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Farewell From the Editor's Desk

After four years at the helm, I step down from the editor-in-chief's post, both with a sense of relief and a tinge of regret. However, I look forward to continued support to the journal in the future, as a contributor and a reviewer.

I had started my tenure with a few plans [1], and was fortunate enough to carry out most of them, despite the intervening pandemic [2]. One of the major achievements, other than the continued publication of the journal during the pandemic [3], was the launching of (and now DOAJ indexing) of a new journal from our stable, *Indian Pediatrics Case Reports* (*IPCaRes*) [4,5]. For this, the two editors, Dr Sharmila B Mukherjee (2021-22) and Dr Kirtisudha Mishra (2023 onwards) merit accolades. We also achieved one of our highest Impact Factors in 2021, and shifted to a new more-responsive website in 2023. The section on Iconic Pediatric Institutions was well received by readers, and I hope to see more publications documenting the history of pediatrics in the country.

Journal publishing is presently undergoing rapid changes; and keeping up with these needs the support of core professionals, rather than in-house staff trained in editorial processes almost a decade back. I feel that after six decades of regular self publishing of the journal, it is an opportune time to explore partnership with a publishing house, both to increase the reach of the content through the rapidly expanding alternative communication interfaces, and also bring out the journal in line with the current publishing best practices.

Dr Pooja Dewan, who is taking over as the Editor-in-Chief, has been a diligent member of the journal editorial board for a long time. I hope that she will not only continue charting the journal's course of being both a reporting and responding journal for the "general'' pediatricians in India and the developing world, but will also explore hitherto uncharted waters, to take the journal to newer heights.

Journal editorial boards are meant to be both the gatekeepers and also leading voices in the medical field. I was fortunate to be assisted by editorial board members who had both a wide experience in their disciplines, and also willingness to step up to take up important journal responsibilities. Their generosity and perseverance assisted me in handling a large number of manuscripts from a wide variety of sub-specialties with varying theoretical perspectives and methodological approaches.

This tenure has contributed immensely to my growth as a professional and as a person, and for that I remain thankful to our ever-expanding pool of contributors and reviewers, whose efforts have launched the journal on its current growth trajectory. I close this write-up with this partial quote from *Nitisatakam*, which has guided me during my tenure and may also be helpful to others who follow:

"... विघ्नैः पुनः पुनरपि प्रतिहन्यमानाः
प्रारभ्य चोत्तमजनाः न परित्यजन्ति ।।"

–Nitisatakam by Bhartrhari

(*….the best class of people, despite being repeatedly discouraged by obstacles, never abandon the job till they achieve success*)

DEVENDRA MISHRA
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PRESIDENT'S PAGE

Addressing Violence Against Children in India

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India has traversed an eventful journey of evolution and implementation of child health care policies and programs since independence. The vision and focus of these programs have changed over the years, as understanding of child health grew. As I write the concluding president's page, what I have tried to do in this year long journey is to draw your attention to some of the key focused areas where we need to put in extra efforts as changing times also means newer challenges in child health.

India is home to the largest child population (440 million) under the age of 18 years in the world. An estimated 24.7 million children are born every year in India. Given the range of adverse socioeconomic circumstances children are born into, their right to health, welfare and protection are public health concerns. Needless to say, the health and security of our country's children is integral to any vision for its progress and development. In 1992, India accepted the obligations of the United Nations Convention on the Rights of the Child (UNCRC) [1], and our domestic policies have been framed in consonance with the same, recognizing the rights of children under four key priority areas viz., survival, development, protection and participation. In the last two decades, the Government of India has taken several positive steps towards overtly advancing children's rights to protection [2,3]. These include the formation of the National Commission for Protection of Child Rights (2005), National Policy for Children (2013), National Plan of Action for Children (2016); legislations such as Right to Education Bill (2009), Protection of Children from Sexual Offences (POCSO) Act 2012 and amendment to Juvenile Justice Act (2015) to protect, promote and defend child rights. Despite these initiatives, for a huge population base, amidst adverse socioeconomic situations, poverty, illiteracy, violence, poor resources and access to health services in backward aspirational districts of our country have led to considerable adverse childhood experiences (ACE), particularly for younger children during their early formative years. Child abuse, neglect, exploitation and violence against children (VAC) are widely prevalent child rights violations, but an under reported public health problem in our country [4]. In 2007, a study conducted by the Ministry of Women and Child Development, Government of India revealed that the prevalence of all forms of child abuse is extremely high, including physical abuse (66%), sexual abuse (50%) and emotional abuse (50%). The Indian Academy of Pediatrics (IAP) recognizes VAC exerts a multitude of short- and long-term health effects on children [5], leading to serious and often lifelong consequences for mental and physical health, reproductive health, academic performance, and social functioning. According to a major American epidemiologic ACE research study, a powerful relationship has been established between child maltreatment and VAC to adverse health effects in adult life, including development of adulthood high-risk health behaviors such as smoking, alcohol and drug abuse, promiscuity, and severe obesity, and correlated with ill-health including depression, heart disease, cancer, chronic lung disease and shortened lifespan [6].

Pediatricians, doctors and allied health professionals are often the first point of contact for children who experience abuse or neglect. They play a key role in detecting abuse, and provide immediate and long-term support to the children and their families. As first point-of-care, we should believe, support, reassure, treat, and ensure rehabilitation of victims, keeping the best interest of the child as our primary goal. However, often our knowledge in the early recognition and response to various forms of VAC is limited. The Indian Child Abuse Neglect and Child Labor (ICANCL) group of IAP has been working relentlessly in this field for past 25 years [7]. Under the IAP Child Rights and Protection program (2007), published in *Indian Pediatrics*, the IAP committee recommended that pediatricians in India should be trained to recognize and respond to child abuse [8]. The training to prevent and respond to VAC has not been imparted in recent times [4]; thus, there is an urgent felt need to impart training to pediatricians, doctors and allied medical professionals to prevent and respond to VAC. Pediatricians and allied medical professionals should be updated about the Indian child protection systems and laws, such as the ones mentioned in the opening lines. The comprehensive knowledge of the child protection systems and health can contribute to improved health care, protection, development, management, social reintegration and rehabilitation of

children affected by violence. Such efforts shall also contribute to India's efforts to realize child rights as per UNCRC and achieve its targets as per sustainable development goals (SDG).

