in 42 (Enterovirus: 31, Human herpes virus 6: 9, Varicella zoster virus: 1, and Cytomegalovirus: 1) Bacterial pathogens were identified in 6 (*Streptococcus pneumoniae*: 2, *Streptococcus agalactiae*: 2, *Hemophilus influenzae*: 1, and *Escherischia coli*: 1). Fungal etiology (*Cryptococcus neoformans*) was detected in one child. Antibiotics could be stopped within 72 hours of initiation in 42 children in whom a viral etiology was established. Acyclovir could be stopped in 21 out of 32 children within 72 hours after the FAME panel testing. FAME panel was presumed to be false positive in 4 children.

Conclusion: Etiology of AES could be established in nearly a third of children with AES using the rapid diagnostic FAME panel testing in CSF and it was found to be effective in reducing empirical antibiotic/antiviral therapy.

Keywords: *Acute encephalitis syndrome, BioFire, FAME panel, Film Array Meningoencephalitis panel, Polymerase chain reaction*

INTRODUCTION

Acute encephalitis syndrome (AES) is defined by World Health Organization (WHO), as a person of any age presenting at any time of year with acute onset of fever and a change in mental status (including symptoms like confusion, disorientation, coma, or inability to talk) and / or new onset of seizures (excluding simple febrile seizures) [1].

Cerebrospinal fluid (CSF) cytology and biochemistry can provide valuable clues to differentiate between viral and bacterial etiology, but can often be nonspecific which makes the treatment challenging. CSF bacterial culture, though accurate, has poor yield due to high rates of early empirical antibiotic administration. Identification of individual viral pathogens by polymerase chain reaction (PCR) is expensive and time-consuming. The long processing time leads to unnecessary antimicrobial therapy in most children.

Film Array Meningoencephalitis (FAME) panel (BioFire Diagnostics, USA) is an automated multiplex PCR system that can identify 14 different viral, bacterial, and fungal pathogens in CSF. It includes *Escherichia coli* K1, *Hemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, Cytomegalovirus (CMV), Enterovirus (EV), Herpes Simplex Virus 1 (HSV-1), Herpes Simplex Virus 2 (HSV-2), Human Herpes Virus 6 (HHV-6), Human Parechovirus (HPeV), Varicella Zoster virus (VZV), and *Cryptococcus neoformans*. The test requires a small amount of CSF and has a turn around time of two hours. PCR-based molecular diagnosis is recommended for the evaluation of encephalitis syndromes as per the Infectious Diseases Society of America guidelines [2]. However, there is a scarcity of literature on PCR-based diagnostic studies in the pediatric population in India.

Our primary objective was to describe the utility of the FAME panel in the diagnosis and treatment of children with AES. The secondary objective was to describe the

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clinical features, investigations and outcomes of children with confirmed meningoencephalitis.

METHODS

This retrospective observational study was conducted at a single tertiary care centre in South India between January 2017 and July 2022. Medical records of all children aged under 18 years, with a diagnosis of AES as per the WHO definition [3], who underwent CSF analysis and FAME panel within 48 hours of admission were included in the study. Prior approval was obtained from the institutional ethics committee.

Demographic profile, history, findings of clinical examination, laboratory investigations (blood culture, serology as per clinical indications including scrub typhus, dengue virus, JE antibody test and neuroimaging study), treatment given, course of hospital stay and outcomes were retrieved from electronic records. Details of CSF analysis including total counts, differential counts, proteins, sugars, Gram stain, staining for acid-fast bacteria (AFB), India ink staining, and KOH preparation, CSF culture and sensitivity for bacterial, fungal, and *Mycobacterium tuberculosis* were recorded along with CSF FAME panel results.

Statistical analysis: The statistical analysis was done by using SPSS version 25.0 (IBM Corp, New York, NY). Descriptive data was expressed as numbers (n) and percentages (%) for categorical data and median values with interquartile ranges for continuous variables. The clinical and radiological features were compared between FAME panel positive and negative cases. The results of the FAME panel were compared with those of CSF culture, gram stain, and blood culture in cases of bacterial meningitis.

RESULTS

A total of 316 children were admitted at our centre from January 2017 to July 2022 with a diagnosis of AES. FAME panel was sent for 157 children (49.68%).The age group of the study population ranged from 5 days to 18 years. Among them, 48.5% of children were aged less than five years (76/157).

Out of 157 CSF samples sent for FAME panel, 49 (31.4%) tested positive; viral pathogens constituted 42 out of 49 positive cases. These included Enterovirus 31, HHV-6 9, VZV 1 and CMV 1. Bacterial pathogens were identified in six samples. *Cryptococcus neoformans* was detected in one child.

Final diagnosis of 154 children, at discharge included aseptic meningitis (n = 54, 34.7%), viral encephalitis (n = 29, 18.8%), bacterial meningitis (n = 9, 5.9%), febrile status (n = 18, 11.7%), sepsis (n = 6, 3.9%), autoimmune causes (acute disseminated encephalomyelitis/auto-immune encephalitis) (n = 38, 25%), based on the clinical recovery, CSF studies and neuroimaging findings. There was one case each of dengue viral encephalitis, Japanese encephalitis and Scrub typhus based on serological testing

Enteroviral encephalitis was the most common viral pathogen identified and remained the most common etiology of aseptic meningitis/meningoencephalitis in children. HHV-6 was the next common viral pathogen detected. Out of 9 children who tested positive for HHV-6, seven children presented with febrile status epilepticus.

Among the 9 cases of bacterial meningitis, identified based on clinical features and CSF cytology, the panel detected the causative bacteria in 6 cases (*S. pneumoniae* 2, *S. agalactiae* 2, *H. influenzae* 1 and *E. coli* 1). The CSF bacterial culture report came as negative in all cases, but the bacteria was identified in Gram stain and blood culture in 4 out of 6 cases. In an unimmunized infant with subdural effusion, *H. influenzae* was identified only in the film array. **Table I** summarizes the CSF analysis and clinical features of children with bacterial, enteroviral and HHV infection.

Four cases were presumed to be false positive on FAME panel. In the first case, a 7-year-old child with prolonged fever, seizures, meningeal signs and an eschar on the back, CSF showed lymphocytic pleocytosis, high protein and normal sugar; the PCR for scrub typhus came as positive, but FAME panel detected *E. coli* although the blood culture, CSF culture and gram stain were negative. He recovered completely after receiving a course of doxycycline. *E. coli* was codetected with *S. pneumoniae* in another child where the blood culture grew only *S. pneumoniae*. *Cryptococcus neoformans* was detected in one child with febrile status and normal CSF findings, CSF KOH stain, fungal culture and India Ink study came as negative. The child recovered spontaneously without any specific treatment. In the fourth case, CMV was codetected with *S. pneumoniae* in whom, PCR for CMV in the CSF sample was negative.

Empirical antibiotic administration could be stopped within 72 hours in 42 out of 49 children in whom viral pathogens were detected. Acyclovir, which was empirically administered in 32 children, could be stopped within 72 hours in 21 of them based on the FAME panel testing. Acyclovir was continued in 8 patients with suspected HSV encephalitis (persistent sensorial alteration beyond 48 hours, frontotemporal involvement in neuroimaging, CSF cytology, and biochemistry suggestive of viral meningitis) despite CSF film array being negative for HSV. Acyclovir was also continued in two children with severe HHV-6 encephalitis and one child with

Table I Comparative CSF Parameters and Clinical Profile of Children Diagnosed Based on Film Array Meningoencephalitis Panel

	Enteroviral encephalitis (*n* = 31)	*HHV6 encephalitis* (*n* = 9)	*Bacterial Meningitis* (*n* = 6)
Cerebrospinal fluid analysis			
Total cell count (cells/mm^3)[a]	76 (14, 144)	8 (4, 130)	277.5 (54, 1197.7)
Protein (g/dL) [a]	24.7 (18.9, 40.6)	34.8 (13.15, 36.4)	227.25 (42.15, 530.25)
Glucose (mg/dL) [a]	66 (62, 74)	59.3 (55.3, 67.95)	35 (2, 67.05)
CSF pleocytosis[b]	26 (83.8)	4 (44.4)	6 (100)
CSF neutrophilic predominance[b]	9 (29.1)	1 (11.1)	3 (50)
CSF lymphocytic predominance[b]	17 (54.9)	3 (33.3)	3 (50)
Clinical Features			
Seizures[b]	2 (6.4)	5 (55.5)	1 (16.6)
Altered sensorium[b]	4 (12.9)	5 (55.5)	5 (83.3)
Headache and vomiting[b]	27 (87.1)	5 (55.5)	2 (33.3)

[a] *Values expressed as* [a]*median (IQR) or* [b]*n (%)*

Varicella zoster encephalitis confirmed with FAME panel.

DISCUSSION

Our study shows that one third of children with AES tested positive using FAME panel on CSF. CSF cytology and biochemistry could be normal in many children and is nonspecific especially in cases of viral meningoencephalitis and decisions based solely on conventional CSF analysis can lead to diagnostic and treatment delay as well as unnecessary and prolonged empirical administration of antibiotics /antivirals.

Early pathogen detection was possible in children with meningoencephalitis using the FAME panel. Standard diagnostic tests such as CSF culture sensitivity were found to be time-consuming and had poor diagnostic yield in children with bacterial meningitis. The positivity rate of FAME panel was 31.6% compared to 10.4% and 23.6% in two previous Indian studies done in the adult population [3,4]. A higher positivity rate of 46.4% was also observed in another study conducted in children [5].

The diagnostic accuracy of the FAME panel has been studied, and a recent Meta-analysis reported moderate sensitivity and high specificity. The sensitivity was found to be lower for certain bacteria when compared to viruses; however the specificity was optimal for both bacteria and viruses. Authors suggested that the panel testing is better to rule in the disease than to rule out and cautioned the clinicians regarding the chances of high false positivity of the test in specific scenarios [11]. False positivity was observed in four cases in our study.

Viral pathogens constituted the majority of positive cases in our study, which is in line with previous studies where viruses constituted a majority of the pathogens in meningoencephalits ranging from 57-80% [12]. The prevalence of enteroviral encephalitis is as high as 21–22% in encephalitis in endemic areas [13]. In a study conducted by Beig et al in 2010, enteroviral encephalitis constituted 42.1% of viral encephalitis in children [13]. HHV-6 was identified as a major pathogen in children, and in contrast to some of the previous studies, HSV was not detected in our children [6,7].

Severe HHV-6 encephalitis occurred in two previously healthy, immunologically competent children, out of which one child died and the other child recovered with mild neurological deficits. HHV-6 related mortality in immunocompetent children is relatively rare [8].

FAME panel aided antimicrobial stewardship and early discontinuation of antibiotics and acyclovir within 72 hours of admission in many children. Similar findings were observed in a few studies concerning the utility of the film array panel in antimicrobial stewardship [9,10]. The use of FAME panel could possibly benefit by reducing the duration of hospital stay and expenditure, as early antimicrobial de-escalation is feasible. Whether decreased hospital stay and expenditure could compensate for the high cost of the FAME panel and justify its use needs to be analyzed with further studies. At present, implementing the FAME panel should be individualized based on each patient's clinical situation and need.

A major drawback of the FAME panel is that it does not include detection of Dengue encephalitis, Japanese encephalitis, Scrub typhus, and *Mycobacterium tuberculosis*, all of which have epidemiological significance in our country.

WHAT THIS STUDY ADDS?

- Film Array Meningoencephalitis (FAME) panel is a useful tool in early identification of specific etiology in children with acute encephalitis syndrome.
- FAME can aid early treatment decisions including antimicrobial de-escalation.

We conclude that the FAME panel is a rapid diagnostic test with a positivity rate of 31.6% in our study. The FAME panel testing can aid earlier pathogen detection and definitive diagnosis in children with meningoencephalitis when compared to the conventional CSF testing. Early treatment decisions and antimicrobial de-escalation are possible within 72 hours in children with AES using rapid FAME panel. FAME panel could be an addition to the diagnostic armamentarium in evaluating children with AES.

Ethics clearance: KIMS/IHEC/12/2023/01 dated Jan 12, 2023.

Contributors: DT: Conception, data collection and analysis, drafting the work, critical appraisal and revision of the draft; DK: Conception, drafting the work; PAKM: Critical inputs and revision of the draft; GB: Drafting the work; PJ, NG: Conception, developing protocol, data collection and analysis, drafting the work. All authors approved final version of manuscript and are accountable.

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RESEARCH LETTER

Neurosonographic Findings in Infants with Rhesus Hemolytic Disease of Newborn: A Prospective Observational Study

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ABSTRACT

We estimated the incidence of intraventricular hemorrhage (IVH) and/or periventricular leukomalacia/echogenicity (PVL/E) in Rhesus isoimmunized infants. Seventy-one infants underwent cranial ultrasound within the first 3 days of life or discharge, whichever was earlier. Of these, 27 (38%) infants had IVH/ PVL/E. On multivariate analysis, lower gestational age (P = 0.035), small for gestational age [aOR (95% CI) 10.6 (1.9, 58.9)], and sepsis [aOR (95% CI) 4.5 (1.1, 18.4)] were independently associated with IVH/PVL.

Keywords: *Anemia, Cranial ultrasound, Intraventricular hemorrhage, Neurodevelopmental outcome*

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Infants born to women with Rhesus (Rh) isoimmunization during pregnancy are at risk for fetal anemia. Many of them undergo multiple intrauterine transfusions (IUTs) from the second trimester onwards. In-utero anemia coupled with hemodynamic fluctuations associated with IUT may increase the risk of fetal brain injury [1,2]. A few cohort studies have shown an increased incidence of intraventricular hemorrhage (IVH), cerebellar hemorrhage, and periventricular leukomalacia/echogenicity (PVL/E) following IUT in the fetal period [2–4]. There is very limited data on the neurosonographic abnormalities in the neonatal period [1,5], although the prevalence of IVH/PVL in infants with IUTs has been reported to vary from 35 to 57% [1,5].

Approximately 45% of infants born to Rh isoimmunized women in our unit require IUT. Assuming an incidence of IVH/PVL of 25% (50-55% of enrolled will be without IUT) and a 10% margin of error, a sample size of 72 participants was needed. The objective of this prospective observational study was to estimate the incidence and determine the predictors of IVH and/or PVL/E in Rh-isoimmunized infants.

Infants born between July 2020 and December 2022 to women with Rh isoimmunization and indirect coomb's test titers ≥ 1:16 were enrolled, irrespective of IUT status. Infants born to mothers with pregnancy-induced hypertension, chorioamnionitis, and immune thrombocytopenic purpura were excluded. Ethics approval and written informed parental consent were obtained.

Fetal anemia and the need for IUT were assessed per standard parameters during pregnancy [1]. Fetuses with middle cerebral artery peak systolic velocity > 1.5 multiples of the median were considered to have moderate to severe fetal anemia. They underwent IUT and invasive fetal blood sampling. In cases of IUT, pre-IUT fetal hematocrit of < 30% was considered anemia, and < 21% severe anemia [1]. Structured cranial ultrasound (CUS) was performed within the first three days of life or discharge, whichever was earlier [1,6]. The ultrasound scans were performed by pediatric radiologists, except in neonates admitted in the neonatal intensive care unit (NICU), where a trained neonatologist did the CUS using a multifrequency (4-12 MHz) phased array probe. Infants with abnormal CUS findings in the first instance were re-evaluated on day 7 of life. Periventricular echogenicity (PVE) was defined as confluent areas of increased echogenicity (iso/hyperechoic in comparison to the choroid plexus in the periventricular region) observed in the coronal and sagittal planes. Persistent flare/PVE for ≥ 7 days was considered abnormal and was labeled as PVL. PVL and IVH were classified according to de Vries and Volpe's classification, respectively [7]. Hearing screening was performed before discharge using automated *auditory* brainstem response (*AABR*).

We described categorical variables as percentages,

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normally distributed numerical variables as mean (SD), and those with skewed distributions as median (1st, 3rd quartile). We determined skewness by the Shapiro-Wilk test. We assessed the relationship between the aforementioned risk factors and the abnormal CUS findings using Chi-square/Fischer exact tests for categorical outcomes and Mann Whitney-U test/Student's t-test for continuous outcomes, respectively. *P* value < 0.05 was considered statistically significant. Variables with *P* value ≤ 0.1 on univariate analysis and meeting prerequisites (independence, linearity, normality, and homoscedasticity) for multivariate logistic regression were forced into the model (Enter method) for binary logistic regression. The Hosmer-Lemeshow test was used to assess the overall fit of the logistic regression model. The model's discriminative ability was evaluated using concordance statistics (Cstatistics). SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.) was used for analysis.

Seventy four infants were eligible; three died before performing CUS, and 71 infants were included in the analysis. Of these, 31 (44%) received one or more IUTs. Twenty seven (38%) infants had IVH (*n* = 23), PVL (*n* = 17), or both (*n* = 13). Most of the IVH were mild (Grade I = 12, Grade II = 10) except one infant who developed extensive periventricular hemorrhagic infarction (PVHI). Similarly, most had grade I (*n* = 12) or grade II (*n* = 5) PVL. There was no significant difference in the incidence of IVH/PVL among 15 (56%) infants who received IUT compared to the 12 (44%) who did not (*P* = 0.1). Two infants had proven sepsis. Two infants (one with PVHI and another with severe sepsis) died before discharge. None of the enrolled infants had cerebellar hemorrhage or significant structural anomalies. All had normal hearing on automated auditory brainstem response (AABR).

The profile of risk factors of IVH/PVL is given in **Table 1**. On univariate analysis, lower gestation, lower birthweight, ≥ 3 IUTs, lower gestational age at first IUT, perinatal asphyxia, neonatal sepsis (early-onset), and hypoglycemia were significantly associated with IVH/PVL. On multivariate analysis, lower gestation, small for gestational age (SGA) status, and neonatal sepsis were independently associated with the outcome. The multivariate regression model was a good fit (*P* = 0.2). The area under the curve (AUC, 95% CI) assessed by Cstatistics for the model was 0.85 (0.70, 0.99, *P* = 0.001), suggesting that the model has excellent discriminatory ability (**Fig. 1**). Among those who received IUTs, receipt of multiple IUTs (≥ 3) was independently associated with IVH/PVL.

In this study, more than one-third of infants had IVH or PVL or both, though most were mild. Prematurity, SGA, and neonatal sepsis were independent predictors for IVH/PVL. Among those who received IUT, receipt of ≥ 3 IUTs was associated with an increased risk for cranial abnormalities. We did not observe a significant association between the severity of anemia and IUTs with IVH/PVL.

Published data on brain injury in Rh-isoimmunized infants is limited. We could identify only two cohort studies on reviewing the literature [1,5]. Leijser et al studied 127 neonates who received IUT [5] and observed CUS abnormalities in 57%, most of which were mild. The higher prevalence in this study than ours might have been due to earlier scanning (median 2 days) and possible inclusion of transient PVE. Sanchez-Duvan enrolled 41 neonates who received IUTs and screened them with CUS and/or magnetic resonance imaging (MRI) [1]. Cranial abnormalities were observed in 14 (35%), most of which were also mild. Leijser et al assessed neurodevelopmental outcomes in the neonatal period and at two years of age, whereas Sanchez-Duvan followed up the infants for neurodevelopmental assessment until a median age of 6.5 years (range, 3 months to 19 years) [1,5]. In both studies, the cranial abnormalities were not associated with adverse neurodevelopmental outcomes [1,5].