The Executive Board of IAP 2023 stands committed to address early recognition and response to VAC in our country scenario and tackle its many entrenched problems. The IAP has recently succeeded in obtaining a grant award from Dr Maichel Social Capital, a nonprofit liability company, registered under German commercial law to implement a project to prevent VAC. A memorandum of understanding (MOU) has been established to achieve the following aims. First, to create and disseminate an educational program to enhance the capacity of pediatricians, doctors, allied professionals, teachers, caregivers and parents to prevent and respond to such cases of VAC. In this program, IAP shall be engaging with IMA, FOGSI and allied medical societies in order to train 250 committed doctors as master trainers through five (50 doctors each) Zonal Training of Trainers (TOT) workshops. Secondly, patient education materials such as videos and screening tools will be created in English and 10 major Indian local languages, and can be disseminated for parents, teachers, police persons, legal professionals, frontline health workers, children and NGOs. Thirdly, at present, the technical expert faculty group is undertaking the task to develop a prevention of VAC training module with specific learning objectives (SLOs). The SLOs shall have a clear intent, content, methodology and process, both in person and online telemedicine training module to improve prevention and response to violence against children. The objective is to provide simple, yet important and critical take home messages and development of knowledge-based practice standard operating protocols (SOPs) for the pediatricians and allied medical professionals. The SLOs will specifically focus on various common forms of VAC, and will be evidence-based, reliable and time bound.

We endeavor to launch the first two in-person P-VAC training module in two zones in November and December, 2023, and the remaining trainings in the subsequent years for our membership and our partners. I urge and request all of you to reach out and register at the central IAP office and take advantage of these initial training of trainers (TOT). After becoming master trainers, our trained expert members can implement the above program through further TOTs in their regions. Child health outcomes, and so also our profession of pediatrics is tightly linked with the prevalence of violence against children in our country. I do hope that you will choose to participate in this program to be better equipped to address VAC, one clinical case at a time.

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PERSPECTIVE

Pediatric Sepsis: New Strategies for Reducing Sepsis Related Mortality

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Sepsis is one of the leading causes of morbidity and mortality in children. Timely recognition and management of sepsis with fluid resuscitation and antibiotic administration leads to better clinical outcomes. However, clinical recognition of sepsis in children is challenging given its rare occurrence, the overlap of clinical features with other common febrile illness, lack of specific diagnostic biomarkers and the ability of children to compensate until the late stages of shock. Despite updating of pediatric sepsis definition and implementation of screening tools to facilitate early recognition, mortality from sepsis continues to be high. Continued education, research and advocacy efforts are needed to improve patient outcomes in pediatric sepsis.

Keywords: *Biomarker, Death, SIRS*.

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The international consensus conference on pediatric sepsis in 2005 [1] published definitions for systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock. Sepsis was defined as SIRS in the presence of or secondary to suspected or proven infection, while severe sepsis defined as sepsis with organ dysfunction and septic shock defined as sepsis with cardiovascular dysfunction. Severe sepsis and septic shock is a leading cause of mortality in children and accounts for majority of the 4 million deaths secondary to infectious diseases in children under five years of age [2]. The Sepsis PRevalence, OUtcomes, and Therapies Study (SPROUT Study) conducted in 6,925 children admitted to 128 pediatric intensive care units (PICU) from 26 countries reported an overall prevalence rate of 8.2% for severe sepsis with wide variation of 6.2% to 23.1% between developed and developing countries [3]. Flieschmann-Struzek, et al. [4] in their systematic analysis of the global burden of pediatric and neonatal sepsis reported an aggregate estimate of 48 (95% CI : 27-86) cases of sepsis and 22 (95% CI 14-33) cases of severe sepsis cases in children per 100,000 person-years. The mortality ranged between 1-5% for sepsis and 9-20% for severe sepsis.

Common risk factors for pediatric sepsis include presence of indwelling central venous device, bone marrow or solid organ transplantation and presence of an underlying chronic disease [5,6]. While *Staphylococcus aureus* is the most common pathogen identified in sepsis in healthy and children with comorbidities, the other prevalent organisms include *Streptococcal* species and *Escherichia coli* in healthy children, and *Candida* and *Pseudomonas* in children with chronic diseases [7,8]. However, it should be noted that a bacterial pathogen is identified only in approximately 50% of children with sepsis [7].

MORTALITY

A systematic review and meta-analysis of 7561 patients showed a decline in the pediatric sepsis pooled case fatality rate from 43.1% to 22.8% over the last two decades [9]. However, the authors noted a significant disparity, with a higher case fatality rate in developing countries compared to developed countries [9]. Children with medical comorbidities have been shown to have a significantly higher in-hospital mortality secondary to sepsis compared to healthy children (5.1% vs 0.7%) [7]. Younger age, organ dysfunction and septic shock are also associated with a higher mortality rate [8,9]. Cvektovic, et al. [10] evaluated the timing of death in children with sepsis and found that majority of deaths occurred within the first 24 hours of referral. More importantly, approximately 25% of deaths occurred even prior to referral to the intensive care unit [10]. While early deaths from pediatric sepsis are usually secondary to refractory shock, late deaths are attributed to multiple organ dysfunction with persistent organ dysfunction preceding most deaths [11].

While host and infectious agent characteristics and environmental factors such as poor nutrition, sanitary conditions and low immunization rates contribute to suboptimal patient outcomes, the most common reasons for persistent high mortality rates from sepsis are believed to be secondary to delayed recognition, treatment, and lack of adherence to sepsis treatment guidelines. This is due to a lack of familiarity with guidelines and proficiency in lifesaving and time-sensitive performance of interventions such as

airway management or central venous catheter placement [12,13].