In this study, the infants were mostly late preterm and hence not considered to be at risk for IVH or PVL (in the absence of other obstetric risk factors) [8]. Previous studies have reported that hypoxia/ischemia secondary to fetal anemia predisposes to PVL in fetal life. It is hypothesized that hyperdynamic circulation due to fetal anemia might injure the blood vessels in the immature brain with an increased predisposition to bleeding. IUT leads to rapid hemodynamic changes by acute volume overload coupled with a rise in hematocrit (and viscosity) in a relatively short period, further predisposing for bleeding [2,3,5]. Anemia and hypoxia are thought to be one of the risk factors for adverse neurodevelopmental outcomes among Rh isoimmunized infants [9]. The LOTUS study is the largest cohort study that enrolled 451 anemic fetuses who received IUTs and followed them until 17 years of age for neurodevelopmental outcomes [9]. These children (n=291) were assessed between 2-17 years of age (median 8.2 years) for physical, neurological, and cognitive development using age-appropriate standardized tests. In this study, all infants were anemic, but >95% had normal neurodevelopmental outcomes, similar to the general population. Anemia and IUT were not associated with poor neurodevelopmental outcomes. Like this study, Leijser et al found no relationship between IVH/PVL, anemia, and IUT [5]. Though theoretically, it is possible that fetal anemia/IUT may make the fetus/neonate vulnerable to brain injury, while their presence or severity

Table I Characteristics and Predictors for Neurosonogram Abnormalities in Infants Born to Rh Immunized Women

Parameters	*Total Cohort (n = 71)*	*Comparison between Infants with and without IVH/PVL (Univariate analysis)*				*Multivariate analysis*	
		Neurosonogram abnormalities (n = 27)	*No Abnormalities (n = 44)*	*P value*[d]	*Odds Ratio (95% CI)*	*Adjusted Odds Ratio (95% CI)*	*P value*
Gestational age (weeks)[a]	36 (35, 37)	36 (33, 36)	36 (35, 37)	0.012	-	0.7 (0.50, 0.97)	0.035
Birth weight (grams)[b]	2545 (540)	2356 (655)	2662 (413)	0.04	-		
Small for gestational age[c]	11 (15.5)	7 (25.2)	4 (9.1%)	0.09		10.6 (1.9, 58.7)	0.007
Female[c]	30 (42.3)	12 (44.4)	18 (40.9%)	0.8	0.9 (0.3, 2.3)		
Intrauterine Characteristics							
Received IUT[c]	31 (43.7)	15 (55.6)	16 (36.4)	0.1	2.2 (0.8, 5.8)	3.3 (0.91, 11.9)	0.069
Received ≥ 3 IUTs[c]	13 (18.3)	9 (33.3)	4 (9.1)	0.01	5 (1.4, 18.4)		
Number of IUT/ infant[a]	310 (0, 2)	151 (0, 3)	160 (0, 1)	0.076	-		
Gestational age at first IUT (weeks)[b]	27.7 (4.3)	26 (4)	29.3 (4.1)	0.034	-		
Severe fetal anemia (Hct < 21%)[c]	22 (31)	12 (44.4)	10 (22.7)	0.055	2.7 (0.97, 7.7)		
Fetal hydrops[c]	7 (9.9)	4 (14.8)	3 (6.8)	0.4	2.4 (0.5, 11.6)		
Neonatal Characteristics							
Perinatal asphyxia[c]	10 (14.1)	7 (25.69)	3 (6.8)	0.036	4.8 (1.1, 20.5)	1.6 (0.3, 10.3)	0.6
Received DVET[c]	17 (23.9)	7 (25.9)	10 (22.7)	0.8	1.2 (0.4, 3.6)		
Neonatal sepsis (Probable or Definite)[c]	28 (39.4)[e]	17 (63)	11 (25)	0.001	5.1 (1.8, 14.4)	4.5 (1.1, 18.4)	0.035
Hypoglycemia[c]	6 (8.5)	5 (18.5)	1 (2.3)	0.027	9.8 (1.1, 88.9)	2.4 (0.2, 30.2)	0.5
Required NICU admission[c]	19 (26.8)	14 (51.9)	5 (11.4)	< 0.001	-		
Duration of hospital stay (d)[a]	9 (7, 12)	11.5 (8, 19.8)	8 (6, 10)	< 0.001	-		
Death before discharge[c]	2 (2.8)	2	0	0.1	-		

Values expressed as [a]median (IQR), [b]mean (SD) or [c]n (%)
CI Confidence interval, DVET Double Volume Exchange Transfusion, IUT Intrauterine Transfusion, IVH Intraventricular hemorrhage, OR Odds Ratio, PVL Periventricular leukomalacia, SD Standard Deviation
[d] Chi-square/Fischer exact test for categorical variables; Student-t test or Mann Whitney U test for continuous variables
[e]Proven sepsis, n = 2

may not have a direct effect on the occurrence or severity of IVH/PVL [5,9,10]. However, the data is insufficient to establish or refute this hypothesis. There is a need for additional exploratory studies for better insight.

There are certain limitations in this study. We did not perform any fetal ultrasound; therefore, whether these findings were present even before the IUT is uncertain. As the first ultrasound was done within the first 72 hours, most findings (at least PVL) were presumed to be of fetal origin, consistent with previous studies. As the event rate for IVH/PVL was less than ideally required for the predictor variables chosen in this study, the results on predictors should be interpreted cautiously. We did not have long-term follow-up data; hence, the relationship between CUS abnormalities and neurodevelopmental outcomes could not be ascertained.

We conclude that more than one-third of infants born to Rh isoimmunized mothers had IVH and/or PVL in the first 3 days of life. Further larger studies beginning from the fetal period (to determine the timing of occurrence) are required to estimate the true incidence and predictors for cranial abnormalities. Long-term follow-up to determine the association of the milder abnormalities with neurodevelopmental outcomes would be invaluable.

Ethics clearance: PGIMER Institute ethics committee approved the study (INT/IEC/2020/SPL-521) dated Apr 22, 2020.

Contributors: SB: Study design, data collection, analysis, and manuscript review; JK: Conceived the idea, wrote the protocol, supervised data collection, analyzed the data, and wrote the first draft of the manuscript; SCS, SD, PK: Conceived idea, supervised data collection, data analysis, and critically reviewed the manuscript.

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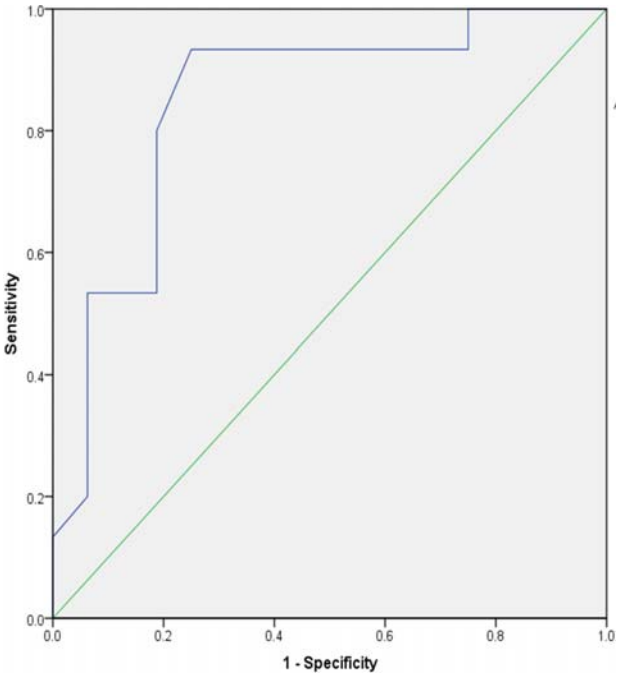

Area under curve = 0.85 (95% CI: 0.70 to 0.99): P 0.001

Fig. 1 Receiver Operator Characteristic (ROC) Curve showing the predictive ability of the multivariate logistic regression model (expressed as Cstatistics)

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RESEARCH LETTER

Impact of Seasonal Variation in Temperature on Dehydration in Neonates

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ABSTRACT

The study was conducted to compare the incidence and severity of dehydration in newborns admitted during warmer and cooler months. 55 out of 941 (5.8%) neonates were admitted with dehydration during the study duration. Dehydration warranting medical support was common in both cooler and warmer months of the year. 26 (47.2%) neonates were admitted in the cooler months and 29 (52.7%) in the warmer months. The severity of dehydration was marginally higher in warmer months (P = 0.09).

Keywords: *Dehydration, Newborns, Warm, Hypernatremia*.

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Weight loss of up to 10% in the immediate postnatal period, with its nadir around 3 to 4 days of life, is an established phenomenon. Factors like inadequate milk in the initial days, wrong feeding technique and increased ambient temperature can aggravate the above phenomenon [1].

In vitro studies have suggested that high temperatures (39°C) induce high lactation whereas long-term exposure to 41°C leads to a decline in milk production [2]. These findings lead to the possibility of ambient temperature playing a significant role in the development of postnatal dehydration needing medical management. Hence, this study was planned to compare the incidence and severity of postnatal dehydration during warmer and cooler months.

We conducted a prospective study wherein we assessed the impact of ambient temperature caused by seasonal variation on the incidence of severe dehydration in term neonates between July 2021 to June 2022. We included neonates delivered at term gestation and admitted with severe dehydration to the neonatal intensive care unit of JSS Hospital, Mysuru, a tertiary care unit in South India. Severe dehydration was defined as cumulative weight loss > 10% of birth weight, weight loss (<10%) associated with hypernatremia and/or increase in blood urea [2]. We excluded septic newborns and neonates with congenital malformations including renal and endocrinal abnormalities from the study. The study was approved by the institutional ethics committee. Informed consent was obtained from the parents or immediate caregivers. Based on the convenient sampling method, all babies admitted during this period and fulfilling the inclusion and exclusion criteria were recruited in the study.

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The average ambient temperature at the study location during the study period was 24.6°C. Furthermore, the Government of India has declared an indoor ambient temperature of 24°C to be comfortable for humans. Accordingly, February to June were considered as warm months (26.1°C) and July to January were considered cool months (23.9°C) for this study.

A total of 55 neonates out of the total NICU admissions (n = 941) 5.8% were admitted with significant weight loss during this study period. Among these, 26 (47.2%) were admitted in the cooler months and 29 (52.7%) in the warmer months. 32 (58.2%) were females and 42 (76.3%) babies were delivered by cesarean section. Nearly 80% of the babies were born to first-time mothers. 35 (63.6%) babies were exclusively breastfed and 20 (36.3%) had been receiving some top feeds. The top feeds could not be quantified as these babies had been referred from another hospital. The baseline characteristics of the neonates are depicted in **Table I**.

Out of the 55 neonates, 47 (85.4%) had hypernatremia; 5 (9%) of them had very high sodium levels (>170 mmol/L), 25 (45.4%) had fever, 9 (16.3%) had hypoglycemia and 8 (14.5%) had decreased activity.

The median (IQR) weight at admission was 2540 (2350 - 2720) g in the cooler months and 2720 (2080 - 2940) g in the warmer months. The median (IQR) weight loss (g) in cooler months was lesser compared to that in

Table I Characteristics of Babies Admitted During Cool and Warm Months

	Cool (n=26)	*Warm (n=29)*	*P value*
Qualitative variables[a]			
Parity			
Primi	23 (88.5)	21 (72.5)	0.06
Multi	3 (11.5)	8 (27.5)	
Mode of delivery			
Cesarean section	19 (73)	23 (79.3)	0.35
Vaginal	7 (27)	6 (20.7)	
Gender			
Male	9 (34.6)	14 (48.2)	0.15
Female	17 (65.4)	15 (51.8)	
Source of admission			
Outborn	10 (38.4)	14 (48.2)	0.27
Inborn	16 (61.6)	15 (51.7)	
Quantitative variables[b]			
Maternal age (y)	28 (26, 29)	26 (24, 29)	0.24
Weight on admission (g)	2540 (2350, 2720)	2720 (2080, 2940)	0.47
Age on admission (d)	4.5 (3, 7.8)	4 (2, 6)	0.34
Duration of stay (d)	3 (3, 4)	3 (2, 5)	0.34
Discharge weight (g)	2750 (2485, 2900)	2900 (2200, 3160)	0.52
Total weight loss (g)	400 (300, 455)	480 (300, 620)	0.09
Weight loss (%)	12.9 (11.7, 14.1)	15 (10.7, 17.7)	0.15
Weight loss per day (%)	2.7 (1.7, 4.1)	3.6 (2, 5.7)	0.09

Values expressed as [a]*n (%) or* [b]*median (IQR)*

warmer months [400 (300, 455) vs 480 (300, 620); *P* = 0.09]. The difference in the average weight loss between the cooler and warmer months was marginal (**Table I**).

The incidence of dehydration needing medical support in the immediate postnatal period was 5.8%. The incidence did not differ significantly between the cooler and the warmer months. Few studies have shown that newborn babies maintain their hydration status and no supplemental feeds are required even in hot environments (3)]. Overall the incidence of postnatal weight loss and dehydration has been shown to vary widely from as low as 0.2% [4] to 19.7% [5]. This wide variation across the world is likely due to the cultural differences and postnatal management plans of supplemental feeds adopted by various units till breastfeeding is satisfactorily achieved [6]. Dehydration needing medical intervention and leading to morbidity is reported in hotter months in adults and older children [6,7]. Applying the same understanding to neonates who are further disadvantaged by precarious fluid intake during their initial few days of life makes one believe that the problem of weight loss and dehydration is higher in warmer months compared to cooler months. This is further accentuated by the fact that with an increase in temperature, the duration of breastfeeding decreases whereas insensible water loss increases [8,9]. Contrary to this, we did not find any statistically significant difference in the incidence of dehydration between cooler and warmer months.

In our study, the average maximum temperature in warmer months was 31.6°C and that in cooler months was 27.7°C with the difference being 3.9°C. The average minimum temperature in warmer months was 20.4°C and that in cooler months was 19.6°C with the difference being 0.8°C (**Fig.1**). A significantly higher percentage of weight loss in warm months was also noticed by Kusuma et al [9] in late preterm babies and by Rekha et al [2] in term babies. Zia et al reported no difference in the incidence of significant dehydration with seasonal variation in temperature in their study. However, their study environment was thermally regulated as per the legal norm [10].

Our findings suggest that babies who are nursed in cotton cloth cocoons, regardless of the ambient temperature, keep the babies warm. Such cocoons are common practice in our set-up. These thermal nests create their inner milieu negating the effect of ambient temperature

In our study, out of 50 babies born to primigravida, 47 (85.4%) babies had high sodium levels (serum sodium > 145 mEq/L). The high incidence of breastfeeding-associated hypernatremia among infants born to first-time mothers may be attributed to the fact that primiparous women produce significantly less milk than multiparous

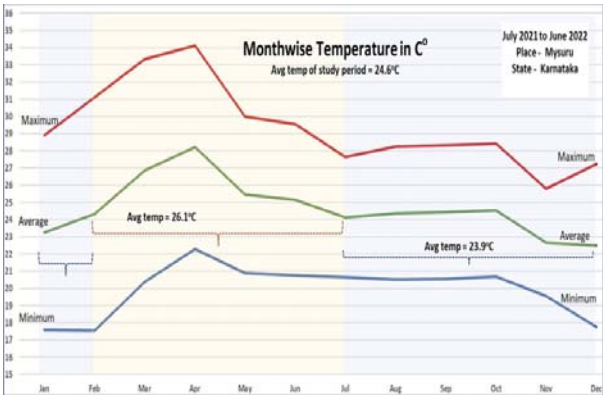

Fig. 1 Month-wise temperature in °C

women during the first postpartum week, with a subset of primiparous women having very low production of breastmilk in initial postnatal days [2].

Though we noted a higher degree of weight loss in warmer months compared to cooler months, the frequency of significant weight loss was not significantly different between these two months. Thus, suggesting that significant dehydration is equally common in both cooler and warmer months, the degree of dehydration being marginally higher in warmer months. Though this does not achieve statistical significance, it is important for clinical management. Our findings must be interpreted keeping in mind the location of the study centre as India is a vast country and temperature extremes are related to the latitude. Northern India which has much higher maximum temperatures reaching up to 45ºC in summer and often 2-4ºC in winter, may witness a difference in incidence of dehydration due to seasonal variation, although the same is not seen in South India. The study was limited by its small sample size and inability to measure breastmilk sodium levels.

In conclusion**,** dehydration needing medical support is common in both cooler and warmer months of the year. The severity of dehydration is marginally higher in warmer months.

Ethics clearance: Institutional Ethics Committee, JSSMC; No. JSSMC/IEC/050722/13NCT/2022-2023), dated July 08, 2022**.**

Contributors: SK: Study design, analyzing the data, preparing the manuscript; DT: Data collection, literature search, drafting the manuscript; SMD: Conceptualization, protocol development, analysis of data, manuscript preparation. All authors approved the final manuscript.

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Skill or Competency: What Should we be Assessing?

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ABSTRACT

India introduced competency-based medical education (CBME) in the year 2019. There is often confusion between terms like ability, skill, and competency. The provided curriculum encourages teaching and assessing skills rather than competencies. Though competency includes skill, it is more than a mere skill, and ignoring the other aspects like communication, ethics, and professionalism can compromise the teaching of competencies as well as their intended benefits to the patient and the society. The focus on skills also undermines the assessment of relevant knowledge. This paper clarifies the differences between ability, skill, and competency, and re-emphasizes the role of relevant knowledge and its assessment throughout clinical training. It is also emphasized that competency assessment is not a one-shot process; rather, it must be a longitudinal process where the assessment should bring out the achievement level of the student. Many of the components of competencies are not assessable by purely objective methods and there is a need to use expert subjective judgments, especially for the formative and classroom assessments. A mentor adds to the success of a competency-based curriculum.

Keywords: *Clinical competence, Competency-Based Medical Education, Knowledge, Skill assessment*

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INTRODUCTION

India introduced competency-based medical education (CBME) in the year 2019. While the need to keep pace with global trends would have been a reason for the change, a perceived lack of skills amongst Indian medical graduates seems to be the other major reason. Little wonder that a major emphasis in the new CBME curriculum has been on skills. The faculty were trained in the art and science of teaching and assessing clinical skills, skill labs were mandated and a list of skills to be learned or demonstrated was provided.

The concept of medical competence has been rather fuzzy [1] and perspective plays a major role in its conceptualization. The emphasis on teaching and assessing skills is expected as skills form an important component of competency, which is amply illustrated by the iconic definition of competence provided by Epstein and Hundert [2]. They defined clinical competence as *"the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served"*. This definition includes dimensions of competence in various other domains required for patient care, which also need as much attention. Competence is a multi-layered construct and many ways to describe these layers are possible. Ten Cate et al have suggested viewing competence in three layers *viz.* a core layer of canonical competence, a layer of contextual competence, and a layer of personalized competence [1]. While the canonical layer can be standardized in terms of outcomes and assessment methods, the other two need personalization. In the conceptualization and implementation phase of CBME, a semantic problem with the terms like ability, skill, competency, and competence, seems to have compounded the issue. These terms are often used interchangeably. It is not surprising because the dictionary meaning of all boils down to 'doing something'. However, educationally, and especially in the context of CBME, there are differences in the meaning and intent which can have an important bearing on the way we deliver and assess the curriculum. The competencies are deconstructed into learning objectives for teaching and assessment; sometimes they are labelled as 'knowledge competency' or 'skill competency' (although this goes against the very meaning and concept of competency), and this further complicates the problem.

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Ability, Skill, and Competency

Let's first look at competence and competency. Competence is an overall umbrella term, which includes several competencies required for the individual to be called competent. The National Institute of Health [3] defines competency as 'an observable combination of knowledge, skills, ability, and behavior that contribute to individual and organizational performance'. Inherent in this is the fact that competency implies using its various components in the actual workplace. Read together with the definition of clinical competence, it means that the task is being *performed in the workplace* for the benefit of the patient. Skill on the other hand denotes a specific learned proficiency that enables one to accomplish a specific task [4]. Ability refers to an innate potential to perform (e.g., possessing requisite knowledge, technique, dexterity, coordination, etc.); in a sense, the ability doesn't mean actual performance but only *the potential* to perform by possession of attributes needed for performing a task. The important factors that distinguish a skill from a competency therefore stand out as context and benefit to the individual being served. This can be better understood with the examples given in **Table I**.