CLINICAL MANIFESTATIONS

Early symptoms of sepsis in neonates can be nonspecific and include irritability, lethargy, or poor feeding. Further neonates may present with hypothermia rather than fever and can have a normal physical examination. A high index of suspicion is needed and physicians should have a low threshold for performing a diagnostic workup, especially in those neonates with risk factors such as prematurity and maternal history of positive *Group B Streptococcus* status, chorioamnionitis and prolonged rupture of membranes. The hemodynamic response of children is also different from that of adults. Children with sepsis have significantly lower cardiac reserve, profound hypovolemia and often present with low cardiac output and elevated systemic vascular resistance (cold shock) with hypotension being a late sign.

Early Recognition Sepsis Screens

The American College of Critical Care Medicine update, 2014 [14] of practice parameters for hemodynamic support for neonatal and pediatric septic shock recommended institution-specific use of sepsis bundles viz., *i*) Recognition bundle: a trigger tool for rapid identification of patients with septic shock, *ii*) Resuscitation and Stabilization Bundle: for adherence to best practice principles, and *iii*) a Performance Bundle: to identify and overcome perceived barriers to adherence of best practice principles for improvement of clinical outcomes in pediatric sepsis. In response, sepsis screens such as the 'Best Practice Alert' and the Pediatric Septic Shock Collaborative's (PSSC) screening tools have been implemented in emergency departments to rapidly recognize children at risk for sepsis [15,16]. These screens involve a combination of abnormal vital signs and physical examination findings in the context of a suspected infection and presence of comorbid conditions that increase the risk of sepsis. The performance characteristics of these screens are further optimized by addition of a clinician input and judgment. Despite the ease of integration of sepsis screening tools into the electronic health records and the high sensitivity, their effect on clinical outcomes remains unclear. Further, given the rare occurrence of sepsis when compared to other febrile illnesses, the intentional high sensitivity of these screens leads to substantial number of false positive triggers, leading to alarm fatigue. False positives on these screens can lead to unnecessary fluid resuscitation and antibiotic administration in many children without sepsis. Excessive reliance on these triggers can also lead clinicians to miss the diagnosis of sepsis if the screen is not triggered.

Machine learning and artificial intelligence can include large amounts of electronic health record data without need for manual entry and incorporate dynamic changes in vital signs and create algorithms that may be able to predict sepsis and adverse outcomes related to sepsis earlier and more accurately than the existing sepsis screening tools. Indeed, in a study by Le, et al. [17] of 9,486 children aged 2-17 years of whom 101 were categorized as severe sepsis, machine learning based prediction algorithm significantly outperformed the Pediatric Logistic Organ Dysfunction score (PELOD-2) and pediatric systemic inflammatory response syndrome (SIRS) in the prediction of severe sepsis 4 hours before onset.

Risk Stratification Strategies

SIRS criteria are widely used in many EDs for early recognition of children with sepsis but lack sensitivity to identify critically ill children, and have low specificity. The pediatric and neonatal Sequential Organ Dysfunction Assessment (pSOFA and nSOFA) scores and the PELOD-2 scores have all been shown to be useful in predicting mortality but have only modest prognostic accuracy for other adverse outcomes. Further, studies of these scoring systems are predominantly from developed countries and hence their applicability to global settings is limited.

Biomarkers in Pediatric Sepsis

There is currently no single biomarker that has diagnostic and prognostic capabilities in pediatric sepsis. C-reactive protein (CRP) is the most widely used biomarker. Its utility as a biomarker has been extensively studied in neonates and febrile infants <60 days of age. In settings where procalcitonin is unavailable, CRP in conjunction with absolute neutrophil count and height of fever can be used for risk stratification of febrile infants. A single measurement of CRP has limited sensitivity and specificity in differentiating bacterial from non-bacterial infection in children; though, serial measurements may improve its predictive value. Procalcitonin is more specific for diagnosis of bacterial infection. especially invasive bacterial infection. However, there is lack of prognostic and risk stratification studies, especially in older children. Serial measurements of procalcitonin can serve as a guide to antibiotic therapy with persistently elevated levels indicating an inadequately treated infection and need for escalation of therapy, and a declining/normal level an indicator to cessation of antibiotics. Interleukin-6 (IL-6) is a proinflammatory cytokine whose levels have been found to be higher in children with sepsis, especially those with severe sepsis, but is not routinely tested in clinical practice due to low availability and high cost. Wong, et al. [18] successfully derived and validated PERSEVERE model, a set of five biomarkers (C-Cchemokineligand3 (CCL3), interleukin 8 (IL-8), heat shock protein 70kDa1B (HSPA1B), granzymeB (GZMB) and matrix metallopeptidase 8 (MMP8), which

identified children at risk of death from sepsis. They further modified this initial model with addition of platelet count and elements of the tumor protein 53 pathway, which further improved the predictive capability of their model. However, these studies were limited to the intensive care settings in children with known sepsis. Further studies are needed to determine the role of biomarkers in risk stratification and prognostication of pediatric sepsis.

MANAGEMENT OF PEDIATRIC SEPSIS

The surviving sepsis campaign published new guidelines for management of pediatric sepsis in 2020 [19]. While these guidelines provide a framework for management, the panel acknowledged that translation of these guidelines into clinical practice should take into account the variation in availability of healthcare resources. Systematic screening for sepsis and implementation of protocol/guideline for management of septic shock is recommended. Antimicrobial therapy should be initiated within three hours for those children with sepsis induced organ dysfunction without shock and within one hour for those in septic shock. If possible, cultures from appropriate biological specimens as indicated (blood, urine, wound) should be obtained prior to, but should not delay, the administration of antibiotics. Cerebrospinal fluid analysis should be obtained in neonates with sepsis as the incidence of concomitant meningitis ranges from 0.3-3%. Given that respiratory infections are the most common source of pediatric sepsis [8], chest *X*-ray should be considered, especially in those with respiratory symptoms. Cultures of indwelling catheters, endotracheal tubes and results of nasopharyngeal swabs and expanded viral panel testing results can be used to guide the choice, duration, and de-escalation of antimicrobial therapy.