Some other interesting facts are also visible in perusing the meaning of skill and competency. One can note that skill is a component of competency but is not the only component. Integrating other components like communication, knowledge, clinical reasoning, emotions, values, and reflections is required for a skill to become a competency – with the rider that these are used *habitually* and *judiciously*. The integration in CBME, therefore, is not limited to subject matter but must extend to knowledge, skills, attitudes, clinical reasoning, emotions, values, and reflections relevant to a particular competency. Another important aspect is the fact that the purpose of CBME does not end with the student acquiring competencies but with her being able to use these competencies in practice – habitually and judiciously – to improve the health status of society [5].

Implications for Assessment

What influence will this distinction between skill and competency have on how we assess students under CBME? There are two important implications- first, assessment must rise above non-contextual knowledge and skill assessment, and second, since the competency behaviors must be demonstrated habitually and consistently, a single assessment, however perfect, will never be enough to certify the competency (and student as competent). The

Table I Ability, Skill, and Competency

Term	*What it means*	*Example*
Ability	Having the required attributes for performing the task.	A second-year medical student, who knows about the anatomy and physiology of the upper gastrointestinal tract, indications, and contraindications for passing a nasogastric tube and the procedure required thereof, has good hand-eye coordination and dexterity, can be considered to have the *ability* to insert a nasogastric tube.
Skill	A learned proficiency- through education, practice, or experience- and an actual performance on a specific task.	When this student learns more about the procedure, observes the demonstration given by the tutors, practices it in the skills lab, and then correctly performs the actual procedure on a manikin, she has acquired the *skill* of passing a nasogastric tube.
Competency	The task as described above, when performed in a clinical setting for the benefit of the patient, integrating the knowledge, skills, communications, and professionalism, which contributes to individual and organizational effectiveness.	When the same student during her final year or internship, passes a nasogastric tube in the emergency department on a 2-year-old child brought with suspected ingestion of some tablets and aspirates the gastric contents after taking appropriate history, performing a relevant physical examination, comforting the child, communicating with the parents, obtaining proper consent, documenting the procedure in the case file, seeking expert help to decide on further course of action, and advising the parents of preventive action, has demonstrated the *competency*.
Competence	A collection of various related competencies, which are used habitually and judiciously for the benefit of the patient and community being served.	Accumulation of many other related competencies would entitle her to be called competent to provide initial care for emergencies in children in a hospital setting.

**Please note in the above example that just like the student learned, prepared for, and practiced the skill of nasogastric tube insertion, she also needs to prepare for and practice (and be assessed for) the other components of the competency mentioned above.*

need for CBME arose because the graduates were not able to integrate knowledge, skills, attitudes, communication, etc., taught and assessed separately into a meaningful whole and therefore could not provide quality care. It is alright to deconstruct competencies into narrow and narrower learning objectives for teaching purposes, but the learners may not be automatically able to construct these back into a competency [6]. The tendency to assess only at the level of learning objectives strikes at the very reason for the advent of CBME.

Attributes of Good Assessment

Any discussion on assessment must include the important attributes of assessment viz. validity, reliability, feasibility, acceptability, and educational impact [7]. Of these five attributes, the first two are 'intrinsic' to the results of assessment and the last three depend on the 'context' or educational environment and together provide a very useful notional concept of the *utility of assessment*. This concept tells us that a meaningful trade-off can be made between various attributes depending on the purpose of assessment (e.g., high reliability for selection tests versus high educational impact for formative or classroom tests) and that if any one attribute has a value of zero (e.g., an assessment prompting students to adopt only surface learning), then the utility of entire assessment becomes zero. Let us look at them in some more detail.

Validity

The conceptualization of validity has undergone many changes since the turn of the 20th century. Validity is now considered a unitary concept, synonymous with construct validity [8,9]. It refers to the interpretation that is made from the assessment data and not to the tools that are used. It implies that the assessment must include the 'contents' of the task, which in the context of a given competency, would include knowledge, communication, attitudes, values, etc., in addition to the psychomotor skills.

Points to be kept in mind to enhance the validity of competency assessment include:

1) The role of knowledge in competency assessment

Knowledge is the basic requirement for proceeding further in any educational system; it is especially so in CBME, as it is an important component of competency. Knowledge is the first step in making a clinical diagnosis, which becomes the starting point of any therapeutic intervention. Without a correct diagnosis, no amount of skill proficiency is going to help. Unfortunately, clinical reasoning skills have been put on a backseat due to our newfound emphasis on skills. There are reports to suggest that students lack the relevant knowledge of commonly taught skills and that proficiency in skills alone doesn't translate into good professional practice [10]. Two other aspects that become important in this context are that experts are experts because they *know more* and not because they can perform more or have specialized skills, [11] and that there is the phenomenon of content specificity which prevents us from generalizing the proficiency in one skill to others [12]. A recent publication has highlighted the role of contextual knowledge and its implications for competency assessment [13]. A lot of voices are also being raised that despite being at the top of Miller's pyramid, performance assessment is not inherently superior in predicting clinical competence [14], and that over-emphasis on skills forces the students to be selective in studying and ignoring the knowledge component [15]. This adverse educational impact threatens validity; it also brings into question the rationale of compensating marks in knowledge with those of clinical/practical or vice versa.

2) The importance of context

Competency assessment must be contextual, especially at the formative and ongoing assessment stage (contrasted to large-scale selection or licensing examinations which strip off the context to ensure comparability between different students). Given the phenomenon of content specificity, [12] it is a bad educational practice, for example, to assess communication at a separate OSCE station. It is the addition of context, that allows us to help the development of level two of competence [1] without which such assessments become only artifacts.

3) Meaningful aggregation of the various attributes

A meaningful aggregation of knowledge, skills, attitudes, communication, and other attributes relevant to the given competency is a key feature of competency assessment. It makes little sense, for example, to club the scores on knowledge of competency "A" with skills of competency "B" and communication of competency "C" and then average out the result. As Schuwirth and Ash [6] put it, *"No doctor would tell his/her patients that their sodium level is too low but fortunately their glucose level is too high and so, on average, they are healthy."* Incorporating a meaningful aggregation in the Indian settings as a blended version of programmatic assessment has earlier been described [16].

Reliability

Reliability is commonly seen as referring to the reproducibility of scores [17]. The important points to be remembered include- first, the fact that reliability is mostly useful for norm-referenced testing (*not* criterion-referenced as required for CBME), and second, that the clarity of the task decides the degree of reproducibility.

Reliability does not co-vary with objectivity, however [18]. The traditional teaching has been that there is no validity without reliability, but it has been repeatedly shown that in practice, there is often a trade-off between validity and reliability [19]. Sample size (tasks, contexts, assessors, and tools) positively influences both, validity, and reliability. The important points to keep in mind to enhance the reliability of competency assessment are as follows:

1) Multiple assessments

If reliability is to be viewed as the degree of confidence that can be placed in the results of our assessment, then there is a need to have multiple assessments. This requires using more assessors for more tasks, in more settings using an assessment toolbox [20], applying the concept of the 'quarter model' to provide a more holistic unbiased picture [21].

2) The role of expert subjective judgments

There should be no shying away from expert subjective judgments for the assessment of domain-independent aspects of professional competence [22]. A common problem with most assessments is the appeal of objectivity to improve 'reliability'. Reliability looks at consistency of marking rather than consistency of performance. There are many flaws in looking at reliability as only reproducibility of results. One is that reliability doesn't co-vary with objectivity, and expert subjective judgments can give as, or even more, reliable results for many tasks [23]. Secondly, by keeping objectivity as one of the criteria, many important 'authentic' measures of doctoring (like communication, professionalism, ethics, empathy, reflections, etc.) get excluded from the assessment process [24]. Thirdly, while objectivity presumes one and only one correct answer, clinical scenarios can have more than one correct answer which may not be objectively assessable. The wheel of assessment has taken a full circle and the importance of contextual expert subjective judgment for CBME is again being recognised [25]. Fortunately, the new curriculum provides for 'only formative' assessments and doesn't require internal assessment marks to be added to final scores, providing a lot of freedom to focus on the educational impact of assessment rather than only on objectivity.

PUTTING THE PRINCIPLES INTO PRACTICE

The inherent difficulty - competencies are acquired incrementally, but assessment must be holistic

Conventionally, the competency statements are end-of-course competencies. However, the process of attaining these competencies is incremental. Say for example the competency of history-taking. The student first learns the basics of communication and the technique of data gathering; then she learns about taking specific history related to various diseases, and then moves on to learning how to elicit sensitive information in a given context, within a specific timeframe, and so on. The teaching is step-by-step, but the assessment has to be integrated, in the sense, that we need to know whether finally, the student will be able to use this competency in a variety of clinical contexts, *habitually and judiciously*, for the benefit of the patients. How to embed a meaningful assessment for this purpose looks like a problem.

How to Circumvent this Problem?

One of the ways to circumvent this problem is to use milestones or Entrustable Professional Activities (EPAs) [26]. However, since our curriculum has not used these concepts, a lot depends on the wisdom of the teachers to match the level of competency acquisition with the level of training. Just as timetables are planned for teaching purposes, assessment tables must be planned, such that the entire spectrum of competency is assessed by the time the course is completed. This can be done only during formative and internal assessment. University examination (or exit examination, when implemented) is not the right place for competency assessment due to the unique nature of competencies. They should be used for quality assurance but not for competency certification.

Choice of Appropriate Tools and the Role of the Assessor

In the initial years of learning (pre-final years), the assessment may be more of knowledge, as it is the foundation on which the competency would be built, along with the assessment of a few basic communication and psychomotor skills, attitude, and professionalism. Theory tests, case presentations, objective structured clinical examination (OSCE), objective structured long examination record (OSLER), assessment in the skills lab, and viva-voce may be used for this purpose. Formative assessment can also be made meaningful by interactions and feedback in classrooms and clinics.

As the students begin engaging more in the clinical context (final year and internship) various workplace-based assessment tools such as direct observation, mini clinical evaluation exercise (m-CEX), and direct observation of procedural skills (DOPS) may be used. As they gradually master cognitive and clinical skills (during PG training), tools such as mini peer assessment tool (m-PAT), multi-source feedback (MSF), and patient satisfaction surveys (PSF) may be added. At this stage, the

assessment predominantly focuses on their clinical performance; however, the assessment of contextual knowledge must continue with the help of case presentations, viva, or theory tests, so that we do not undermine the importance of contextual knowledge as the foundation of clinical performance. Throughout their learning phase, self-assessment, and assessment by logbook and reflections must continue.

Having said that, the assessor is always more important than the tool that is used for competency assessment [27]. The teachers need to use their wisdom not only in the choice of tool - but also in designing the questions and tasks related to each tool so that it is within the context of the competency and not a stand-alone test of knowledge or skill.

CONCLUSION

Before concluding, we would like to recall some aspects of the story of Mahabharata [28] which perfectly illustrates these concepts. The first character which attracts attention is Eklavya [29]. He had mastered the skill of archery to the extent that he could fill the mouth of a barking dog with arrows to silence it but without harming it. But he could not use the divine weapons (like *Brahmastra*, a highly destructive weapon as per legend) nor could he command an army. This was because he learned *shastra* (the skill of using weapons) but not *shaastra* (the science behind weapons and war). Duryodhan [28] was another person, who had learned both *shastra* and *shaastra* but lacked ethics and professionalism. In an era where the opponent had to be invited for a battle and only if he consented could battle take place, Duryodhana wanted to acquire kingdom by defeating Pandavas in the game of dice (*chausar*, a game prevalent in those times). And then there was Arjun, who had learned *shastra* and *shaastra* and was ethical and professional in his approach. He had mastered the skills and learned the use of divine weapons from the best of the teachers and was competent in the true sense. However, just before the war, he declined to use his skills because the *context* changed. His dys-competence, diagnosed and addressed by Krishna, was not due to his lack of knowledge and skills. It was an *expert subjective assessment*, in the true sense, by Krishna as a mentor, who diagnosed his learning needs and made an effective intervention. Indeed, it needed the genius of a Krishna to not send him for another class, skill lab session, course, or fellowship; rather, he helped Arjun to navigate through ethical and professional conflicts and make a decision to act. The entire focus of the discourse between Arjun and Krishna in the form of *Gita* was on positive outcomes, much like the focus of competencies is on being used for the benefit of the patient.

Nothing but these characters from the great epic could have brought out the importance of knowledge, skills, ethics, professionalism, reflections, and training in multiple contexts; their story equally strongly emphasizes the role of an expert teacher and an expert mentor for the success of competency-based education.

Excellent resources are available describing the importance, uniqueness, and other details of competency-based assessment [6,27, 30-32]. However, with the above example, we want to reiterate that there is a difference between skills and competencies; and in a CBME curriculum, we should be assessing competencies and not knowledge or skills related learning objectives alone. The purpose of CBME, after all, is not merely to equip the graduate with knowledge and skills but to ensure that the graduate develops the competency to use these for the benefit of the patient and the community.

We could not have found a better way to end this paper than to recall the description of CBME provided by Frank et al [33] on behalf of International CBME collaborators, "CBME is an outcome-based approach to the design, implementation, student assessment and evaluation of medical education programmes using an organizing framework of competencies."

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SPECIAL ARTICLE

Compensation in Neonatal Clinical Trials: A Perspective

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ABSTRACT

Well conducted clinical trials are the mainstay for generating evidence on preferred treatments. In order to adequately protect the interests of the trial participants, the Central Licensing Authority of India has formulated guidelines to determine the quantum of compensation in cases of regulatory clinical trial related injury or death. However, these guidelines do not address the nuances of trials recruiting children aged under 16 years, within which, neonates are the most vulnerable population. Thus, there is a need for addressing this lacuna in the current guidelines. This article examines the challenges in determining the quantum of compensation in neonatal clinical trials using the current formula, which is a corollary to the challenges faced by the authors in procuring clinical trial insurance for the Probiotic supplementation for Prevention of Neonatal Sepsis (ProSPoNS) trial. Further, it suggests a template for a differential formula using birthweight of infants, which is one of the many important factors impacting neonatal mortality.

Keywords: *Compensation, CDSCO, DCGI, Regulatory trials*

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INTRODUCTION

A discernible knowledge gap remains in evidence-based pediatric treatments particularly in neonates, resulting from inadequacies in drug evaluation for children [1]. The practice of extrapolating drug safety and efficacy data from adults for use in neonates is widespread. Such off-label use of drugs in neonates makes their safety and efficacy questionable and puts the neonatal population at a risk of unexpected adverse effects and under / over dosing [2]. Children, in particular neonates, are a unique population with distinct developmental and physiological differences from adults. Clinical trials in neonates are essential to develop age-specific, empirically-verified interventions and therapies to estimate and improvise optimum therapeutic solutions, but these also come with their own set of challenges [3,4]. With respect to drug/ clinical trial participation, neonates show increased vulnerability owing to poor drug metabolism due to hepatic and renal immaturity, larger surface area requiring higher doses, immunological immaturity, limited body responses, clinical symptomatology, dependence on parents etc [5]. The risk is further heightened when a neonate is born underweight / overweight [6].

Special care and protection are required for children participating in clinical trials [7]. In India, the National Ethical Guidelines for Biomedical Research Involving Children by the Indian Council of Medical Research (ICMR), enlist the requirements for conducting clinical trials in the pediatric population [8]. Clinical trials which involve an Investigational New Drug (IND) or a New Chemical Entity (NCE) are governed by the New Drug and Clinical Trials Rules (NDCT 2019). Also, the rules describe in detail every aspect of conducting clinical trials including compensation for trial participants. Justifiable compensation for trial-related injury or death is a priority under the NDCT, 2019, and is considered one of the most important areas of clinical trials in India [9,10].

This article discusses how compensation guidelines related to pediatric clinical trials vary globally and discusses in detail the guidelines in India. An example of a formula based on birth weight, is proposed for calculating

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compensation in neonatal clinical trials, for consideration and further deliberations by the experts and regulatory authorities.

Clinical Trial Compensation for Neonates: Global *vs* Indian scenario

Clinical trial compensation guidelines vary globally. The World Medical Association, Declaration of Helsinki [11] and the International Conference on Harmonization-GCP (ICH-GCP, addendum 2017) [12] require that compensation or treatment be offered for any trial-related injuries. Some others like the Association of the British Pharmaceutical Industry (ABPI, 2014) and the Council for International Organizations of Medical Sciences (CIOMS), provide detailed compensation approaches for various clinical research phases, whereas the US Food and Drug Administration's (FDA) informed consent regulation requires that the participants be informed about the availability of compensation and medical treatment in case of injury [13-16].

In most countries compensation for clinical trial participants is based on the 'Tort's Law'. This implies that the court of law, on hearing from investigator, sponsor, and patient decides on the compensation [17,18]. Globally, compensation in clinical trials also includes the money or reimbursements provided to the participants of the trial [19,20].

India is the only country which protects the interests of its trial participants by awarding compensation in cases of trial-related injury or death by means of rules laid down by the Central Licensing Authority (CLA), the Central Drug Standard Control Organisation (CDSCO). The Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Participants, the Indian Good Clinical Practice (GCP) Guidelines, and NDCT 2019 recommend compensation to be given to clinical trial participants who suffer from trial-related injury [8,9].

Any untoward or adverse medical occurrence in the clinical trial participant that results in hospitalization or its prolongation, permanent disability, or death of the participant is classified as a serious adverse event (SAE). Clinical trial participants who suffer from any SAE which is deemed 'related' to the trial as opined by the expert committee, are entitled to financial compensation; in case of death, their dependents are entitled to financial compensation. Also, the trial sponsor is required to provide free medical care for all trial-related injuries to the participant as long as required (as per opinion of investigator) or till such time it is established that the injury is not related to the clinical trial, whichever is earlier. The amount of compensation in case of injury or death in a clinical trial or bioavailability or bioequivalence study of a new drug or investigational new drug is determined by the compensation formula given in NDCT 2019 under Chapter VI, Rule 39 to Rule 43 [9,21].

Genesis of the Clinical Trial Compensation Formula in India

The unique standpoint of India in clinical trial compensation has a long history stemming from the Drugs and Cosmetics Act, 1940 [22]. In 2005/2006, the Drugs Controller General of India (DCGI) established an expert group committee to review and draft the rules for determining compensation in clinical trial injuries in India and a '*No Fault Compensation*' model was adopted for the Indian population as opposed to the '*Tort's Law*' in other countries. The '*No Fault Compensation*' translates as, regardless of the fact that the trial participant has given informed consent (in case of neonates, the parents or the legally authorized representatives) after having fully understood the risks involved in the clinical trial, they will still be entitled to compensation in case of related SAE upheld by the DCGI as a clinical trial injury by virtue of participation in the trial. The committee, took into consideration several factors, including the participant's age, qualification, gender, insurance coverage, urban/rural, place of death/hospitalization, and level of education. Based on their deliberations, the committee unanimously agreed on the following two factors as the basis of the compensation formula:

1. Age: The compensation amount should be proportionate to the productive age group the patient is likely to live in. This means that a younger person with a longer life expectancy and higher earning potential should receive a larger compensation amount than an older person who is likely to live for a shorter period and earn less. This is in accordance with the Workmen Compensation Act which provides a table of compensation based on age [22].
2. Seriousness: The compensation amount should also be based on the severity of the illness or condition suffered by the participant. If a person is suffering from a terminal illness, they are less likely to survive, and therefore should receive lower compensation than someone with a minor ailment, such as a cold or fever. A healthy volunteer with no existing health risks warrants the highest compensation.

Quantum of Compensation for Trial-related Injury or Death

Separate compensation formulas address different types of clinical trial injuries namely permanent disability,

congenital anomaly or birth defect, chronic life-threatening disease, and Reversible SAE in case it is resolved. For example, in case of death of the trial participant, the compensation is calculated as follows:

Compensation = (B x F x R) / 99.37

Where, B = Base amount (i.e. INR 800,000/-); F = Factor depending on the age of the participant (based on Workmen Compensation Act); R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as follows:

0.50 terminally ill participant (expected survival not more than 6 months)

1.0 Participant with high risk (expected survival between 6 to 24 months)

2.0 Participant with moderate risk

3.0 Participant with mild risk

4.0 Healthy volunteers or participants with no identifiable risk

This can be interpreted as follows: If a participant has an expected survival of not more than 6 months, the risk factor (R) can be assigned as 0.5, which translates to half of the maximum compensation amount.

Another factor that was included in the formula was a fixed baseline amount (INR 8,00,000/-) based on the highest average wage/daily wage per month given to a person employed by any of the state governments at that time which was INR 7200 per month. It was assumed that if this money was put into a fixed deposit at 12% interest at that time, it would yield the baseline amount.

Factor F ranges from 99.37 (for age of 65 or more) to 228.54 (of age not more than 16) depending upon the age of the injured. Thus, it can be seen that according to the formula, the compensation amount varies from a minimum of INR 4,00,000/- to a maximum of INR 73,60,000/- depending on the age of the deceased and the risk factor. However, it was decided that in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of INR 2,00,000/- should be given.

Challenges in Assigning Risk Factor in Neonates

Although compensation for clinical trial injuries in adults has been addressed, the issue of compensation for neonates remains unclear. There are several issues that need to be considered in neonatal trials that are not adequately addressed in the compensation formula.

High Risk of Mortality

One such issue is the high risk of mortality among infants in India. It is unclear what risk factor should be assigned to a normal infant - should it be 4 (the value for a normal volunteer), or less than 4? Should socio-economic status be taken into account before deciding the risk factor, and if so, how should this be factored in calculations? These considerations may give rise to moral and ethical debates.

Severity of Congenital Disease

Another issue is that of correcting mild/moderate/severe conditions in neonates, where neglect or delay can lead to fatal outcomes. The inherent risk in such cases needs to be carefully considered, especially when the neonate is suffering from a condition where mortality could be high if no optimum available treatment is given.

Vulnerability

In vulnerable populations, like children or people with intellectual or mental disabilities, compensation is a special concern. This population is considered as relatively or absolutely incapable of protecting their own interests. The Indian Council for Medical Research (ICMR) National Ethical Guidelines for Conduct of Biomedical Research recommend that study protocols involving neonates should take into consideration the vulnerability of this group within the pediatric population in terms of the risk of long-term effects of interventions, including developmental effects.

There are two important challenges in ascertaining the relatedness of SAE and deciding the quantum of compensation in neonates. *Central Drugs Standard Control Organisation* (*CDSCO*) guidelines for adults recommend calculating the compensation amount based on the risk factor assigned based on the expected survival of the study participants at the time of enrollment, the age of the participant, and a base amount of INR 8,00,000/-. However, it is difficult to decide the risk factor in infants delivered preterm or lower than normal birth weight or small for gestational age (SGA) for the following reasons:

i) Despite providing the standard of care, many neonates die due to the co-morbidities associated with pre-maturity and SGA

ii) The majority of these deaths occur within hours to days while surviving neonates may have near normal life expectancy.

The compensation formula of adults considers ages 0-16 years as the same without any differentiation of various weight categories in the vulnerable population. The current formula for compensation is made keeping in mind

the adult population. 'F' is determined by the Workmen's compensation formula which is actually impractical to apply in case of neonates. In actuality, even within the neonates there are subclassifications as mentioned earlier.

Experience from the ProSPoNS trial

Although not many regulatory clinical trials in the pediatric age group have been documented but a few examples from vaccine trials [23,24] or the recent Goat Lung Surfactant Study (GLSE) exist where compensation was awarded to some participants [25,26]. But in all these cases the compensation awarded has been based on the adult formula. While conducting the ProSPoNS trial [27] which is a large, phase III multi-centric trial in neonates, currently being conducted at six sites in India, an important aspect of the compensation rules came into light. As the NDCT 2019 rules require sponsors to obtain clinical trial insurance to provide compensation to subjects, we had to calculate the limit of liability to obtain clinical trial insurance, based on the supposed compensation that can be awarded in the trial. This calculation was done based on the compensation formula provided in the seventh rule of NDCT 19 rules [9]. However, it was realised that the compensation formula used does not have any sub-classification for the pediatric population, particularly for the neonates. Thus, it was challenging for the trialists to assign a risk factor and calculate the amount of compensation that should be accounted for in the trial insurance. Therefore, it was realized that a more comprehensive system of determining the compensation in the neonatal population is required to address this lacuna.

Proposed Formula

Based on the mortality and morbidity risk associated with the different categories of birth weight, we propose a template to assign different risk factors for neonates in clinical trials as shown in **Table I** [28]. The compensation amount in case of death can then be calculated according to the earlier formula as: Compensation = (B x F x RA) / 99.37

However, these assumptions need to be reviewed again based on the economic development since the period of their conception, the average salary has increased. However, the interest rates of fixed deposits have decreased.

DISCUSSION

Clinical trials in neonates are faced with multiple challenges and raise some unique ethical considerations owing to the very nature of the population involved. The complexity of research in this population, coupled with the apprehension of causing unintended harm to vulnerable neonates, has led us to propose a modification in the current formula for calculating the compensation involving research in neonates. Further, the inability of this population to provide informed consent and the reliance on obtaining surrogate consent from parents adds to the challenge. There have been instances in neonatal research where the trials have come under the scanner for ethical issues. For instance, the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized) Trial, carried out in the US between 2004-09, had aimed to enhance knowledge on the optimum oxygen saturation level in very premature newborns. The study presented some important findings to the scientific community but simultaneously came under the scanner for a faulty informed consent process with failure to disclose potential risks to participants. It was later that scientific groups and leaders in bioethics and pediatrics came out in support of the trial urging the Office for Human Research and Protection (OHRP) to withdraw the notice given to the institutions involved in this trial as they feared it would set a precedence that would hamper ongoing and future patient-centred outcomes in trials. Such incidences bring to light the difficulty in conducting clinical trials in neonates.

Even much before this controversy, in the 1970s, many acts and guidelines like the Belmont Report, issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research,1978, were passed in the US, to protect children's rights during research. But these impeded clinical trials and pediatric drug development for the next two decades until new

Table I Risk Factor Assigned by Birth Weight

Weight category	*Risk*	*Risk factor assigned (RA)*
Micro preemie < 800 gm	Very high risk (Expected survival not more than 48 hrs)	0.5
Extremely low birthweight (ELBW 800-1000 g)	High risk (expected survival between 48 hrs – 2 months)	1.0
Very low birthweight (VLBW 1000-1500 g)	Moderate risk	2.0
Low birthweight (LBW 1500-2500 g)	Mild risk	3.0
Normal birthweight (NBW 2500-4000 g)	Lowest risk (Healthy neonates with no underlying conditions)	4.0
Higher than normal (HBW > 4000 g)	Mild risk	3.0

measures were implemented. It took another decade and new laws and funding passage for good research to begin. India experienced a similar scenario after specific amendments were introduced in the Drugs & Cosmetics (Amendment) Bill in August 2007. Subsequent amendments vide Gazette Notification G.S.R. 53(E) came in 2013. These regulatory changes brought about stricter rules for conduct of clinical trials and compensation in India and hampered clinical trials in India for almost a decade for the fear of compensation, etc. Thus, thoughtfully designed government regulations are needed to guide and promote ethical research: In context of compensation for neonates in trials, it is essential that the compensation safeguards the interests of participants in concordance with the Declaration of Helsinki, while simultaneously safeguarding the interest of scientifically and ethically conducted clinical trials in neonates for advancement in medical sciences.

Compensation in case of clinical trial-related injury or death is an important aspect of conducting regulatory trials in India. The present formula given in the NDCT 2019 rules for calculating compensation does not address the issues of the pediatric / neonatal population and the various risk factors associated with various categories in the pediatric age group within which neonates form the most vulnerable sub group. This results in calculation of a broad compensation which may not be appropriate for that age group.

Although, in this example, we have proposed a new marking system for 'R' in the formula based on the risk assigned to neonates according to their birthweight, the base line amount 'B' and 'F' also need to be re-evaluated in the current context. The Workmen's compensation formula which forms a part of the compensation clause, assigns equal weightage to all ages between 0-16 years ('F' = 228.54). We suggest that children as the future citizens of the country should be assigned a 'value of life' to be considered in the compensation formula. Adaptation to the neonatal context while estimating the quantum of compensation for trial-related injury/death among neonatal participants has been suggested by Sivanandan et at 2019 [25]. They suggested an adaptation of 'R' factored in the calculation for severity of neonatal diseases, prematurity, comorbidity and presence of risk factors. We have suggested a method of assigning value to 'R' based on risk associated with birth weight. For calculating the 'F' factor for children, other methods can be used for instance 'Life tables'. Life tables give estimates of the mortality which can be used to find the remaining period of expected life of children [29,30]. Another method could be determining the statistical value of life [35]. The formula proposed here in this manuscript has certain limitations as mentioned above. Considering the uncertainty of outcomes in this population owing to multiple biological and socio-economic factors etc, there is a need for deliberation by experts from the fields of neonatology, pediatrics, biomedical statistics, ethicists, etc. and a more comprehensive formula needs to be developed for determining compensation in trials involving neonates as participants.

CONCLUSION

Considering the paucity of the data available from neonatal trials in Indian population and the dire need for tailor-made drugs for the neonatal population, it is imperative to set an environment more conducive for conduct of drug trials for the neonatal population in India. The ICMR is contributing by creating national facilities such as centralized ethics committees for multicenter trials, Indian Clinical Trial and Education Network (INTENT) etc. Given the vulnerability of this population, they are at a high risk of facing adverse events. In case of SAEs, a broad formula as per the Clinical Trial Regulations of India seems insufficient. We therefore suggest a differential formula for trials specific to the neonates.

ANNEXURE

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Disclaimer: The authors would like to declare that this formula should not be considered prescriptive and further deliberation on the matter by an expert committee is required to create a comprehensive formula that can be adapted to the needs of the neonatal population.

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SPECIAL ARTICLE

The Indian Academy of Pediatrics and Directorate General of Health Services, Government of India White Paper on Transition of Care for Youth with Special Health Care Needs

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ABSTRACT

Over the years, survival of children with chronic diseases has significantly improved and a large proportion of them now are entering into adulthood. Transition of Care (ToC) of such patients with having childhood onset of chronic diseases to the adult health care system is well organized in developed countries, although it is an emerging concept in India. In situations where the systems for ToC are not in place, such cases are fraught with unsatisfactory health outcomes. With proper ToC in place, these patients are likely to receive uninterrupted care by the adult care physicians and hence reach their full potential. This document highlights the need, rationale and way forward for ToC of youth with special health care needs (YSHCN) across the country. It also describes the standard operating procedures to develop the ToC at a hospital level for clinicians and administrators.

Keywords: *Adolescent, Chronic, Self-care, Therapy, Young adult*

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PREAMBLE

The Maternal and Child Health Bureau (MCHB) of the United States of America (USA) defines Youth With Special Health Care Needs (YSHCN) as "*Those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally*." Hence, a proper transition (transition of health care) to adult care system is required for these patients once they attain adulthood.

Over the past two to three decades, significant improvements have taken place in the care of children with chronic diseases. As these patients reach their adolescence, their specific needs for the underlying medical conditions get compounded by the challenges specific to this age-group (**Box 1**). It is a common trend, especially in public sector hospitals, to direct the adolescent and young adult patients to the Medical rather than the Pediatric out-patient services, when they are beyond the cut-off age for pediatric services for that particular hospital. This method works well for otherwise healthy people attending the hospital for intercurrent illnesses; however, it can be challenging for patients with chronic illnesses needing a continuum of care. Transition of Care (ToC) is a crucial aspect of health care which can smoothen this process.

Currently, there are no guidelines in place for such a transition of care in India. Taking cognizance of this fact, in early 2023, Indian Academy of Pediatrics (IAP) approached the Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MoHFW), Government of India, for framing a ToC policy

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Box 1 Special Health Needs Adolescents with Chronic Illness

- Nearly 30% of adolescents and young adults have one or more chronic illness
- Nearly 25% of these youth with special health care needs (YSHCN) have at least one unmet need which may affect their physical and psychological well-being
- With improved survival of YSHCN, newer complications are being encountered
- Poor adherence to treatment is a problem among adolescents resulting in poor health outcomes
- With proper ToC, better satisfaction is seen among YSHCN which leads to improved treatment adherence
- Proper ToC leads to improved self-care
- Without proper ToC, control of chronic diseases goes haywire resulting in increased emergency room visits and other poor health outcomes

that could be uniformly implemented across the country. A meeting of experts from pediatric and adult care teams of central government teaching hospitals and All India Institute of Medical Sciences, New Delhi, was organized by the DGHS (**Annexure**). After deliberations on the subject, IAP was asked to prepare a policy document on ToC which was submitted to DGHS in due course. The same was circulated online among experts and finalized based on the feedback received. IAP was then asked to develop standard operative procedures (SOPs) for its implementation which were finalized following deliberations and inputs from experts from the pediatric and adult care teams. After necessary approvals, the ToC policy and the SOPs were circulated by the DGHS nationwide in December 2023. Additional Chief Secretary, Principal Secretary and Secretary Health of all States and Union Territories, Director General (Medical Education) and Director General (Health) of all States and Union Territories, Director General (Employees State Insurance Corporation), Government of India, have been requested to disseminate the ToC policy along with SOPs to all the health care facilities ranging from District Hospitals to Tertiary Care Hospitals, autonomous institutes and major private hospitals in their jurisdiction. National Medical Commission has been requested to include the ToC in the Postgraduate (Pediatrics and Medicine) and Super specialty curriculum.

Definition

Transition of Care (ToC) is defined as "*purposeful, planned process that addresses the medical, psychosocial, educational and vocational needs of adolescents and young adults with chronic medical and physical conditions as they move from child-centered to adult-oriented healthcare systems* [1]." In practice, this translates to a shift from a child- and family-centered environment of pediatrics to a patient-centered adult medicine setting. ToC is often used interchangeably with Transfer of Care; however, the latter is the final outcome, a single event where care is handed over from a pediatric care provider to adult care provider, while ToC is a gradual process.

Goals of Transition of Care

The American Academy of Pediatrics states, "*The goal of transition in health care for YSHCN is to maximize lifelong functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood* [2]." With continued good quality health care, the young adult is envisaged to attain full developmental potential and will be a productive member of the society.

Rationale for Transition of Care

According to the National Survey of Children's Health, funded by the US Department of Health and Human Services, almost 31% of adolescents have one moderate to severe chronic illness, such as asthma or a mental health condition. Other common chronic illnesses include cancer, cardiac conditions, HIV infection, spastic quadriplegia, developmental disabilities and epilepsy. One in every 4 adolescents with a chronic illness has at least one unmet health need that may affect their physical growth and development, including attaining puberty, overall health status as well as future adult health [3]. Data on the prevalence of specific chronic diseases among adolescents highlights the magnitude of the problem in our country. Recently, data from India on 514 patients with transfusion-dependent thalassemia (TDT) in North India revealed that 43% (n = 222) of them are aged above 18 years [4]. Likewise, a large thalassemia centre in Mumbai has 35% adult TDT patients (M Manglani, personal communication, June 15, 2023). Prevalence of epilepsy among 15 to 18-year-old boys and girls has been estimated to be 821 and 625 per 100,000 respectively [5]. According to 2022

estimates, over 8,50,000 children and adolescents are affected by juvenile diabetes; with an annual increase of 6.7% this figure is likely to be over 17,00,000 by the year 2040 [6]. The prevalence of asthma in children with mean age of 12 years is estimated to be 7.9 % [7]. According to estimates quoted by Indian Council of Medical research (ICMR), there are 80,000-1,00,000 children with severe hemophilia in India [8]. In some developed countries including USA, policy statements and guidelines on ToC of YSHCN are in place for over 3-4 decades [3,9], although the same is not true for most developing countries including India.

Need for ToC Guidelines

It is stated that ToC is "*to affirm that just as children receive optimal primary care in a medical practice experienced in the care of children, so too adults benefit from receiving care from physicians who are trained and experienced in adult medicine* [2]."

With increased survival of patients with chronic diseases, newer long-term complications and disabilities have emerged which require focused attention. Some examples include (*a*) Patients with transfusion-dependent thalassemia (TDT) are now at greater risk of atherosclerotic cardiovascular disease and associated impaired glucose metabolism; (*b*) Cystic fibrosis (CF) associated diabetes mellitus which occurs only in 2% of pediatric patients with CF, but increases several fold in adolescence and adulthood; (*c*) Survivors of childhood cancer will develop health issues such as obesity, hypertension and hyperlipidemia [10-12].

Another reason for ToC is to ensure ongoing treatment adherence. In the absence of proper ToC, adolescents are likely to have non-adherence to treatment. HIV-infected adolescents on anti-retroviral therapy (ART) remain largely asymptomatic and they may not feel the need for continuing ART; left unsupervised, they are at risk for poor adherence to treatment and treatment failure [13]. Similarly, poor glycemic control and higher emergency room visits among patients with type 1 diabetes mellitus, and transplant rejection among kidney transplant recipients due to loss to follow-up are described when ToC is not well addressed [14-17]. Better satisfaction among YSHCN is described when ToC is well planned. This facilitates improved adherence and compliance to therapy [14,18]. Positive youth development programs associated with ToC have shown better self-care and advocacy as well [18,19].

Barriers to ToC

Despite perceived need for proper ToC for YSHCN for their attaining full developmental potential, there are several barriers to ToC. These barriers exist at the level of pediatricians, family and patients, physicians and administrators.

Pediatricians may feel less comfortable referring their patients to an adult provider who is perceived to be less familiar with childhood-onset conditions. There is a fear of missing out/ losing contact with the patients for whom they have cared for years. There may be negative "research consequences" of reduction in patient numbers and a loss in long term follow-up. In private set up, there may be issues related to negative financial consequences.

If informed suddenly, patients and families are unable to cope with the transition to adult care and develop anxiety. Patients may feel anxious and distressed due to their emotional attachment to their pediatric health care providers and may fear going to an unfamiliar set-up for further care. They may experience grief and loss when these trusting relationships end. Moving to adult services may be viewed by them as a step closer to disease complications. Adjustments are required for individuals rather than family-approach of adult physicians. Parents may suddenly feel excluded from all decision making.

Acceptance by the physicians and taking the YSCHN under their care is the most important aspect of ToC. However, physicians may have limited interest in pediatric diseases which they do not encounter in their day-to-day practice. It may appear to be an additional responsibility as they may have their own areas of interests. When the ToC services are still developing, physicians may feel inadequately equipped in care of childhood onset diseases. Administrators may also be unaware of the concept of ToC; in the absence of an existing hospital policy, they may be reluctant to provide support in terms of staff and logistics.

Overcoming the Barriers

This policy document describes interventions to overcome these barriers and ensure a smooth ToC in place [20-22].

1. Securing Support of Senior Leadership to Develop a ToC Policy (National, State, Regional, Hospital Level): Appropriate administrative heads at the state, district and hospital level (such as medical superintendent of the hospital) should be approached to solicit support. The administrators should be apprised of how investing in ToC will help to retain YSCHN in care and improve patient satisfaction and outcomes. The administrators may be provided with the data on the need for ToC, such as the number of youth who will need transition to adult services over the next five years in the system/state/practice or the percentage of youth not receiving ToC services from

health care providers in the state/ hospital. Leadership should be made aware of the evidence that population health outcomes are improved with a structured ToC approach.