The following factors should be considered in the choice of antimicrobial therapy: age, site of infection, comorbid diseases, presence of indwelling devices, immune status of the host and local antimicrobial resistance. In previously healthy children, suggested choice for empiric antibiotic therapy includes a third-generation cephalosporin and vancomycin. Immunosuppressed children and those with central venous catheters often require antipseudomonal coverage along with an extended beta lactamase or carbapenem coverage along with vancomycin. Patients with suspected intra abdominal pathology benefit from addition of metronidazole or clindamycin and the latter is also beneficial in toxic shock syndrome. Antimicrobial therapy in neonates in should include coverage for *Group B Streptococcus, Listeria monocytogens* and *Herpes simplex* virus. Empiric antimalarial treatment is indicated where malaria is endemic and in clinical presentations consistent with an acute encephalitis syndrome (altered mental status, seizures, and metabolic acidosis), and can be discontinued if testing for malarial antigen is negative. Administration of fluid bolus of 40-60 mL/kg in the first hour is recommended for children with septic shock in healthcare settings with access to intensive care resources. In those settings with lack of easy access to intensive care, administration of lower volumes of crystalloids (aliquots of 10-20 mL/kg up to a maximum of 40 mL/kg) is recommended as rapid fluid resuscitation has been shown to be associated with increased mortality [20]. Indeed, if blood pressures are normal, fluid boluses should be deferred and maintenance fluids should be initiated. Buffered or balanced crystalloids such as lactated ringer are preferred over normal saline to avoid hyperchloremic metabolic acidosis and acute kidney injury. The categorization of shock in to warm and cold is no longer recommended. The guidelines also recommend the use of epinephrine and norepinephrine as first line vasoactive agents over dopamine as they have been shown to be associated with lower risk of mortality and increased organ failure free days among survivors. There was no consensus recommendation for use of vasopressin, and administration of hydrocortisone was suggested to be considered in those children with fluid and vasoactive refractory shock. Endotracheal intubation is recommended in those children with fluid and catecholamine resistant shock, irrespective of respiratory failure. Despite the lack of evidence from pediatric studies, the guidelines suggest against the use of etomidate for rapid sequence intubation in children with septic shock. The guidelines recommend against PRBC transfusion for those children who are hemodynamically stable and whose hemoglobin concentration is ≥7 g/dL.

Sepsis involves changes in microcirculation, and it is postulated that early recognition of these microcirculatory changes could lead to improved outcomes in pediatric sepsis. While measurements of serum lactate and central venous oxygen levels are invasive means to evaluate the microcirculatory changes, recent focus has been on noninvasive measures such as near infrared spectroscopy (NIRS). NIRS measures tissue oxygen saturation (StO2), which is an indirect measure of adequacy of microcirculation. Changes in StO2 precede changes in lactate and studies in adults have shown a correlation between StO2 levels and mortality. Further studies are needed on the role of NIRS and StO2 levels in risk stratification of children with sepsis.

PEDIATRIC SEPSIS IN RESOURCE LIMITED SETTINGS

There are significant differences in patient population, spectrum of disease and resource availability (pediatric intensive care unit beds, equipment such as infusion pumps, ventilators, lack of transport teams and support personnel such as radiology) between developed countries and developing countries that existing sepsis guidelines may not

be applicable in resource poor settings. The presence of malnutrition and diseases such as malaria and dengue warrant a less aggressive fluid resuscitation and use of a colloids rather than crystalloid [21]. An expert representative panel from the intensive care chapter of the Indian Academy of Pediatrics published sepsis guidelines keeping in view the unique patient population and limited availability of equipment and resources [22]. The recommendations call for rapid cardiopulmonary assessment and greater use of physical examination for achieving therapeutic endpoints. They summarized that interventions such as early oxygen therapy, aggressive fluid resuscitation and use of vasopressors through peripheral venous access in fluid refractory shock could be performed at the level of even primary and secondary health facilities rather than a pediatric intensive care unit, and can reduce mortality from pediatric sepsis.

FUTURE RESEARCH

Despite a large body of evidence on identification and management of pediatric sepsis, significant knowledge gaps still exist. Most of the current published literature on pediatric sepsis is based on observational studies and is predominantly from developed countries. Further, three fourths of the recommendations regarding management of pediatric sepsis from the Surviving Sepsis Campaign International Guidelines [19] were weak and based on low quality of evidence or just best-practice statements. Multicenter, prospective global studies are needed to provide robust evidence for management and interventions tailored to the patient population and resource availability to reduce morbidity and mortality from pediatric sepsis in various settings.

CONCLUSIONS

Pediatric sepsis continues to be a leading cause of morbidity and mortality in children. Early recognition and effective management are critical to reduce mortality and morbidity. A quality improvement focused approach with implementation of sepsis bundles with computerized decision support systems and additional clinician input can prevent delays in recognition and adherence to guidelines leading to improved outcomes in children with sepsis.

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RESEARCH PAPER

Comparison of Anthropometry and Body Composition Using Air Displacement Plethysmography in Term Small for Gestational Age and Appropriate for Gestational Age Neonates

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Background: Small for gestational age (SGA) neonates are prone to growth deficits in early life, which may be associated with later life metabolic abnormalities.

Objectives: To compare anthropometry and body composition using air-displacement plethysmography (ADP) in term SGA and appropriate for gestational age (AGA) neonates, and assess if sexual dimorphism existed in estimates of body composition.

Study design: Cross-sectional analytical study.

Participants: 413 term neonates (91 SGA and 322 AGA) at birth (≤7days).

Methods: Neonatal anthropometry and body composition were measured using ADP. Length corrected fat mass index (FMI) and fat free mass index (FFMI) were calculated.

Outcome: Anthropometry and body composition estimates of SGA and AGA neonates, segregated by sex.

Results: The mean (SD) birth weight of SGA and AGA neonates was 2.5 (0.2) kg and 3.1 (0.3) kg, respectively. SGA neonates had significantly lower % body fat (BF) (2.0%), fat mass (94.4 g), fat free mass (FFM) (349.7 g), FMI (0.34 kg/m^2), and FFMI (0.76 kg/m^2), but higher %FFM (2.0%) compared to AGA neonates (*P*<0.001). Males had significantly higher %FFM [91.2 (3.1) vs 90.2 (3.5); *P*=0.001], FFM [2604 (280) vs 2442 (233) g; *P*<0.001], and FFMI [11.1 (0.8) vs 10.8 (0.8) kg/m^2; *P*=0.005], but lower % BF [8.8 (3.1) vs 9.8 (3.5); *P*=0.001] and FMI [1.1(0.4) vs 1.2 (0.5) kg/m^2; *P*=0.008], compared to females.