2. Defining the Age of Transition: Opinion remains divided around the optimal age for transition. The USA 'Got Transition' recommends initiating transition discussion at 12-14 years of age and completion of all steps of transition by 18-23 years [20]. The cut-off ages of 12 years, 13 years and 18 years are suggested by others, based on hospital policy. Some have recommended a flexible approach, taking into account not only the chronological age but also the emotional and developmental maturity of the individual [23]. Yet others feel that this may be counterproductive as the adolescents may feel upset while comparing with peers. Across our country, the cut-offs for transition from pediatric to adult care for general patients are extremely variable across states and hospitals as well as differ in public versus private sector. Increasing the age of transition from pediatric to adult care from 12 years to 18 years, may have following implications: (1) It will increase the number of patients visiting the pediatric out-patient services as well as pediatric inpatient services; (2) Increased patient load may require additional staffing in Pediatrics. Given the economic implications, it may mean reducing the staff on the Medicine side. This staff rearrangement may have implications related to National Medical Commission regulations; (3) It will necessitate modifications in the ward arrangements, i.e., developing separate wards for adolescent boys and girls.

As adolescent care falls under pediatrics in India and in most parts of the world, YSHCN should be managed by pediatricians till these patients attain 18 years age. For the time being, in view of the above implications, the cut-off age for ToC of YSHCN may be allowed to remain the same as that for adolescents without special health care needs. However, in the long run, a uniform age cut-off of 18 years for ToC of YSHCN should be mandated for the country.

3. *Self-management/Self-care*: Self-care or self-management is the practice of activities that an individual initiates and performs on his or her own behalf to maintain life, health, and well-being. Self-management is a patient-driven operational process with the ultimate goal of empowering the patient in his/ her own care.

Education program of self-management for chronic diseases has shifted from the traditional approach to the empowerment model. Empowerment is defined as helping people to discover their innate ability to control their diseases and situation. Due to increased number of patients with chronic diseases, it is necessary to pay attention to patient empowerment. However, physical, psychological and emotional maturity of the patient should be taken into account while embarking on coaching on self-management. In cases where the patient him/ herself is deemed unfit; a caregiver should be identified who should receive coaching in self-care. Empowerment on self-care entails the understanding of the disease, the treatment rationale, the source of symptoms, recognizing deterioration-clinical- versus laboratory-based, and taking appropriate action including seeking help from health professionals and operating within the medical system [24]. Psychological empowerment of patients is important for their active participation in self-care. To achieve this, preparation must begin well before the anticipated transfer time, preferably in early adolescence, when a series of educational interventions should discuss about ToC. Various methods suggested for coaching in self-care include lecture session, question and answer, presentation of PowerPoint, photo presentation, educational pamphlets, and peer training to which several digital forms of training methods may be added. In addition to the disease-related information, the content of sessions should consist of daily activities, fitness and health, nourishment, stress relief, job and home environment, time management and expression and creativity.

4. Transition Initiation and Assessment of Readiness: The patients and their families should be informed well in advance about ToC. Got Transition (USA) suggests initiating the process at 12-14 years, which is 6-8 years before the actual transition takes place. However, the process of ToC should be initiated at least one year before the actual transition [25]. It is important to periodically assess whether the YSCHN are adequately equipped in self-care, health care utilization skills, decision making skills and self-advocacy. This assessment allows the care providers and patients and their families to know the gaps and to act upon the required areas. Studies on the assessment of transition readiness using specific questionnaires addressing different domains have highlighted a correlation between transition readiness and outcome. Assessment of transition readiness is also important to understand the needs of the patients and their families so that resources around health care, education, and psychosocial needs can be individualized. There are validated tools available for such screening, such as the Transition Readiness Assessment Questionnaire (TRAQ) - a tool that is not disease-specific, and easy to administer [2,26].

5. Communication With the Receiving Team of Physicians: In developed countries, it is easy to decide about transfer of YSHCN as there are well developed systems in place. In our country, as the system is being initiated now, it is important as a first step to identify a physician who will be entrusted with the task of caring for patients with specific diseases. Currently, there are institutional differences regarding the availability of speciality/ sub-speciality care. In institutions with specialty services, one or two adult care physicians/ specialists may be identified to take care of young adults of the concerned specialty. In situations where the YSHCN have to be transferred to the adult Medicine department, a physician(s) who will be interested in looking after the patients with specific diseases needs to be identified. This may be done with the help of the administration. Communication regarding the need for ToC should be developed with the identified physician(s). They need to be apprised about specific needs of the adolescents and young adults with specific diseases. An ongoing communication needs to be built between the receiving adult-care team and the pediatric team as and when needed. The adult physicians may be provided with relevant resource material. Collaborative partnership with the physician team is important for the process of transition, including organizing joint clinics, transition completion and transition registry. Patients who need ToC usually have a long and often complex medical history. A detailed ToC document should be prepared by the treating pediatric team and provided to the receiving physician for future reference. This is especially needed if the medical records are not automatically transferred with the patient's transition.
6. Process of Transition: A hospital policy describing in detail the actual process of ToC needs to be available with duties on both ends clearly delineated. Casual agreement is easy to make, but it is less likely to succeed in the long run. See. At a minimum, a hospital ToC policy should state (i) the age of transition, (ii) transition initiation and assessing readiness, (iii) nominated care providers - both pediatrician(s) and the receiving physician(s), (iv) joint care clinics, (v) care coordinator/ counsellor/ nurse(s). It is important to educate all staff about ToC. For information of patients and families, a patient information sheet for ToC should be developed which should be validated.
7. Joint Clinics: Joint Clinics are the clinics which are attended by both the pediatric and adult care teams. These joint clinics aim at familiarizing the patients with the staff and environment they are moving to. These should also be attended by the care coordinators and the nurses. It is important to transfer the records and relevant data regarding the patients' illness at the time of actual transfer or before that. Special needs of the patients should be discussed by both the teams and management plan be drawn in advance. The place where the joint clinic is organized should be closer to the adult care department. A visit to the department should be organized. Frequency of such meetings can vary depending upon the number of YSHCN requiring transition.

Transition Completion, Transition Registry and Follow-up

A summary of patient's record should be prepared carrying information about the specific health issues if any, requiring attention. The summary should be handed over to adult care team at the time of transfer of the patient. A nurse or a counsellor (transition navigator) needs to be identified for any assistance required during the transfer. The navigator may be disease-specific, if the numbers of YSHCN are large enough. In settings with a small number of cases requiring transition, only one navigator can be entrusted with the task. To minimize the chances of loss of follow up, a transition registry needs to be maintained [27]. The registry should be maintained by the transition navigator under the supervision of the pediatric team. Administration should make arrangements for secretarial help required. A follow-up visit 3-6 months after the transition is recommended to ascertain if YSHCN is attending the adult care services.

Standard Operating Procedures (SOPs) for Implementation of ToC

We suggest the following instructions to be in place to ensure uniformity in ToC across the country.

At the National / State Level

The ToC policy should be circulated from the MoHFW or DGHS to the following:

- Health Secretary of the State / Union Territory (UT)
- Directorate of Health Services / Medical Education of the States and UTs
- Director General, Employee State Insurance Corporation (ESIC), Ministry of Labour and Employment
- The MoHFW / DGHS should also share the policy with the National Medical Commission (NMC) for including ToC in the postgraduate (Pediatrics, Internal Medicine) and super-specialty curriculum.
- State Health Secretariat/ DHS of the State/DG- ESIC should share the document with all medical colleges/

PG institutions/autonomous institutions such as AIIMS/District Hospitals/Missionary Hospitals/ Children Hospitals in public and private sector

- The Medical Superintendent/Principal/Dean/ Director of the Institution/Hospital should discuss the ToC with the Head of Department (HOD) of Internal Medicine/ concerned specialty and Pediatrics and take necessary steps for implementation (see below)

At the Hospital Level (Medical colleges, Autonomous institutions, District hospitals)

Step 1: Define the age of ToC taking into account prevailing age cut-off for Pediatrics / adult care in the particular hospital.

Step 2: Identify the pediatrician/ specialist pediatrician from whom the YSHCN needs to be transitioned, the physician/ specialist who will be receiving the YSHCN and the transition coordinator/ navigator (medical social worker/ Counselor / nursing officer).

Step 3: Responsibilities of the pediatrics team must be defined. The formalities for transition for YSHCN should begin at least one year before the actual ToC.

- A written document can be prepared for patients and caregivers explaining the need of ToC and its timing.
- A program of self-care and patient empowerment for self-management of the particular disease should be developed. This includes developing written material/ leaflets/ lectures and group discussion for the patients, caregivers and treating team.
- Assess the readiness for transition
- Joint Clinics for patients to be transitioned should be established with collaboration of the pediatric and adult care teams
- Patient management plans should be discussed with adult care team
- The complete records / copy of records to be transferred (physical/ digitized) should be finalized
- The pediatric team should be accessible to both the adult care team and the transitioned patients (need-based)

Step 4: Responsibilities of the adult care team include:

- Participation in the Joint Clinics
- Providing uninterrupted care to YSHCNs

Step 5: Maintaining disease-specific transition registry at the hospital level (transition coordinator/ navigator should be doing this task)

Step 6: Follow up of transition 3- 6 months after actual transfer of the patients for transition completion and picking up loss of follow-up (transition coordinator / navigator should do this task)

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ANNEXURE

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Ethical Challenges and Guidance Related to Adolescent Pregnancy

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ABSTRACT

An emergency team was challenged with ethical issues while managing an unmarried adolescent girl who presented with an acute abdomen wherein a ruptured ectopic pregnancy was suspected. Consent remained at the center of this dilemma given the age of the patient and the nature of the issues. Herein, we deliberate upon the challenges faced by the treating team in accessing the reproductive history, obtaining consent for performing pregnancy tests and for therapeutic interventions.

Keywords: *Abortion, Ethics, Consent, Parent, Reproduction, Sexual Behavior*

By 2025, India is predicted to have the highest population of teenagers globally. Adolescence is a critical life stage characterized by profound physical, mental and emotional changes. Socio-cultural transformations and the lack of comprehensive sexuality education has led to a high-risk sexual behavior, sexual abuse, teenage pregnancies, unsafe abortions, and increased risk for sexually transmitted infections. Investing in sexual health of adolescents is the need of the hour given that pregnancy-related complications and unsafe abortions have been reported as the leading cause of death among adolescent girls [1]. Reports suggest that 15% to over 50% of adolescents in India have engaged in sexual activity before the age of 18 years [2]. Dealing with adolescent pregnancy is particularly challenging for any treatment team. Understanding the ethical concept of 'Autonomy' is a first step in dealing with adolescent girls with reproductive issues.

CASE DESCRIPTION

A 16-year-old unmarried girl was brought by her parents to the emergency room with abdominal distension, obstipation, vomiting and pain abdomen of one-week duration. Examination revealed decompensated shock, pallor, and a tender distended abdomen with absent bowel sounds. After stabilization, a diagnostic paracentesis revealed hemorrhagic fluid. Computed tomogram of the abdomen revealed dilatation of the small bowel till the ileocecal junction with a 6 cm right hetero-dense, ill-defined adnexal mass. Possibility of an acute surgical abdomen due to a ruptured ectopic pregnancy or a complicated adnexal torsion was considered and reproductive history was elicited. In the presence of her parents, the girl denied any menstrual abnormalities, vaginal bleeding, amenorrhea, or sexual activity. The child in private finally revealed a 3-week history of intermittent vaginal spotting and intake of high-dose over-the-counter estrogen pills following sexual contact 2 months ago. Urine pregnancy tests were negative and serum beta-human chorionic gonadotropin levels were equivocal at 20 mIU/mL.

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OUTCOME

Following counseling of the family and after obtaining informed consent from the parents, the adolescent girl was operated upon to find a large clotted right adnexal mass, possibly due to acute rupture of a chronic ectopic pregnancy with collections enmeshing several bowel loops causing acute small bowel obstruction. A right salpingo-oopherectomy, resection of non-viable ileal loops and loop ileostomy and laparostomy were performed. On follow up, a reversal of the ileostomy and abdominoplasty was performed, and she was well six months later.

COMMENTARIES

The above adolescent girl was cared for by an emergency surgeon (NG) whose team identified challenges and a

summary was independently shared with a Pediatrician and Ethicist (BD), a Legal Researcher (SR), and a Senior Police Officer (RPM) for discussion.

Surgeon (NG): The surgical team was faced with a child under the age of 18 years with potential reproductive issues. In such a situation, obtaining a reproductive history and testing for pregnancy requires the consent of a parent. It is common that minors refrain from discussing reproductive issues with their parents given societal inhibitions and norms regarding teenage sexual activities, or the parents may feign ignorance given social stigmatization and hassles of dealing with law, if reported to police. It was decided by the team to manage the entire family as victims and with tact. Some of the challenges were:

Stigma and discrimination: In our socio-cultural context, the need to remain empathetic while dealing with the parents if of primary concern. Resolution with repeated counseling and discussion, rather than dismissiveness and hard sermons were required. Privacy needs to be respected and assured through sensitive discussions by senior doctors with responsible family members and adolescents, both individually and together. The urgency to ensure life-saving measures always take precedence over other considerations.

Legal responsibilities: Further complicating the situation was that all underaged sexual activity, especially if a sexual assault by a known or unknown person(s), mandates reporting to the police. The team thought that if there was any such suspicion, the provisions of the Protection of Children from Sexual Offences Act (POCSO) apply [3], and the case must be registered as a medico-legal case (MLC) with information to the local police. Failure to do so may be considered an omission by the treating team and make them legally liable. In this critical situation, all concerned parties had a low threshold for an MLC. An MLC alone should not lead to procedural delays, and this was explained to the family to gain their confidence. Later, the patient was clear about consensual sex (i.e. sex that all parties involved in agree to, both prior to the sexual activity and throughout it), and the team did not register an MLC at that time. Similar full-term pregnancies have delivered to married women though obviously underaged.

Non-maleficence and beneficence: A life-saving intervention had to be performed on a critically ill minor, with outcomes ranging from risk to life, complications, cosmesis, changes in body image and future reproductive potential. Priority was always to save life.

Pediatrician and Ethicist (BD): Adolescents may be considered as mature minors depending on their ability to take responsible decisions weighing risks and benefits involved in any given situation that reflects their increasing autonomy [4]. In this scenario, the patients and the family must be taken into confidence and made to understand that the physician and the healthcare team are acting in the best interest of the child while being non-judgmental. The parents should be counseled that the team are working as co-fiduciaries along with them to attain the best possible healthcare and/or social outcome for the child in question [5]. Since the child is 16 years old, it is equally crucial to understand her wishes/feelings and give due recognition to her preferences while making any decision that will affect her in future, while following the principle of respect for '*autonomy*' and the concept of '*shared decision making*'. A written assent from the child since she is more than 12 years of age (*ethical but not legal*) along with *parental consent* is mandatory before any intervention including conducting pregnancy tests. Since unmarried pregnant girls/women and their families may be stigmatized, teams need to be sensitive while eliciting menstrual/sexual history after taking the patient and immediate family into confidence that all efforts shall be taken to maintain the privacy and confidentiality. Complying with POSCO requires the team to mandatorily inform the police if sexual activity is reported in children less than 18 years of age. One must strictly maintain confidentiality, and without any undue disclosure to any third party or media personnel to avoid stigma (*non-maleficence*). The team keeps '*beneficence*' in mind while obtaining history, performing tests, and performing any therapeutic intervention.

Legal Researcher (SR): In the case of rape, consent of the victim, including minors, must be sought before medical examination [3]. The Ministry of Health and Family Welfare (MoHFW) Guidelines for medico-legal care for survivors/victims of sexual violence recognize that children above 12 years can provide informed consent for medical examination [6]. In accordance with their primary obligation to offer treatment, the medical practitioners rightly prioritized the medical care and did not seek any First Information Report (FIR) as a prerequisite. However, doctors are under an obligation to inform the police or the *Special Juvenile Police Unit* about the commission of a sexual offence and failure to do so is a punishable offence. Since the law is silent on the time within which the information is to be given, the doctors can do so after the patient's health improves and prepare them for such reporting. Mandatory reporting intends to break the culture of silence around sexual abuse and enable children's access to support and justice. However, there are concerns that children and families will not approach doctors to avoid the matter being reported to the police and

the ensuing stigma, shame, and harassment. The Supreme Court of India has recognized the conflict between the POCSO Act, privacy obligation under the Medical Termination of Pregnancy Act, 1971, and the reproductive autonomy of minors, and has clarified that in the case of minors engaging in consensual sexual activity and seeking a termination of pregnancy, the practitioner "*only on request of the minor and the guardian of the minor, need not disclose the identity and other personal details of the minor in the information provided under Section 19(1) of the POCSO Act*." The Rashtriya Kishor Swasthya Karyakram (RKSK) standards emphasize that removing the barrier to freely access sexual and reproductive health services is the need of the hour for all adolescents and recognizes the ensuing challenges [7]. Further, doctors must be guided by the Hippocratic Oath, and must in keep in mind the best interest of the child, while adhering to legal obligations related to reporting.

Senior Police Officer (RPM): In India, 'majority' is achieved at an age of 18 years which is considered a legal age for giving a valid consent for treatment as per Indian Majority Act, Guardian and Wards Act, and Indian Contract Act [8].

- A child below 12 years (minor) cannot give consent, and parents/guardian must consent for their medical/ surgical procedures.
- A child between 12-18 years can give consent only for medical examination, but not for any procedure.
- For children who are orphans or unknown or street children, the court is appointed as a guardian and any procedure/treatment requires permission of the court.
- In case of emergency, when parents/guardians are not available to consent, a person in charge of the child like the school principal or teacher can consent for medical treatment (*loco parentis*).
- A legal age of 18 years has been set to consent for termination of pregnancy (MTP Act 1971), donation of blood and donation of organs (Transplantation of Human Organ Act 1994).

In all circumstances, it is mandatory to seek an *informed consent/refusal* for examination and collection of evidence. Consent should be taken for the following purposes: examination, sample collection for clinical and forensic examination, treatment, and police intimation. Section 164A sub-clause (7) of CrPC clearly points out that it would be illegal for anything done during medical examination which is outside the scope of consent of the patient. Consent can either be sought from the patient herself or from legally established agencies/persons acting in the best interest of the patient where the patient is unable to give consent either due to age, trauma, mental condition, or disabilities. Doctors shall inform the person being examined about the nature and purpose of examination, and in case of a child to the child's parent/guardian/or a person in whom the child reposes trust. Reading the MTP Act in harmony with the POCSO Act, the court exempted physicians from disclosing the identity of the minor in legal proceedings under the POCSO Act, noting that it would ease the tension between the legal obligation of reporting a crime, the rights of privacy and autonomy of the minor.

DISCUSSION

The focus of this scenario was *consent* and *autonomy* of children aged under 18 years. *Autonomy* derived from the Greek word *autis* (self) and *nomos* (rule), includes persons with three conditions: who decide intentionally, with understanding and without controlling influences that determine decisions. To be able to make decisions one needs to be able to weigh the pros and cons, compare the alternative options and understand the consequences, both short and long term. An adolescent's competence to make decisions and ensuring confidentiality is described in guidelines elsewhere [9,10]. 'The Rule of Sevens' suggests that children aged under 7 years lack relevant capacities and these develop between age 7 and 13 years. After 14 years it is presumed that they do have decision-making capacities. This grey area reminds us that autonomy of adolescents develops with time, and no definitive universal age exists when it is confirmed. Therefore, one is required to make individual assessments of decision-making capabilities.

Consent from children aged 12 to 18 years to elicit history and examine is a requirement. Consent for interventions requires parents to consent for this age-group. However, evolution of consent in some countries has led to minors being able to legally make decisions regarding their own healthcare; exceptions based on specific diagnostic/care categories, the mature minor exception, and legal emancipation for healthcare needs related to sexual activity including treatment of sexually transmitted infections (STIs) and provision of contra-ceptive services, prenatal care, and abortion services that has expanded over several decades [11]. Adolescent's confidentiality guidelines are less widespread. With primary prevention now available in the form of Human Papilloma Virus (HPV) vaccination, this too raises potential challenges in our settings [11].

Risk factors for early sexual intercourse have included adolescent and parental substance use, aggression and conduct disorders, decreased family attachment, high parental overprotection, poor school achievement, and

lower maternal education [12]. Trends have shown that young male adolescents have early sexual debuts, lower prevalence of condom use at first sexual experience, inclination for live-in-relationships, and alcohol consumption reflective of hazardous interconnection between such behaviors among adolescent boys which placed them at higher- risk sexual behavior as compared to young men [13].

Challenges arise as the POSCO Act mandates police reporting of every child aged under 18 years involved in sexual activity, consensual or non-consensual. One need not disclose the identity and other personal details of the minor in the information provided under POSCO except on request of the minor and the guardian. Involving parents is optimal since they are in most cases ideal to make decisions for their children as it is assumed that they care and know the needs of their children; have their own children's best interest in mind; and bear the consequences of their decisions in their continued care. However, even parents need to be competent to decide, possess adequate knowledge, be emotionally stable and committed to fulfill this role. Assent is not consent but allows respect of developing autonomy of a child. The physician must, on an individual basis, take decisions that protect the health of the child (*beneficence*, *non-maleficence*), decide on balancing consent preferably from both (Child and Parent) as well as abide by the law while documenting all decisions with rationale. Finally, one must remember that in an ideal world, all adolescents should be able to turn to parents for support and guidance knowing that families may fall 'short of the ideal'. A concern is that disclosure resulting from legal compulsion rather than flowing from family relationships interferes with communication [14].

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UPDATE

Classroom as the Site for Type 1 Diabetes Self-Care Activities

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ABSTRACT

Children and adolescents with Type 1 diabetes (T1D) require bolus insulin before each meal, necessitating self-care activities including blood glucose checking to determine insulin dose (or check for hypoglycemia) and injecting insulin during school hours. Though these activities are essential for optimizing glycemic control, they are met with reluctance from parents, the child, school authorities, and sometimes peers. This requires ongoing education and support for the child, school staff, and other students, by the diabetes care team. Many problems of performing self-care activities can be greatly reduced by allowing them in the child's classroom itself, a strategy which offers several logistical, safety, psychological and social benefits. The glucometer and strips, continuous glucose monitoring device, insulin in a cool case, and hypoglycemia kit are kept in the teacher's custody, and used by the child as needed, under supervision. This normalizes diabetes and its care, obviates concealment of diabetes, enhances the child's and teacher's confidence, optimizes diabetes care by ensuring timely and consistent insulin dosing, encourages hypoglycemia prevention and management, and reduces the chances of the child being bullied. It also promotes acceptance of diabetes by peers and greater community awareness. Other places for self-care like the medical room or the toilet have disadvantages. Possible limitations of this strategy could be objections occasionally raised by some school staff, lack of privacy needed by adolescents, or bullying by classmates: issues which need proactive handling. The diabetes care team may do well to emphasize performing self-care activities in the classroom, working with school staff and parents to this end.

Keywords: *Glucose, Insulin, School, Self-management*

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Children and adolescents with Type 1 diabetes (T1D) require frequent blood glucose (BG) checks and multiple doses of insulin for managing glycemic control well. A child spends almost half the waking hours in school, where one or more meals or snacks are consumed, and varying degrees of physical activity occur. Diabetes self-care activities that include testing BG (whether by finger prick using glucometer, or by continuous glucose monitoring i.e. CGM), insulin administration, and managing emergencies like hypoglycemia and ketosis in school, are essential, and must be facilitated by the school staff.

The International Society for Pediatric & Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2022 on diabetes care in school emphasize the need to maintain normoglycemia at school to ensure proper learning and prevent acute and long-term complications of T1D [1]. For this, the Guidelines reiterate the responsibility of the school to provide care, support, supervision and encouragement to students with diabetes. This includes permitting and assisting in/ supervising such activities by "licensed (e.g., registered nurse) and unlicensed staff (e.g., teachers, education and special needs assistants, administrative staff)."

Across the world, attempts are being made to increase awareness among school staff to enable children to perform diabetes self-care activities under supervision. Diabetes self-care in school can be a challenge even in well-resourced countries [2]. In under-resourced areas, many children continue to face significant difficulties in managing diabetes in school, with varying degrees of support or resistance from the school staff. In India, the National Commission for Child Rights (NCPCR), having received several complaints of the difficulties faced by school-going children, issued a directive in March 2023 that stated it is the duty of schools to ensure proper care and required facilities for care of a child with T1D at school [3]. The directive states "A child with T1D may require checking blood glucose, injecting insulin, taking a mid-morning or mid-afternoon snack, or doing other diabetes self-care activities, as advised by a medical person. These should be permitted by the class teacher to do so during exams and otherwise also."

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However, even in reasonably optimal conditions, advice to perform self-care activities in school is met with considerable resistance and reluctance from the parents, the child, and school authorities. A study was conducted in pediatric diabetes clinics providing specialized diabetes education, in different parts of India, of the parents' assessment of the status of care of their children. About 70% of these children were attending private (fee paying) schools, and over half of the parents were of high educational status [4]. The study revealed that only 24.4% of the children with T1D were checking BG regularly at school; less than half were administering insulin; and 17.1% parents visited school daily for self-care activities. Testing and insulin administration were done in the classroom (26.2%), medical room (16.1%), staffroom (7.8%), or toilet (2.5%). School insisted on secrecy in 12.6%, excluded children with T1D from sports and excursions in 17.9%, refused permission for injecting in 4.3%, for testing in 15.9%, and for pre-activity snack in 7.6%.

As can be seen from this sample, the site for self-care activities varied, with some insisting on maintaining secrecy; most children were not provided comfortable choices. T1D care professionals are increasingly emphasizing the need to facilitate care in school. There are several advantages of performing such activities in the classroom itself, with the child permitted to keep the glucometer and strips, or CGM reader/ mobile phone, and insulin kept in a cool case, in the teacher's custody, and to use them as necessary. This approach offers several short-term and long-term benefits, in terms of logistics, safety, psychological and social advantages, and can help overcome many of the objections raised. This strategy undoubtedly requires ongoing education and support for school staff and families by the diabetes care team.

When discussing how this approach tackles commonly faced issues, the first and foremost issue is that many parents and children, particularly adolescents, try to conceal diabetes from school staff and peers, which can be dangerous. At the time of initial diagnosis, the diabetes care team should emphasize the necessity of self-care activities in school. Simultaneously emphasizing the classroom as the site for performing these activities will make it easier for the parents/ child to overcome their desire for concealment. It will also obviate the insistence of some school staff to conceal the T1D status of the child.

The logistic benefits are obvious. The tiffin break in most schools is for 15-30 minutes, during which time the children have to eat, bond and play. In this limited time, the child with T1D must also perform self-care activities. Ideally there should a gap of 5-15 minutes between taking the rapid-acting analog insulin dose and eating; Regular (soluble) insulin requires a gap of 30 minutes or more between taking the dose and eating. The process of checking BG and taking insulin, if performed in the classroom itself, saves time and increases the likelihood of getting a few minutes gap between insulin and meal. It also becomes practical for the child on Regular insulin to check BG and take insulin one period before the break, so that there is adequate time for onset of action, and BG control is smoother. During the day (for the school dose and before lunch dose), the abdomen is perhaps the best site to inject insulin. For most young school children, it is quite easy to take this shot by just going into a corner of the room, after confirming the dose with the teacher.

Self-care activities inevitably disrupt the class routine for the child with T1D, and for others. Performing them in the classroom rather than going elsewhere in school minimizes the disruption. It is quite practical for the teacher to supervise the child in the classroom itself, ensuring fewer omissions and occasions for playing mischief. This ensures safety for the child, gives confidence to the teacher, and reassures parents about their child's safety and well-being. Since the sharps and insulin are in the teacher's custody, it ensures they are out of reach of other children, and thus keeps them safe also.

The use of CGM often requires a mobile phone for the child to read the BG values and trends, for others (e.g. parents) to access this information (via bluetooth), and for receiving alarms for low and very high BG. Schools do not permit children to have mobile phones during school hours, so the child using CGM in any case has to deposit the phone with the teacher at the beginning of the day, go to the teacher whenever the BG value has to be read, expect the teacher to get alarms and react to them, and retrieve the phone before returning home. Planning to do all self-care activities at the teacher's desk streamlines the process, with the child checking the BG and injecting insulin daily at the teacher's desk. The daily routine of these activities promotes normalization of diabetes (analogous to wearing spectacles for myopia or a hearing aid for deafness), reduces the child's embarrassment, leads to awareness and usually greater acceptance of the child's T1D among the classmates, and eventually to greater levels of awareness among schoolmates' families and the wider community. The general awareness of diabetes makes it easier to tackle other children's bullying or teasing. It invalidates the notion of diabetes being contagious or as a barrier for the child to behave like a normal person.

The healthcare team and parents can request the teacher to discuss diabetes and hypoglycemia with the entire class; thus creating awareness regarding acute

emergencies among the classmates, thereby enhancing the safety of the child for timely detection of any episode of hypoglycemia or sickness. It is easier for the teachers who supervise self-care activities to remember that they may need to give time to the child to finish tiffin, to permit a snack to avoid hypoglycemia before any unexpected activity, or to check if BG is drifting towards hypoglycemia. In general, it is recommended that in case hypoglycemia occurs, corrective actions (giving sugar, followed by a snack) should be done in situ, rather than sending the child to the medical room. This becomes easier if the teacher and classmates are already familiar with daily self-care activities under supervision.

Schools with medical rooms often insist the child go there for performing self-care activities. This means the child must go to the medical room every day, wait for the attention of the nurse, and then check BG and inject insulin. This is time-consuming, limiting the child's time to play and bond with friends, and increasing the chances of the child missing or forgetting the self-care activities. The need to visit the medical room daily also increases the perception of schoolmates and staff that the child is "unwell", which can make it difficult for them to treat the child as normal, and increase the chances of her/ him being excluded from activities and discriminated against.

Other options have their own disadvantages. The child using the staff room daily interferes with the privacy of the teachers and may cause some resentment. The toilet is an unsanitary place to perform self-care activities, and suggests that there is a sense of shame associated with diabetes. During break time, the toilet is a crowded place, with many children jostling, so it is best avoided for diabetes care.

The acceptance of self-care activities by school staff and even peers, may not be easy, with challenges likely to arise from time to time. Occasionally a teacher may refuse to cooperate, the adolescent may need privacy, or peers may bully. The child himself/ herself may try to take undue advantage of his/her diabetes. Using the classroom for delivery of care may reduce and ease problems. At all times, school authorities, parents, and the diabetes care team must stay alert to hindrances and work together to overcome them, in the best interest of the child and other children.

To conclude, the diabetes care team should advise parents from the beginning to inform school authorities about diabetes, make sure they insist that the child is supported in management of T1D in school, and consider emphasizing that these self-care activities are to be performed in the classroom itself.

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The Last 50 years of Hemophilia Care: A Golden Era

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Five decades back a summary of hemophilia care was published in the May 1974 issue of *Indian Pediatrics* [1]. Hemophilia was then a poorly recognized, dreaded X-linked recessive bleeding disorder associated with low levels of FVIII (FVIII, hemophilia A) or factor IX (FIX, hemophilia B). Low factor levels were known to corelate with severe and even spontaneous bleeding warranting treatment with large volumes of fresh frozen plasma or cryoprecipitate. Although, the development of plasma fractionation technology in the 1970s led to the initiation of modern management using plasma-derived clotting factor concentrates (CFCs), most patients in India could not access these expensive clotting factor concentrates. Intracranial bleeds or surgeries in these patients were difficult to manage, and life-expectancy even in the West was barely 20 years.

The last 50 years have witnessed a radical change in the management of persons with hemophilia (PwH) due to ground-breaking research by scientists, applications by clinicians and vital inputs from social-scientists as well as patient advocacy groups, as elaborated in **Box 1**.

Plasma-derived Clotting Factor Concentrates and Prophylaxis

Back then, PwH suffered from painful joint or muscle bleeds spontaneously or after trivial trauma with annualized bleed rates (ABR) of >50. Often, these bleeds took days to recover and were followed by debilitating sequelae in the form of contractures, muscle wasting and joint damage. In the 1970s and 1980s the pioneering work of Inga Marie Nilsson of Sweden paved the way for prophylaxis using plasma-derived CFCs [2,3] and this practice was soon adopted in other Nordic countries. As freeze-dried concentrates became available for home-based prophylaxis, a dramatic improvement in the musculoskeletal outcomes of PwHs was seen [4]. However, the limited availability, high costs and scant data on the long-term joint outcomes precluded wide spread adoption of this practice. When the long-term data was published and results from randomized trials documented the clear benefit of such treatment, practice shifted rapidly to achieve this gold standard [5-7]. Unfortunately, the picture was clouded by two serious and seemingly unsurmountable problems - transfusion transmitted infections (TTIs) and the development of inhibitors.

Transfusion Transmitted Infections: HIV/AIDS and Hepatitis

Hemophilia patients were devastated by the harsh epidemics of HIV/AIDS and hepatitis B and C in the 1980s to 1990s due to the use of blood products and CFCs which were then all plasma-derived. Improved safety measures like heat inactivation, solvent detergent treatment and compulsory NAT testing of plasma in the sourcing blood banks were introduced afterwards [8], but it was too late for many who contracted HIV and /or hepatitis C virus (HCV) succumbed to their disease or complications [9,10].

Recombinant- or Laboratory-made Clotting Factor Concentrates

This terrible experience with TTIs, the knowledge that pathogens like prions could not be removed, and the need for larger quantities of CFCs than could be made from the available plasma left over from blood banks lead to the next leap forward. There was an impetus to use the advancements of recombinant DNA technology to synthesize clotting factors in the laboratory. The first recombinant FVIII (rFVIII) was approved in USA by the FDA in 1992, followed by the first recombinant FIX (rFIX) in 1997. The advent of freeze-dried CFC allowed for better accessibility by introducing the concept of home therapy and self-infusion. Prophylaxis with CFCs became

Box 1. Timeline of significant events in management of hemophilia

1970s	Primary prophylaxis therapy experience initiated; Freeze-dried plasma-derived factor concentrates available
1975	Factor eight inhibitor bypass activity (FEIBA) available
1977	Desmopressin used to treat mild hemophilia and von Willebrand disease
1980s	Genes for FVIII, FIX and von Willebrand factor cloned
1982	First reports of HIV/AIDS cases among people with hemophilia by Centres for Disease Control, United States of America (USA)
1985	First viral inactivated plasma derived factor concentrates available
1992	FDA approves first recombinant FVIII products
1995	Prophylaxis becomes standard of treatment in USA
1996	Recombinant FVIIa approved
1997	FDA approves first recombinant FIX products
1998	First gene therapy trials begin
2000s	FDA approves third generation recombinant factor products made without any human or animal plasma
2013	Gene therapy trials in the USA and Europe
2014	Extended half-life FIX approved
2015	Extended half-life FVIII approved
2018	Emicizumab approved for treatment of hemophilia A, with or without inhibitors
2023	Phase 3 trials of Concizumab and Fitusuran published
2023	HEMGENIX, FDA-approved gene therapy for the treatment of adults with hemophilia B (congenital FIX deficiency)
2023	ROCTAVIAN, FDA-approved gene therapy for the treatment of adults with severe hemophilia A (congenital FVIII deficiency)

more common wherein preventive treatment regimens consisted of 2-3 times a week CFCs in PwH. The original protocol from Malmo, Sweden, was the high-dose prophylaxis, subsequently the cost effectiveness and equally good outcomes of the intermediate dose Utrecht protocol proposed by the Dutch pediatrician Simon Van Creveld became accepted as the standard of care [11].

At our centre we recommend the intermediate dose protocol and several experts from India have evaluated the cost-effectiveness and feasibility of this regimen [12]. The World Federation of Hemophilia (WFH) recommends prophylaxis, as only this therapy can prevent musculo-skeletal deformities and disability [13]. Since then, several small studies on the feasibility of low dose CFC prophylaxis have been conducted wherein they were shown to reduce annualized bleed rates (ABR). Until at least 10-year joint health assessment data is available, low dose prophylaxis is not the standard of care, and should be practised as research with close follow-up.

Initiation of primary prophylaxis, defined as regular, continuous replacement therapy, initiated prior to 3 years of age, prevents bleeds and development of joint disease, results in improved health-related quality of life (HRQoL) measures [14]. Secondary prophylaxis, is started in PwH with recurrent joint bleeds, can reduce ABR and slow joint disease progression, with improved HRQoL. Benefit of tertiary prophylaxis, provided after established joint disease, or after joint replacement to maintain mobility and reduce pain has been documented [14].

Logistic barriers to prophylaxis exist due to the only 12-hour half-life of standard FVIII concentrates warranting atleast alternate day intravenous injections for prophylaxis and twice-a-day injections for severe bleeding episodes. Despite these frequent injections, ABRs are not zero and some patients continue to have spontaneous bleeding. Maintaining a trough of just over 1% factor level is not sufficient for all patients' activity and patients with target joints will continue to bleed.

Extended Half- life Recombinant CFCs

Studies showed that clearance of FVIII from circulation was through binding to low-density lipoprotein receptor related protein (LRP) and in LRP-deficient mice the circulation was increased by 30% [15]. This led to interest in technology to prolong the half-life of CFCs and and several pegylated extended half-life (EHL) products are

available in India. Other strategies to extend the half-life are by fusion of the FVIII or FIX with fragment crystallisable (Fc) region of IgG or human albumin. With these three available strategies, we have extended the action of rFIX (3–6 times) and rFVIII (>1.4 times) [16]. This not only leads to reduced venepunctures by 30-60% and less frequent injections for FIX EHL dosing (once every 10 days) [16], but also attainment of higher trough levels to 4-10% and zero bleeds and disappearance of target joints [16].

Joints Matter

When a bleed occurs, it can lead to permanent sequelae, synovitis and arthritis. Earlier in the 1990s radiology scores like the Pettersson score [17] and evaluation of joint health became a norm to document progression of joint damage and decide on timing of orthopedic intervention [18]. Definitive evidence that prophylaxis can maintain the joint health emerged from the Joint Outcome Study [19]. This was a detailed examination of 65 boys aged below 30 months who having received either on-demand recombinant CFC treatment for bleeds or prophylaxis with the same product were followed up for 3 years. By six years of age, only 55% of boys treated with on-demand regimen still had normal joints compared to 93% who received prophylaxis. Boys without overt joint bleeds in the on-demand group had evidence of joint damage on MRI [19]. Now several pediatric and adult HRQoL assessments and detailed joint scoring systems like the Hemophilia Joint Health Score (HJHS) [20,21] are done to closely monitor PwH and advise physiotherapy or increased CFCs for even any minor joint problems, as the goal is to avoid disability all together.

Patient-directed technology is used to improve compliance and empower patients who are self- infusing at home with CFCs. Haemtrack is an electronic diary mobile phone application which the patient or their parents can use to document bleeds and treatment details like the dose and dates of CFC administration [22]. The application can also connect with the treating doctor so that they are aware of the bleeding episode and treatment given and they can connect with the family if necessary.

Inhibitors to FVIII or FIX

The most serious complication of CFC therapy is the development of inhibitors due to immunological reaction to the foreign protein in the CFCs. Inhibitors are polyclonal high-affinity IgG alloantibodies that neutralise the activity both administered clotting factor concentrates or intrinsic factors. Patients with severe hemophilia and those with a strong family history have the highest likelihood of developing inhibitors. Patients with high-risk mutations such as null mutations, large deletions, followed by nonsense mutations are particularly prone; genetic testing can help ascertain the risk [23]. The inhibitor incidence from India appears lower than seen in the west [24], reasons for this are as yet not investigated.