Conclusions: Accurate estimates of body composition in neonates at birth suggest significantly lower body fat and fat free mass in SGA compared to AGA, with sexual dimorphism.

Keywords: *Body fat, Fat mass, Fat free mass, Growth*.

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Neonatal birth weight is often regarded as the primary indicator of intra-uterine growth and development; however, the quality of growth is better determined by estimating early-life body composition [1]. About 19.3% of neonates born in low- and middle-income countries (LMICs) are small for gestational age (SGA), classified by the INTERGROWTH-21st birth weight standard [2]. In India, the national prevalence of SGA is ~36.5% [3]. Neonates born SGA are likely to experience postnatal catch-up growth [4], with increased weight and length velocity, as a compensatory mechanism for reduced intrauterine growth. While the increased growth velocity is important in maximizing the neurological and immunological development [5], it could also predispose the neonates to developing later life non-communicable diseases (NCD) [5].

Existing epidemiological evidence suggests that metabolic abnormalities in later life may be linked to low birth weight [6], birth weight often being used as a marker. However, body composition measurements at birth and early life may be a better indicator of the nutritional status and functional capacity, to associate later life metabolic risk [2]. This is of particular relevance in the South-Asian population, like Indian neonates, postulated to be of the thin fat phenotype, having lower muscle mass and increased body fat, and being proportionally lighter, predisposing them to NCD in later life [7]. Sexual dimorphism in body composition has been observed in the Western population from fetal life and continuing postnatally [8]. Data regarding the same are limited in Indian neonates and infants.

The prediction equations using anthropometric indices and skinfold thickness to assess neonatal body composition may not be suitable for Indian infants, as most of the equations are derived from the Western population and are in poor agreement with criterion techniques [9]. Air-displacement plethysmography (ADP) is practical, accurate,

and safe method, and has been widely used in infants from Western population [10], and recently in India [11].

Body composition data of SGA and AGA Indian neonates using accurate methods are limited. Thus, the objective of the present study was to compare the anthropometry and body composition of term SGA and AGA neonates from southern India at birth, and to assess if there is sexual dimorphism in these parameters.

METHODS

Apparently healthy term neonates (37^{+0} to 41^{+6} weeks of gestational age), from singleton pregnancy of healthy mothers, were recruited from St. John's Medical College Hospital, Bengaluru between July, 2018 to December, 2022. Neonates with birth defects, congenital anomalies, and those requiring intensive hospital care were excluded. The study was approved by the institutional ethical review board of St. John's Medical College Hospital and written informed consent was obtained from the parents. The gestational age was based on the last menstrual period (LMP) of the mothers and the neonates were classified as SGA or AGA based on the INTERGROWTH-21st weight references [2].

The sample size was calculated using body composition data at birth, to observe a difference of 2.0% fat, with an SD of 3.4% between term AGA and SGA neonates [11], with 1% level of significance and 90% power. The required sample size for the present study was estimated to be 87 neonates in each group.

Details on maternal education and income were captured through a semi-structured questionnaire. Obstetric history, parity and pre-pregnancy weight, were obtained from hospital records. Maternal body weight and height were measured using standard methodology [12]. Maternal gestational weight gain was calculated as the difference in body weight between first trimester and third trimester (weight was measured at the last antenatal visit of the mother-2-3 days before delivery).

The following measurements were performed on the neonates at birth. The birth weight and weight on the day of measurement (≤7 days after birth) of the neonates were measured using a calibrated pediatric electronic weighing scale, with an accuracy of 10 grams (Salter 914), length was measured using an infantometer (SECA 417), and head circumference was measured using non-stretchable fiberglass tape (ADC 396) to the nearest 0.1 cm according to World Health Organization (WHO) methodology. All measurements were performed by trained personnel and the inter-observer and intra-observer difference was ≤0.1%.

Body composition was assessed using PEA POD infant body composition system (Software version 3.5.0, 201, COSMED), using the principle of ADP. The PEA POD system measures body volume, which along with measured body weight, is used to calculate body density based on the densitometry principle. The neonate was weighed naked, on an electronic scale, followed by body volume measurement, in a temperature and pressure-calibrated chamber. The neonate's hair was kept flat using a tight cap to avoid body surface artefacts during measurement. From the two-compartment model, using the principle of densitometry, the percent body fat (%BF) was computed, using the assumed density of fat mass (FM) as 0.9007 g/mL and values for density of fat-free mass (FFM) from published literature [13]. Other body proportions, FM (g) as (weight (g) × %BF), %FFM as (100- %BF), and FFM (g) as (weight (g) – FM) were also estimated. Daily calibration and quality checks were performed by measuring a hollow cylinder of known mass (2 kg) and volume (3 litre), and the precision estimate was 0.07% in our laboratory. Height-adjusted body composition indices; fat mass index (FMI) ($kg/m^{2)}$ and fat-free mass index (FFMI) (kg/m^2) were calculated for FM and FFM.

Statistics analysis: Assumptions of normality were tested using Q-Q plot. Data were presented as mean (SD) for maternal age, gestational age, age of the neonate, anthropometry and body composition parameters and as percentage for categorical variables. Independent sample *t* test was used to compare the anthropometry and body composition parameters between SGA and AGA neonates, and between both sexes. Pearson Chi-square tests were used to test the association between SGA and AGA neonates for categorical variables such as education, income, mode of delivery, parity and sex. Analysis of covariance (ANCOVA) was performed to assess the group effect (SGA and AGA group), sex effect and interaction effect (group x sex) for anthropometry and body composition parameters. Multiple linear regression was performed to determine the association of body composition parameters with SGA and AGA categories, adjusted for sex, maternal age, pre-pregnancy BMI and *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26.0 (SPSS Inc).

RESULTS

A total of 91 (37 males) SGA and 322 (147 males) AGA babies were enrolled. The maternal and neonatal characteristics of SGA and AGA neonates are compared in **Table I**. Neonates from both the groups were predominantly born to primiparous mothers (65.9% and 63.7% in SGA and AGA neonates, respectively).

The comparison of body composition parameters between SGA and AGA neonates is depicted in **Fig.1**. The group and sex-wise comparison of anthropometry and body

Table I Maternal and Neonatal Characteristics of Term Small for Gestational Age (SGA) and Appropriate for Gestational Age (AGA) Neonates

Parameter	*SGA(n=91)*	*AGA(n=322)*	*P value*
Maternal age (y)	25.4 (4.5)	26.3 (4.3)	0.116
Maternal weight (kg)	57.7 (11.1)	63.3 (11.0)	<0.001
Maternal height (cm)	152.2 (5.4)	154.6 (5.3)	<0.001
Maternal pre-pregnancy BMI (kg/m^2)	24.5 (4.8)	26.5 (4.2)	<0.001
Gestational weight gain (kg)	11.3 (4.3)	12.0 (4.6)	0.373
Cesarean delivery [a]	27(30.7)	128 (40.5)	0.245
Male sex[a]	37 (40.7)	147 (45.7)	0.397
Gestational age (d)	273.5 (6.2)	272.2 (6.5)	0.198
Birthweight (kg)	2.5 (0.2)	3.1 (0.3)	<0.001
Weight (kg)[b]	2.4 (0.2)	2.9 (0.3)	<0.001
Length (cm)	46.5 (1.3)	48.3 (1.5)	<0.001
Head circumference (cm)	32.5 (1.1)	33.7 (1.2)	<0.001

Data shown as mean (SD) or [a]no.(%). [b]weight on day of measurement; BMI: body mass index.

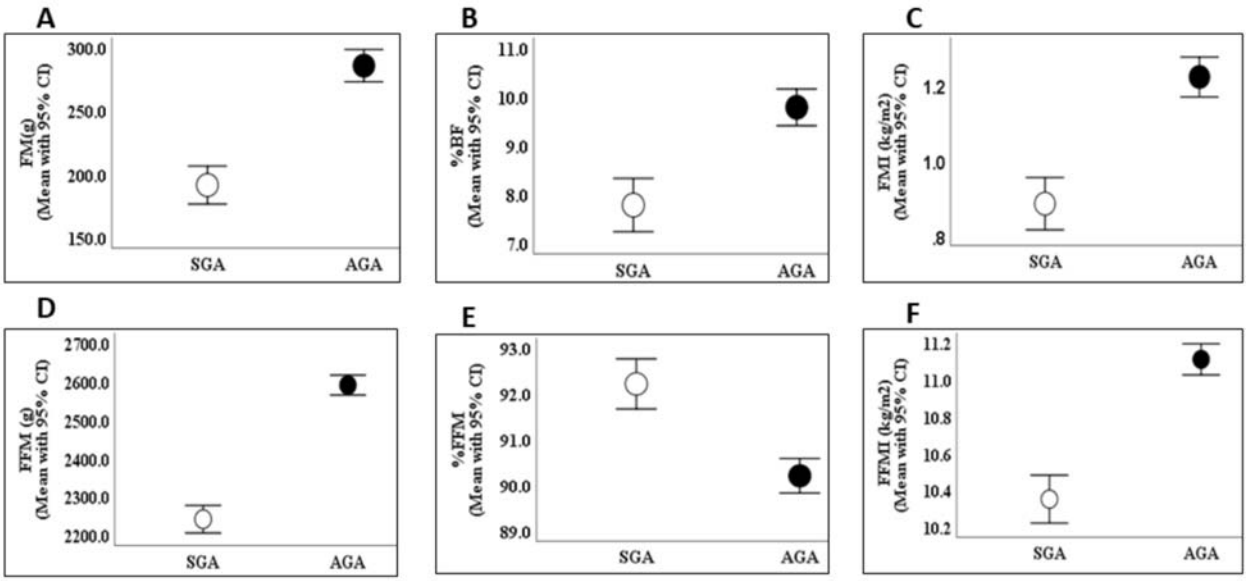
composition is presented in **Table II**. Significant group effect (comparison of SGA vs AGA neonates) was noted for all anthropometric and body composition parameters, with higher mean values in AGA neonates. Except for FM and FFMI, significant sex effect was seen for all the other anthropometric and body composition parameters. However, other than the birthweight, there was no significant interaction effect between the groups by sex.

The results from the unadjusted and adjusted regression models for the association of body composition parameters with SGA and AGA groups are presented in **Table III**. A neonate born SGA had 1.89 units lower %BF, 89.1 g lower FM, 335.7 g lower FFM, 0.32 units lower FMI (kg/m^2), 0.71 units lower FFMI (kg/m^2) and 1.89 units higher %FFM, when compared with the AGA group (*P* value <0.01).

DISCUSSION

The present study provides accurate measurements and comparisons of body composition of term SGA and AGA Indian neonates. Findings of the study suggest that SGA neonates have significantly lower body fat and fat free mass when compared to AGA neonates. Female neonates had significantly lower %FFM and FFM (g), but higher %BF and FMI (kg/m^2) when compared to the males.

A significantly lower FM (g), %BF and FFM (g) were observed, when measured using dual energy *X*-ray absorptiometry (DXA), in term SGA neonates (mean birthweight 2480g) compared to AGA neonates (mean birthweight 3227g) in a study conducted in France [14]. Similar trends of lower %BF in term SGA were observed in Indian infants using measurements of skinfold thickness [15]. The INTERGROWTH-21st study showed that the body composition estimates among SGA neonates; both preterm and term were significantly lower when compared to AGA neonates using ADP [16]. Length normalized indices of FMI and FFMI are useful as they provide weight independent index of body composition; late preterm (34^{+0} to 36^{+6} weeks



FM: fat mass (g); % BF: percent body fat; FMI: fat mass index (kg/m^2); FFM: fat free mass (g); %FFM: percent fat free mass; FFMI: fat free mass index (kg/m^2); AGA: appropriate for gestational age; SGA: small for gestational age.

Fig. 1 Comparison of body composition parameters between SGA and AGA neonates.