Many families fear that prophylaxis can lead to inhibitors, although the risk of inhibitor development is highest in the first 20-30 exposure days (EDs) to CFC. Consequently, the children on prophylaxis have less risk of inhibitor development after this initial high-risk period. To get through this phase without inhibitor development, CFC infusions may be avoided during febrile illnesses or on the same day as vaccines [25]. There has been a lot of controversy about the risk of inhibitor development with plasma-derived versus recombinant CFCs. In a large multi-center randomized controlled trial (RCT) children treated with plasma-derived FVIII (pdFVIII) containing von Willebrand factor had a lower incidence of inhibitors than those treated with rFVIII [26]. On a more detailed analysis, no inhibitors developed in patients receiving pdFVIII who had a low genetic risk, whereas high-risk patients had a cumulative incidence of 31%. The risk among low- and high-risk patients did not differ much when they were treated with rFVIII (43% and 47%, respectively) [27].

Treatment of Inhibitors

Inhibitors should be suspected when CFC administration becomes ineffective or patients develop unusual bleeds. Inhibitor detection and assay for the titres (Bethesda units) is needed to decide the treatment plan [28]. There are two conventional bypassing agents used to treat active bleeding episodes in PwH, *viz* activated prothrombin complex concentrate (APCC) and recombinant activated factor VII (rFVIIa). Currently, the only strategy to eradicate inhibitors is to use immune tolerance inductions (ITI) therapy regimen.

APCC has been available as factor eight inhibitor bypass activity (FEIBA) since 1974 and it contains various activated factors such as II, IX, X and VII and increases thrombin generation. It has a long half-life and is suitable for the management of PwH with inhibitors developing serious life-threatening bleeds or during major surgeries and even prophylactically on alternate day in patients with high ABR. However, it must be used with caution and the maximum dose should not exceed 200 IU/kg/day [28]. rFVIIa, another bypassing agent, is licenced for use in management of inhibitors, inherited bleeding disorders like FVII deficiency and Glanzmann's throm-basthenia, and postpartum hemorrhage, was first developed by Ula Hedner, a Swedish pioneer in 1981 [29]. rFVIIa is safe and effective, although has a very short half-life warranting

administration every 2 hours in the case of serious bleeds or for surgical hemostasis.

The only way to permanently remove inhibitors is ITI which involves long-term treatment (uninterrupted for 6-12 months, maybe up to three years) with high doses of FVIII to overwhelm the immune system. ITI works in about 70-80% of hemophilia A patients with inhibitors. While on ITI patients with bleeds or requiring surgery need to be managed with bypassing agents. The WFH 2020 Guidelines states (recommendation number 8.3.16) that "*Patients with hemophilia A who develop persistent low-responding inhibitors, immune tolerance induction (ITI) be considered* [13]." Results from a multicentric RCT including 115 PwH with inhibitors have shown no difference in success of low dose versus high dose regimens [30]. Hence, in India we routinely have adopted the low dose ITI in our clinical practise [31].

Non-factor Products

Emicizumab, a monoclonal antibody, first developed in Japan, has been approved for treatment for hemophilia A patients with or without inhibitors [32]. Several studies in both adults and children have supported this treatment modality [33,34]. It is long acting and can be given weekly, fortnightly or even monthly, as a subcutaneous injection. Although expensive, it reduces health care burden and need for frequent hospital visits.

Several new non-factor products are being studied on clinical trials, around the world and in India. They work by rebalancing the pro-and anticoagulant system in the body. Concizumab is an antibody directed against Tissue Factor Pathway Inhibitor (TFPI) which enhances the ability of TFPI to support hemostasis and reduces the need for intrinsic pathway for FXa production. This is delivered as a daily subcutaneous injection by a pen-injector device and has been found to be safe and effective [35]. Another agent is an RNAi therapy targeting antithrombin III (ATIII), and reduces the requirement for production of FXa by reducing inhibition of FXa by ATIII, this is also administered subcutaneously and has a long half-life of 4 weeks [36].

Gene Therapy

The advent of gene therapy finally offers hope. The breakthrough hemophilia B gene therapy trial was published in 2011 [37]. Collaborative research was initiated and first efforts to increase gene expression, then efforts to use an adenovirus associated vector (AAV) were attempted using AAV8 virus subtype which has a high affinity for hepatic cells [38]. Although, gene therapy for both hemophilia A and B are now approved for treatment of adults [39,40], some barriers and limitations still exist such as severe hepatic reaction in response to AAV, high costs and ineligibility of those with pre-existing antibodies to AAV or prior inhibitors to FVIII or FIX. It is important to note that the gene therapy does not alter the germline and the disease will still be transmitted in the next generation. CRISPR/CAS gene editing should be explored which can target and correct gene mutations with fewer side effects.

Way Forward

Majority of states are now providing free CFC and bypassing agents for emergency use. Some states have the provision of prophylaxis and even nonfactor treatments for patients in need. Access to diagnostics has been an impediment to obtaining care. The way forward is to utilize and position all these therapeutic products (standard half-life, EHL, bypassing agents, non-factor products) in the best and most cost-effective way to reduce health inequity and prevent disability. Technology in India has led the way and in order to improve access to diagnosis a cost-effective Point-of-Care diagnostics kit for hemophilia has been released by the Indian Council of Medical Research ICMR [40]. Access to curative technologies like gene therapy are limited even in the affluent countries, but indigenous gene therapy projects are being studied and will help to bridge the gap [41].

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Ileo-ileal Knotting: A Ticking Bomb

Ileo-ileal knotting is a rare condition which presents like acute abdomen with non-specific signs and symptoms. The diagnosis is established intra-operatively, and unless picked up in time, the condition of the patient deteriorates rapidly. The treatment is surgical, and should be performed as soon as possible to decrease the incidence of peri-operative mortality and morbidity [1].

We report a 19-month-old boy (weight 9.3 kg, height 80 cm), who presented with multiple episodes of vomiting for few hours. On initial clinical examination, he was irritable with signs of dehydration. Dehydration correction was started, however, within four hours of admission, the child had multiple episodes of hematemesis. On reviewing the child, he was drowsy with compensated shock (cold peripheries, poor peripheral pulses, prolonged capillary refill time with normal blood pressure for age). His abdomen was distended, bowel sounds were absent, with guarding and rigidity. Six hours after admission, the hemoglobin reduced to 6.9 g/dL from 9.2 g/dL at admission. Packed red blood cells were transfused. *X*-ray abdomen showed multiple air fluid levels suggestive of intestinal obstruction. Computed tomography (CT) of the abdomen revealed dilated small bowel loops with intramural air consistent with early small bowel ischemia. His Pediatric Risk of Mortality (PRISM) score was 19.

An emergency exploratory laparotomy revealed ileo-ileal knotting; the entrapped loop of ileum was gangrenous, approximately 50 cm in length, extending up to one foot proximal to ileocecal junction. Resection of the gangrenous segment of ileum was performed and continuity of gut restored by end-to-end anastomosis. Immediate postoperative period was uneventful.

On the sixth postoperative day, after starting feeds, child had a whitish collection in the peritoneal drain suggestive of chylous ascites; serum amylase (264 IU/L), serum lipase (365 IU/L) and drain fluid triglycerides (277 mg/dL). Child was started on octreotide infusion and fat free diet. Abdominal girth and serial ultrasound monitoring did not reveal any collection. Octreotide infusion was gradually tapered and stopped, while introducing feeds. Child was discharged on seventeenth postoperative day. There were no gastrointestinal symptoms or complications after 9 months of follow-up.

In ileo-ileal knotting, one loop of the ileum remains static around which another loop encircles to form a knot [2]. Because of the rarity of the entity, there is no data on age and sex predilection [3]. Ileal knotting caused due to appendix [3] or Meckel diverticulum also has been reported. Once the knot is formed, it sets off a vicious cycle of intestinal occlusion and ischemia due to continuous peristalsis and vascular pulsations, all leading towards to gangrene. When all segments are viable, untying the knot may be enough, since recurrence is uncommon. When irreversible ischemia is present, needle or controlled enterotomy decompression should be done prior to en bloc resection of the congested segments. Manipulation of the knot with intention of untying is not recommended, because of a high risk of perforation. Once the necrotic ileum is extirpated, a primary end to end anastomosis of the small bowel should be done if the distal ileum is not affected. On the other hand, if the remaining segment is closer than 10 cm to the ileocecal valve, end to side ileocolic anastomosis is preferred.

Factors such as freely mobile small intestine and redundant sigmoid colon with a long and narrow mesentery have been implicated in ileo-sigmoid knotting [3]. The mortality rate is approximately 50%. Treatment should be started as early as possible with aggressive IV fluid resuscitation, insertion of nasogastric tube, broad spec-trum IV antibiotics. Once the patient is adequately resuscitated, emergency laparotomy should be performed. Though, ileoileal knotting is a rare clinical entity, it should be considered in the differential diagnosis of patients with signs and symptoms of small bowel obstruction.

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Heparin vs Saline Infusion For Maintaining the Patency of Arterial Catheters in Children

We read the journal article by Kowshik et al with great interest and commend the authors for their efforts in designing and carrying out this trial [1]. However, we would like to draw attention to a few noteworthy findings of this study.

The authors state that one of the inclusion criteria was that children require a peripheral artery catheter for more than 12 hours; however, it is unclear if randomization and recruitment began at 12 hours after catheter insertion or as soon as the catheter was inserted. It is unclear how the catheter dwell time of atleast 12 hours was anticipated if randomization occurred before catheter insertion.

There is a significant difference in diameters of the radial arteries among children of various age groups [2]. However, the study employed only 22G catheters for all children aged 1 month to 18 years, possibly resulting in the recruitment of fewer children aged < 3 years. The authors have not specified which age group had more catheter removals, which could be a confounding factor. Since ultrasonogram guidance was employed, it would have been suitable to determine the internal diameters of the arteries and use an appropriately sized catheter, or stratification of children by age and usage of 24G catheters consistently for children under 3 years.

Following the insertion of peripheral arterial catheters, the catheter-to-vessel ratio (CVR) could have been determined using ultrasonogram and color Doppler to assess the appropriateness of the outer catheter diameter in the vessel and adequate flow around the catheter wall, which is one of the confounding variables to assess the occlusion rate in this study [3].

Because arterial catheters are used for sampling and invasive blood pressure monitoring, the authors should have investigated the influence of the frequency of blood sampling performed in each group, as this can predispose to catheter occlusion.

Additionally, as reported by authors there was a higher catheter occlusion rate in this study compared to previous studies. The level of sickness of each child could have been objectively examined using scores like PRISM III or PIM3 and compared among the groups since factors like sepsis, metabolic milieu, and blood pressures might have influenced the results [4].

Nevertheless, considering the recognized adverse effects associated with the infusion of heparinized saline for maintaining arterial patency, this randomized controlled trial has definitely provided early insights into the potential use of normal saline with comparable effectiveness in children.

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AUTHOR'S REPLY

We thank the authors for their comments. Our response to the queries is as below:

Assessment for eligibility and enrolment began immediately after the arterial catheterization. However, allocation and randomization was done after 12 hours. The initial 12 hours was utilised for clinical evaluation of the child and to rule out exclusion factors like severe thrombocytopenia, coagulopathy, ongoing antiplatelet or anticoagulant therapy. Kindly refer to the Fig. 1 which shows the sequence of enrolment, allocation and randomization.

We would like to highlight some practical aspects in choosing catheters for arterial catheterization in children. There are not many commercially available choices of arterial catheters lesser than sizes of 20G in the market at present. In our PICU we use 2.5 cm length, 22G polyurethane lines by Becton Dickinson India Private Ltd (BD venflon) for arterial catheterization for all children. These lines are are actually intended for venous cannulation. While using 24G catheters for smaller kids is sensible, we found these lesser diameter venflon catheters are not stiff enough for usage as arterial catheters and we encountered frequent issues of dampened arterial pressure tracing during routine clinical practise.

We would also like to mention that no attempt was made to recruit children of a specific age group. The distribution of the children across age groups is in line with the proportion of overall admissions in our PICU. Therefore, recruiting children less than 3 years was not due to using 22G catheters. The age-wise occlusion of catheters was 3/12, 4/16, 5/36 and 3/28 in the age groups < 1year, 1-3 years, 3-10 years and > 10 years, respectively. On a first glance, proportion of catheter occlusion appears to be more in the children < 3 years. But the absolute numbers are few for meaningful statistical significance. A larger sample size would yield better results for age-wise comparison.

We thank the authors for their valuable suggestion on the use of ultrasonogram and color Doppler for assessing the appropriateness of catheter diameter. However, we would like to emphasize that our study focused exclusively on peripheral arterial catheterization. The vessel diameter of a peripheral artery is not a static measure for assessment and varies significantlydepending on the clinical status of the child. For example, the vessel diameter of a child in vasoplegic shock would be different from a child of the same age in hypovolemic shock. Similarly factors like hypothermia, use of vasoactive medications like noradrenaline infusions may affect the diameter of the vessel. In addition, the measurements may vary within the same child at different phases of his/her clinical condition. We also observed that number of attempts made for securing an arterial line can be a significant determinant of vessel diameter. A second attempt at pricking the same arterial vessel for catheterization would be difficult as the vessel might be in vasospasm (and lesser diameter) following a failed initial attempt.

Further, we want to clarify that the frequency of the blood sampling depends on the clinical status and the need for investigations in the child and is not directly in our (investigator) control. Apart from the frequency of blood sampling as mentioned above, factors like technique of catheterization, number of attempts made at cannulation, level of the pressure and the consistency of its maintenance in the pressure bag, volume of the fluid infused, concentration of the heparin used may also be significant confounders. We have made the best attempt possible to standardize the practice that we believe these confounders are distributed uniformly across the two study groups. We have also mentioned these as the limitation of our study. We do have the PIM score in our unit but did not use the same to analyze how severity of illness correlates with catheter life. As mentioned earlier, we have pointed out the limitations of the study in the manuscript clearly and the level of sickness could be one of them.

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Neonates With Absent/Reversed End-Diastolic Flow - Are We Feeding Them Right?

The study done by Anand et al on time to attain full enteral feeds in neonates with absent or reversal of end-diastolic flow (AREDF) makes for an interesting read and generates important insights on practices being followed while managing this vulnerable subset of neonates [1]. The authors have included neonates with fetal restriction, with the study cohort having antenatal umbilical artery doppler findings of AREDF. The differentiation between the AREDF in umbilical artery and other doppler findings (such as the pulsatility index of the umbilical artery, middle cerebral artery and ductus venosus findings) along with the presence of liquor anomalies has not been documented which form an integral part of fetal management because of their significant association with perinatal mortality and morbidity [2].

Feed initiation and advancement protocols seem very guarded in the authors' unit as against the recently done trials where initiation of full enteral feeds in non-high-risk preterm neonates and rapid advancement in high-risk populations have been associated with better outcomes without any increase in the rate of adverse events [3]. Use of a more elaborate and individualized feeding protocol based upon gestational age group strata, severity of intrauterine growth retardation and sickness may have helped decrease the time to full feeds and associated morbidities. The study does not mention the absolute proportion of human milk consumption (mother's own milk - MoM and donor human milk - DHM) in the two groups which is an important confounding factor as it is associated with risk of necrotising enterocolitis (NEC), sepsis, and mortality.

A meta-analysis has demonstrated a significant advantage of multi-strain probiotics containing various strains of *Lactobacillus* and *Bifidobacterium* over probiotics containing *Lactobacillus* species, *Saccharomyces boulardii* or *Bifidobacterium* species alone in terms of mortality and NEC [4]. Most studies on neonates have demonstrated a benefit when probiotics are given at a dose of 10^8 to 10^9 colony-forming units (CFU) for at least 34-36 weeks postmenstrual age or till discharge [5]. However, the neonates in this study received *Lactobacillus rhamnosus* alone at daily dose of 10^5 CFU from feed initiation till full feed attainment (median duration 8-12 days).

In the absence of blinding of the clinical team to antenatal doppler findings, there were higher chances of labelling of neonates with AREDF as stage 1 or suspected NEC and feed intolerance (as defined by non-increment or reduction of feeds).

The neonates in the AREDF group seem to have greater overall sickness (higher incidence of hypoxic ischemic encephalopathy and oxygen dependence). However, the calculation of initial sickness scores, such as SNAPPE scores, is unavailable. Propensity score matching or a nested case-control design could have more efficiently addressed these confounders.

It seems that concerting efforts on providing appropriate nutrition to this sick subgroup in the form of breast milk (MoM or DHM), aggressive and well-standardized feeding protocols, use of appropriate type and duration of probiotics and conducting well-designed trials incorporating long-term outcomes is the need of the hour to answer this critically important aspect of managing these neonates.

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Endotracheal Tube Aspirate Microscopy and Culture vs CDC Criteria for Early Diagnosis of VAP in Special Newborn Care Units

We read with interest the article by Pahwa et al [1]. A few important points need elaboration for a better understanding. The study excluded neonates with suspected/ diagnosed pneumonia at the time of initiation of mechanical ventilation (MV), major congenital malformations, pulmonary hemorrhage, outborn neonates intubated at admission or with a history of MV. With the gestational age (GA) of study population being < 32 weeks, and with exclusion of most conditions for which neonates are intubated at this GA, it is difficult to assume the causes of ventilation of included neonates. As less invasive surfactant administration (LISA) and continuous positive airway pressure (CPAP) is commonly practiced in most units, we are unsure if the included neonates with respiratory distress syndrome (RDS) met the inclusion criteria. A flow diagram mentioning total number of deliveries, number of neonates with antenatal steroids, and the number of excluded neonates with reasons would have been useful.

Authors mentioned that endotracheal aspirate (ETA) samples were collected after 48 hours of MV using an open method. However, critical details regarding procedure remains unclear. Authors need to clarify if they took any growth on culture as indication of VAP and how was any colonization excluded. We would like to know the correlation between blood culture and ETA culture. Although authors mentioned that ETA culture and microscopy were superior to CDC criteria (in terms of time) for diagnosing VAP, the percentage difference between two methods and their correlation if any was not specified.

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AUTHOR'S REPLY

We thank the authors for bringing out these issues. We included preterm neonates with catecholamine resistant shock, severe RDS and perinatal asphyxia who warranted mechanical ventilation. 39 (83%) and 29 (87.9%) neonates were on inotropic support in the ventilator-associated pneumonia (VAP) and non-VAP group, respectively. 16 (34%) and 5 (15.2%) neonates had severe RDS; 14 (29.8%) and 11 (33%) neonates had perinatal asphyxia, in the VAP and non-VAP group, respectively. We do not practice LISA in our unit. Out of 193 neonates who received mechanical ventilation, 122 were ventilated for ≥ 48 hours. We excluded 42 neonates (congenital anomalies 9; congenital pneumonia 14, congenital heart disease 6, pulmonary hemorrhage 7 and refusal of consent 6). Antenatal steroid data were not available for outborn neonates.

Endotracheal aspirates (ETA) were collected after proper hand washing and using all aseptic precautions, by open suction after 48 hours of starting MV. Suction was performed using a sterile feeding tube or disposable mucus extractor. If the yield was less (< 2 mL), then ETA was collected after instilling 1-2 mL of normal saline (drawn from a freshly opened ampoule) into the endotracheal tube. The sample so collected was evaluated for microscopy and culture. Samples collected in night were stored at 40°C overnight and sent to the laboratory next morning. A smear was prepared from ETA for gram staining to determine the type of organisms. ETA culture in VAP group (n = 47), revealed *Klebsiella pneumoniae* (n = 30), *Citrobacter freundii* (n = 5), *Pseudomonas aeruginosa* (n =1), aerobic spores (n = 1) and *Klebsiella pneumoniae* plus *Pseudomonas aeruginosa* (n = 1), while isolates in the non-VAP group (n = 33) were *K. pneumoniae* (n = 5), *P. aeruginosa* (n = 2), and *Acinetobacter baumanii* (n = 2). Blood culture isolates in the VAP group were *K. pneumoniae* (n = 5), *Candida albicans* (n = 4) and MRSA (n = 3) while that in non-VAP group were *K. pneumoniae* (n = 3), MRCONS (n = 3) and *C. albicans* (n = 2). Microbial pattern in the blood culture was different as compared to ETA culture.