Table II Anthropometry and Body Composition Using Air Displacement Plethysmography (*N*=413)

Parameter	*Pooled estimate*		*Small for gestational age (SGA)*		*Appropriate for gestational age (AGA)*		*P value*[b]
	Male (n=184)	*Female (n=229)*	*Male (n=37)*	*Female (n=54)*	*Male (n=147)*	*Female (n=175)*	
Birthweight (kg)	3.0 (0.4)	2.9 (0.3)	2.5 (0.2)	2.5 (0.2)	3.2 (0.3)	3.0 (0.3)	0.002
Weight (kg)[a]	2.9 (0.3)	2.7 (0.3)	2.5 (0.2)	2.4 (0.2)	3.0 (0.3)	2.8 (0.3)	0.002
Length (cm)	48.5 (1.7)	47.4 (1.5)	47.0 (1.3)	46.2 (1.2)	48.8 (1.5)	47.8 (1.4)	<0.001
Head circumference (cm)	33.9 (1.2)	33.0 (1.2)	32.9 (1.2)	32.3 (1.1)	34.2 (1.0)	33.2 (1.1)	<0.001
Percent body fat	8.8 (3.1)	9.8 (3.5)	7.0 (2.1)	8.3 (2.8)	9.2 (3.2)	10.3 (3.6)	0.002
Percent fat free mass	91.2 (3.1)	90.2 (3.5)	93.0 (2.1)	91.7 (2.8)	90.8 (3.2)	89.7 (3.6)	0.002
Fat mass (g)	256 (110)	273 (119)	174 (63)	203 (76)	276 (110)	294 (121)	0.069
Fat free mass (g)	2604 (280)	2442 (233)	2288 (198)	2210 (147)	2689 (238)	2513 (206)	<0.001
Fat mass index (kg/m^2)	1.1 (0.4)	1.2 (0.5)	0.8 (0.3)	1.0 (0.4)	1.2 (0.4)	1.3 (0.5)	0.007
Fat free mass index (kg/m^2)	11.1 (0.8)	10.8 (0.8)	10.4 (0.6)	10.3 (0.6)	11.2 (0.8)	11.0 (0.7)	0.144

Values are mean (SD). [a] Weight measured on the day of body composition assessment. [b] P value for sex effect.

Table III Multiple Linear Regression Model Showing the Association of Body Composition Parameters in SGA/AGA

Parameter	*Adjusted β coefficient*	*P value*
Percent body fat	-1.89 (-2.69, -1.09)	<0.001
Percent fat free mass	1.89 (1.09, 2.69)	<0.001
Fat mass (g)	-89.1 (-115.7, -62.6)	<0.001
Fat free mass (g)	-335.7 (-388.3, -283.1)	<0.001
Fat mass index (kg/m^2)	-0.32 (-0.43, -0.21)	<0.001
Free fat mass index (kg/m^2)	-0.71 (-0.89, -0.52)	<0.001

Adjusted for sex, maternal age, and pre-pregnancy. SGA: small for gestational age; AGA: appropriate for gestational age; BMI: body mass index.

gestational age) SGA neonates had lower FMI when compared to full-term AGA neonates [17]. Contradictory to these findings, the FMI and FFMI measured using deuterium dilution of term AGA and SGA neonates from northern India were comparable [18], and the % body fat of SGA infants in the northern Indian cohort was higher than the present study. Few factors may have contributed to it. The infants of the present cohort were measured close to birth, while the infants were measured at 12.7 (3.1) days in the previous study [18]. The body weight and body composition may change rapidly, notably during the first week of life [19]. Differences in maternal characteristics, birth weight, socioeconomic status may have also played a role. Additionally, two different body composition methods were used in these studies. Future studies standardizing the methods, day of measuring, population and other factors that may confound the results, need to be conducted in order to examine if there was an effect of ethnicity on the body composition estimates among Indian neonates.

There are several factors, including genetics, fetal conditions, maternal nutrition, and environment, which may contribute to lower FM and FFM in SGA neonates [5]. A recent systematic review summarizing the body composition estimates in neonates born with intra-uterine growth restriction (IUGR), observed that SGA neonates had similar pattern of body composition as IUGR [20]. Lower body FM in early childhood is associated with early adiposity rebound, predisposing to late life obesity [21]. In infants born with IUGR or SGA, inadequate growth during fetal and early life may result in permanently constraining their FFM growth, limiting metabolic capacity to endure a rich diet and probably contributing towards metabolic complications in adult life [22]. Thus, the low fat and fat free mass observed in the SGA Indian neonates of the present study at birth may be a matter of concern, as neonates having reduced birthweight experience rapid catch-up growth by two years of life [23], and are more likely to develop central adiposity and fat progression during adulthood [5]. Longitudinal studies with accurate measurements of body composition and careful characterization of dietary and lifestyle patterns in early infancy are warranted to better understand and plan interventions to prevent risk of later life NCD.

Sexual dimorphism at birth in body composition estimates using ADP has been previously reported [10,11,16], with males having higher %FFM estimates compared to females, similar to the present study. The postulated reasons could be fetal sex-specific influence on maternal, placental and fetal expression during the intrauterine life. Among the placental factors, the placental size and placental biomarkers in maternal circulation have been positively associated with fetal growth [24-25]. Maternal metabolic state, maternal circulating hormones

WHAT IS ALREADY KNOWN?

- Small for gestational age (SGA) neonates are lower in birth weight and anthropometric measurements when compared to appropriate for gestational age (AGA) neonates.

WHAT THIS STUDY ADDS?

- SGA neonates had significantly lower fat and fat free mass when compared to AGA neonates at birth.
- Sexual dimorphism exists in body composition among SGA and AGA neonates.

such as glucocorticoids and adiponectin with several other complex epigenetic mechanisms linked to fetal sex hormones, may have an influence on intrauterine growth and body composition [25].

The limitation of the study was that gestational age was computed using LMP, instead of first trimester ultrasound. This study was conducted in infants from middle income families of urban Bangalore, and needs to be extended to different regions across the country to confirm the findings.

In conclusion, this study presents accurate estimates of body composition at birth of SGA and AGA neonates from urban southern India, that provide important insights into the quality of intrauterine growth. These findings can inform the planning and interpretation of longitudinal studies aiming to understand the mechanisms underlying metabolic programming in Indian neonates.