In present study, ETA microscopy was positive in 59.5% neonates of VAP group and 12.1% neonates of non-VAP group. ETA culture was positive in 80.9% neonates of VAP group and 27.3% neonates of non-VAP group. The sensitivity, specificity, PPV and NPV of ETA microscopy in our study was 59.5%, 87.8%, 87.5% and 60.4%, respectively whereas for ETA culture it was 80.8%, 72.7%, 80.8% and 72.7% respectively. CDC criteria for diagnosing VAP was taken as gold standard. The percentage difference between the two methods and their correlation was not evaluated in our study.

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CLIPPINGS: PEDIATRIC NEUROLOGY

Classic ketogenic diet versus further antiseizure medicine in infants with drug-resistant epilepsy (KIWE): A UK, multicentre, open-label, randomised clinical trial (*Lancet Neurol. 2023;22:1113-24*)

This multicentric, open label randomized clinical trial conducted in UK recruited 136 infants (1-24 months) with drug-resistant epilepsy; 78 were assigned to ketogenic diet and 58 to antiseizure medications. The primary outcome was the median number of seizures per day, recorded during weeks 6-8. In the modified intention-to-treat analysis at week 8, data from 61 infants in the ketogenic diet group and 47 infants in the medication group were included. During weeks 6-8, the median (IQR) number of seizures per day was 5 (1, 16) in the ketogenic diet group and 3 (2, 11) in the medication group, with an incidence rate ratio (IRR) of 1.33 (95% CI 0.84, 2.11). Serious adverse events were reported in 51% (40 out of 78) of participants in the ketogenic diet group and 45% (26 out of 58) in the medication group. The most common serious adverse events were seizures in both groups. Three deaths occurred in the ketogenic diet group but were deemed unrelated to treatment. The trial concluded that the ketogenic diet did not differ in efficacy and tolerability from further antiseizure medication in infants with drug-resistant epilepsy and could be considered as a treatment option after trying two antiseizure medications.

Pancreatic replacement therapy for maladaptive behaviours in preschool children with autism spectrum disorder (*JAMA Netw Open. 2023;6:e2344136*)

This study was conducted to evaluate whether high-protease pancreatic therapy in children with autism spectrum disorder (ASD) produces long- and short-term improvements in autism-associated maladaptive behaviors. This multicentric study conducted at 32 sites across the United States from 2015 to 2021, utilized a double-blind parallel group, delayed-start design. 190 children (79% boys) aged 3 to 6 years, were randomized to receive either 900 mg high-protease pancreatic therapy or a placebo for 12 weeks, followed by all receiving the therapy for an additional 24 weeks. The primary outcome, was irritability/agitation subscale of the Aberrant Behavior Checklist (ABC-I). All participants were screened using the Social Communication Questionnaire (SCQ) with diagnosis confirmed by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) for ASD and the Autism Diagnostic Inventory–Revised (ADI-R). Outcomes were measured at the end of the 12-week double-blind segment and at the end of the 24-week open-label segment (total 36 weeks). A significant reduction of -2.49 (95% CI, -4.66 to -0.32; Cohen d = 0.364; P = 0.03) at the 12-week mark., and at the 36-week mark, a reduction of -3.07 (95% CI, -5.81 to -0.33; Cohen d = 0.516; P = 0.03) was noted in ABC-I score. The study concluded a sustained reduction in maladaptive behavior of irritability among preschool children with ASD receiving high-protease pancreatic replacement with no major adverse effects.

Evaluation of safety and efficacy of add-on alpha-lipoic acid on migraine prophylaxis in an adolescent population: A randomized controlled trial (*J Clin Pharmacol. 2023;63:1398-407*)

The study aimed to assess the safety and effectiveness of alpha-lipoic acid (ALA) as an add-on prophylactic treatment for adolescent migraine. Sixty adolescent migraineurs were randomized to receive flunarizine alone or flunarizine with ALA. Clinical evaluation including frequency and severity of migraine attacks, responder rate, Pediatric Migraine Disability Assessment (PedMIDAS) scoring, serum thiol, and serum calcitonin gene-related peptide (CGRP) levels, was assessed at baseline and after 12 weeks of treatment. A significant decrease in the frequency of migraine attacks (P = 0.001) and a higher responder rate (80%) in the ALA group compared to the control group (33.3%) (P = 0.001) was reported. The ALA group experienced a significant reduction in mean (95% CI) monthly migraine headache days (-7.7; -9.1 to -6.3 days; P = 0.010), severity of migraine attacks (P = 0.001) and improved PedMIDAS scores (P = 0.021), compared to the control group. Serum thiol levels increased significantly (18 mmol/L, 95%CI 13.5 to 36.1 mmol/L; P = 0.001), and serum CGRP levels decreased significantly (-122.4 pg/mL, 95%CI -142.3 to -89.0 pg/mL; P = 0.006) with ALA therapy. The study concluded that add-on ALA with flunarizine has potential for prophylactic treatment of adolescent migraine.

Trofinetide treatment demonstrates a benefit over placebo for the ability to communicate in Rett syndrome (*Pediatr Neurol. 2024;152:63-72*)

This randomized controlled trial investigated the effectiveness of trofinetide in improving communication abilities in girls aged 5 to 20 years with Rett syndrome (RTT). Participants were randomized 1:1 to trofinetide or placebo for 12 weeks. The study assessed communication-related endpoints, including caregiver-rated Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS-DP-IT), Social Composite score (Secondary end point) and novel clinician rating scales measuring nonverbal (RTT-COMC) and verbal (RTT-VCOM) communication abilities. Trofinetide demonstrated significant improvement compared to placebo in the CSBS-DP-IT Social Composite score [least squares mean difference (95% CI): 1.0 (0.3, 1.7); P = 0.0257; Cohen d = 0.43] and a nominal improvement in RTT-COMC (LSM difference: -0.3; 95% CI, -0.6 to -0.0; P = 0.0257; Cohen d = 0.36). However, there was no significant difference in RTT-VCOM. These findings suggest that trofinetide holds promise in enhancing communication abilities in individuals with RTT.

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NEWS IN BRIEF

Nano- and Microplastics Pollution: Age Old Solution for a New Problem

Nano- and microplastics (NMPs) are tiny pieces of plastic as small as 5 mm or smaller in size and are found in a variety of daily use items including food and tap water. Studies have documented its presence in human cells including blood vessels and placenta which has been shown to be associated with alteration of gut microbiome, increased risk of cancers, heart attack, stroke and death. Advanced filter systems can help in reducing the NMPs in drinking water supply but this process is neither easily available nor affordable in low- and middle-income countries (LMIC). A team of researchers from China have suggested that the simple practice of boiling of tap water for 5 mins before consumption can reduce the amount of NMPs significantly. At high temperatures calcium carbonate in hard water (> 120 mg/L of $CaCO_3$) starts nucleating on NMPs resulting in the encapsulation and aggregation of NMPs within the incrustants which can be removed from water by standard filtration. This process can remove ~ 80% of polystyrene, polyethylene, and polypropylene NMPs size between 0.1 and 150 µm. (*Ries J. 28 Feb 2024. Boiling Water May Help Remove Up to 90% of Microplastics. Healthline. Retrieved from: https://www.healthline.com/health-news/boiling-water-may-help-remove-up-to-90-of-microplastics*)

Treatment of Rare Diseases Becomes More Affordable

Recently, Delhi High Court has exempted the custom duties on the drugs used for treatment of two life threatening rare diseases - Duchenne Muscular Dystrophy (DMD) and Spinal muscular atrophy (SMA). This order has been passed in response to the petitions filed by parents of children suffering with rare diseases. On an average a basic customs duty charge of 10% is applied on medicines, while some of the life-saving drugs and vaccines attract a duty of 5% or less during import. As medications of these conditions are mostly imported from outside the country and costly – it puts a lot of financial burden on patient's family. This order will reduce the cost of treatment, and will benefit these families significantly. Simultaneously, the court has also instructed the concerned authorities to shorten the clearance time at their end to fasten the drug delivery to the hospitals treating such patients. This is another welcome move after the recent launch of generic version of drugs for the treatment of four rare diseases - Wilson's disease, Gaucher's disease, Tyrosinemia type I and Lennox Gastaut Syndrome by the Ministry of Health and Family Welfare, Government of India towards implementation of the National Policy for Rare Diseases. (*Mukherjee R. 5 Mar 2024, 03:47 IST. Delhi HC exempts customs levies on rare disease drugs. The Times of India. Retrieved from: https://timesofindia.indiatimes.com/city/delhi/delhi-hc-exempts-customs-levies-on-rare-disease-drugs/articleshow/108216241.cms*)

Garbhini-GA2: AI to Reduce Maternal and Infant Mortality Rates in India

Estimation of correct gestational age can help in planning the delivery and postnatal care, thus reducing the maternal and neonatal morbidity and mortality. As a part of 'Interdisciplinary Group for Advanced Research on Birth Outcomes – DBT India Initiative' (GARBH-Ini) program, researchers from the Indian Institute of Technology Madras and Translational Health Science and Technology Institute, Faridabad, have collaborated to develop an artificial intelligence (AI) model – "Garbhini-GA2", to precisely determine the gestational age during second and third trimester in pregnant Indian women. The performance of GARBH-Ini was assessed by comparing the test dataset from GARBH-Ini cohort with an independent validation set from a south India cohort. Results revealed that Garbhini-GA2 reduced the gestational age estimation median error by more than three times compared to the ultrasonic assessment based on Hadlock formula. (*PIB Chennai. 26* Feb *2024, 12:10PM. IIT Madras & THSTI Faridabad Researchers develop the first India-specific AI model to determine the age of the foetus. Retrieved from: https://pib.gov.in/PressReleasePage.aspx?PRID= 2008988*)

India Genome Project: Another Milestone Achieved

Genome India Project was launched in year 2020 with an aim to conduct sequencing of 10,000 genomes of Indian population. This important mission was accomplished on Feb 27, 2024, with completion of sequencing of gene samples of more than 99 ethnic groups collected from across the country to create a reference genetic database of Indian population. Uniqueness of India Genome Project lies in the fact that the Indian subcontinent is home to more than 4,500 anthropologically well-defined population groups which are totally different from population of other countries. This data will help researchers to study genetic variations associated with various diseases and response to certain drugs. Twenty top institutions of the country participated in this project led by Indian Institute of Science (IISc), Bangalore, and the Centre for Cellular and Molecular Biology (CCMB), Hyderabad. (*Mishra A. 28 Feb 2024, 05:31 PM. India largest genetic lab in the world' — what completion of India Genome Project means. The Print. Retrieved from: https://theprint.in/health/india-largest-genetic-lab-in-the-world-what-completion-of-india-genome-project-means/1982036/*)

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Hypohidrotic Ectodermal Dysplasia: Classical Clinical Features

A 9-year-old boy presented to the dermatology OPD with complaints of poor scalp hair growth, loss of sweating, heat intolerance and delayed eruption of teeth. Child was born uneventfully out of a nonconsanguineous marriage at term by vaginal route. He was first in birth order with the other two siblings being normal. Examination revealed frontal bossing, depressed nasal bridge with saddle nose deformity, marked periocular and perioral hyperpigmentation, prominent lips and ears (**Fig. 1**). Oral cavity examination showed only three widely spaced teeth (one upper molar and two lower molars). Scalp hair were sparse, thin and lustreless with scant eyelashes, absent eyebrows and body hair. The skin was overall dry, with reduced dermatoglyphics on palms and soles while nails were normal.

Hypohidrotic ectodermal dysplasia (HED), also known as Christ-Siemens-Touraine syndrome, presents with a triad of hypodontia, hypotrichosis and hypohidrosis. It has variable inheritance as X-linked, autosomal recessive or autosomal dominant. Distinctive cutaneous features include periocular and perioral hyperpigmentation, dry wrinkled skin, eczematous dermatitis and sebaceous hyperplasia. A mid-facial hypoplasia leads to the characteristic facies. The condition is associated with abnormal mucosal glands leading to solidified aural and nasal secretions, dry eyes and recurrent pulmonary infections. Management of HED is challenging, requiring a multidisciplinary approach including prevention of hyperthermia, managing eczematous dermatitis and recurrent pulmonary infections. Early dental intervention to improve the chewing ability improves the overall quality of life.

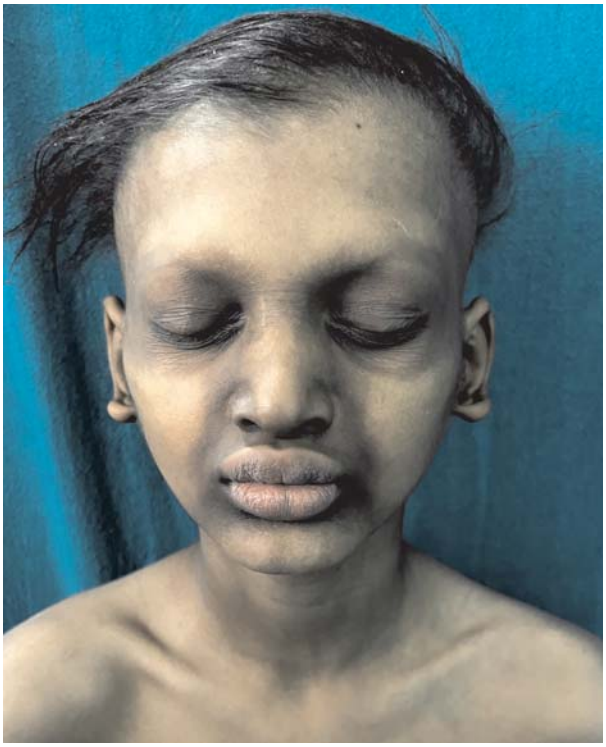

Fig. 1 Characteristic facies showing a broad forehead, sparse eyebrows, depressed nasal bridge, prominent lips, and periocular and perioral hyperpigmentation

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A Chronic Violaceous Cheek Nodule in a Child

An 8-year-old girl presented with a persistent nodule on her left cheek for two months duration for which she had received a 15-day course of topical corticosteroids but showed no improvement. Examination revealed a well-defined, firm, non-tender, violaceous nodule measuring 15×10 mm on her left cheek. Rest of the examination was unremarkable. Skin biopsy revealed chronic granulomatous inflammation characterized by lymphocytes and histiocytes without necrosis. Special staining for bacteria, fungi, and mycobacteria was non-contributory. A diagnosis of idiopathic facial aseptic granuloma was established and she was started on treatment with oral clarithromycin in a dose of 15mg/kg/d for 45 days, along with topical application of ivermectin, to which she responded well.

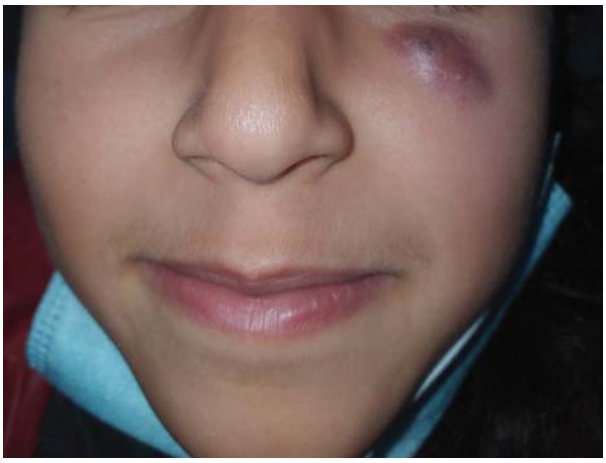

Fig. 1 Violaceous nodule with a smooth surface

Idiopathic facial aseptic granuloma, predominantly found in children on the cheeks, typically manifests as violaceous nodules, either singular or multiple, with a protracted course. It is often a diagnostic challenge as it may mimic various conditions such as skin metastases of neuroblastoma, cutaneous lymphoma, cutaneous sarcoidosis, leukemia cutis, vascular malformations, pyogenic granulomas, epidermal cysts, benign tumors, and localized infections. Histopathology remains crucial for a definitive diagnosis. Treatment options encompass topical agents like metronidazole, azelaic acid, ivermectin, tacrolimus, and nicotinamide. Oral macrolides like clarithromycin and azithromycin, oral metronidazole or oral doxycycline (in older children), may be given for up to 3 months duration, and have proven to be effective. Our patient responded well to oral clarithromycin.

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An Unusual Etiology for Intense Pruritus: Os Odontoideum With Atlantoaxial Dislocation

A 10-year-old boy presented with a gradually progressive weakness of the left upper limb and both lower limbs with neck pain for the past two and half years following a fall from a height of about 10 feet. He also complained of intense itching over his left hand for 10 months. Examination revealed left torticollis, spasticity and weakness of the left upper limb and both lower limbs with power 2/5 and 3/5, respectively, a normal sensory examination, and positive cerebellar signs. The left hand had excoriated and crusted nodular lesions with lichenification secondary to chronic pruritus (**Fig. 1**). Neuroimaging (**Fig. 2A-C**) revealed a cranio-vertebral junction anomaly, as detailed in the legend. Nerve conduction velocity tests were unremarkable. He underwent a surgical correction, following which there was a significant improvement in pruritus. Neuropathic pruritis is a potential cause of itching in patients with craniovertebral junction anomalies, and correction of underlying anatomical lesions improves neuropathic pruritus.

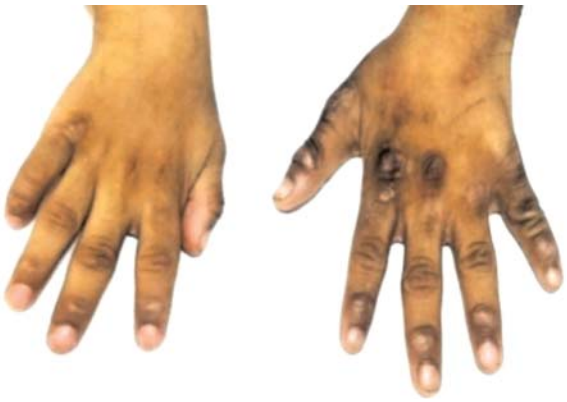

Fig 1 Left hand with excoriated and crusted nodular lesions with lichenification secondary to chronic pruritus

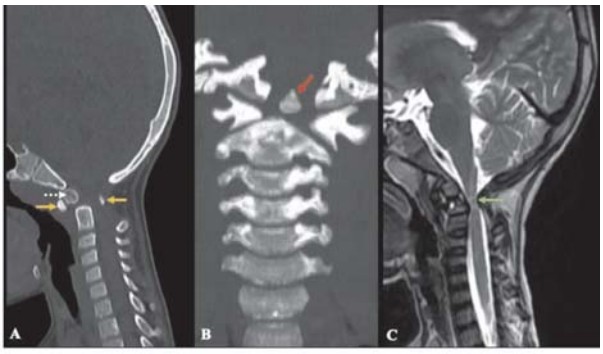

Fig 2 Sagittal CT spine (A and B) and Sagittal MR Spine (T2W sequence) images show Os odontoideum (dashed arrow) with anterolisthesis of the whole of C1 and Os odontoideum over C2 vertebral body, anterior displacement of anterior and posterior arches of the atlas (C1) (yellow arrow) and rotatory atlantoaxial joint subluxation (red arrow in B). The resultant significant narrowing is seen at the C1-C2 level with compression and kinking of cervicomedullary junction with altered signal intensity (green arrow in C).

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