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Contributors: RP: Involved in conducting the research, data collection, prepared the original draft of the manuscript; SRP: Involved in conducting the research and reviewing the draft of the manuscript; SS: Performed statistical analysis, interpretation of findings and reviewed the draft; RK: Conceptualized, designed and supervised the research, interpretation of results, critically reviewed and edited the draft and has primary responsibility for the final content, and all authors have read and approved the final manuscript.
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RESEARCH PAPER

Effect of Oral Zinc Supplementation on Serum Bilirubin Levels in Term Neonates With Hyperbilirubinemia Undergoing Phototherapy: A Double-blind Randomized Controlled Trial

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Background: Enterohepatic bilirubin circulation is one of the determinants of neonatal jaundice.

Objective: To evaluate the role of oral zinc in reducing serum bilirubin in term neonates with hyperbilirubinemia.

Study design: Double-blind, randomized, placebo-controlled trial

Participants: 106 term neonates with jaundice within the phototherapy range admitted to a level III neonatal intensive care unit.

Intervention: Neonates were randomized and allocated to receive either oral zinc sulfate (5 mg/day) or matching placebo for 5 days. Both groups received conventional phototherapy as per American Academy of Pediatrics (AAP) guidelines.

Outcomes: *Primary*: Reduction in total serum bilirubin levels at 24, 48, 72, and 96 hr after intervention.

Secondary: Duration of phototherapy, and hospital stay.

Results: The mean (SD) total serum bilirubin levels in zinc and placebo groups were 15.3 (2.85) vs 17.1 (2.21) mg/dL (MD 1.74; *P*<0.001) at 24 h; 11.7 (4.46) vs. 14.62 (3.83) mg/dL (MD 2.89; *P*<0.001) at 48 h; 6.7 (4.77) vs 9.5 (3.70) mg/dL (MD 2.79; *P* <0.001) at 72 h; and 5.1 (3.95) vs 6.5 (3.70) mg/dL (MD 1,49; *P*=0.045) after 72 hr, respectively. The mean (SD) duration of phototherapy was significantly lower in zinc group than placebo group [53.42 (19.62) vs 71.4 (19.43) h; *P*<0.001]. There was no significant difference in hospital stay between the two groups [mean (SD) 81.05 (19.43) vs 86.25 (20.02) h; *P*= 0.227].

Conclusion: Oral zinc sulfate supplementation at a dose of 5 mg once a day along with phototherapy significantly reduced total and indirect serum bilirubin levels and also reduced the total duration of phototherapy required in the term neonatal hyperbilirubinemia, with minimal or no adverse effects.

Keywords: *Duration, Outcome, Prevention, Supplementation*.

Trial Registration: CTRI: 2018/08/015245.

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Enterohepatic bilirubin circulation (EHC) contributes significantly to neonatal hyperbilirubinemia, and its blockage might be a therapeutic target for this condition. EHC may be exaggerated in the neonatal period, in part because the newborn intestinal tract is not yet colonized with bacteria that convert unconjugated bilirubin (UCB) to urobilinogen. Various substances have been used to bind bilirubin in the intestinal lumen to resist its absorption and prevent enterohepatic circulation [1]. Oral zinc salts flocculate at physiological pH and adsorb unconjugated bilirubin from unsaturated micellar bile salt solutions [2]. This adsorption reduces the enterohepatic circulation of bilirubin, leading to enhanced excretion through stool, thus decreasing the serum bilirubin level. An experimental study in hamsters showed that zinc salts fully absorbed unconjugated bilirubin [3]. The only human study that evaluated the role of zinc salts in the treatment of jaundice in Gilbert syndrome demonstrated that acute and chronic oral administration of zinc causes significant decreases in serum unconjugated bilirubin levels [3].

Based on the available data from animal and adult human studies [3,4], it seems plausible that oral zinc salts may reduce incidence of hyperbilirubinemia and need for phototherapy and exchange transfusion in jaundiced neonates. However, various studies conducted on term neonates to study the effect of zinc salts on serum bilirubin have shown inconclusive results [4,5]. In contrast to this finding, a recent randomized controlled trial (RCT) on preterm neonates showed a significant reduction in serum bilirubin levels within 48 hours of zinc treatment [6]. We, therefore, evaluated the efficacy, safety and dosage of oral zinc sulfate in the reduction of hyperbilirubinemia, duration of phototherapy, and hospital stay in term neonates admitted to the neonatal intensive care unit (NICU).

METHODS

This randomized, double-blind, placebo-controlled clinical trial was conducted in the NICU of a tertiary care government hospital in Maharashtra from December, 2017 to April, 2019. Term neonates admitted to NICU with jaundice in the

phototherapy range [7] were enrolled. Preterm neonates, neonates with direct hyperbilirubinemia, systemic illness, severe sepsis, laboratory evidence of hemolysis at enrolment, severe respiratory disease requiring mechanical ventilation, oral intolerance, major gross congenital anomalies (gastrointestinal malformations, heart defects, neural tube defects and with identifiable genetic syndromes), and patients who refused to stay for the study duration were excluded from the study. The institute's ethics committee approved this research, and trial registration was done.

A minimal sample size of 76 (38 in each group) was calculated using Open EPi software. This allocated sample can detect the reduction of at least 1.6 mg/dL reduction in the mean total serum bilirubin level [8] in the zinc supplementation group compared to the control group with a 95% confidence interval and 95% power. To account for loss to follow-up, 53 newborns were enrolled in each group.

All term neonates admitted to the NICU for hyperbilirubinemia were screened and assessed for eligibility, and those meeting the above inclusion criteria were enrolled. Demographic information such as mode of delivery, birth weight, gestational age, gender, and type of feeding was collected from medical records. Laboratory assessments included complete blood count, red blood cell morphology, blood group of mother and baby, glucose-6-phosphate dehydrogenase (G6PD) level, and serum total, direct and indirect bilirubin levels.

Neonates were allocated into two groups, the Zinc group and the Placebo group, by generating random sequence using permutated blocks of 8 each. Allocation concealment was achieved using sequentially numbered opaque sealed envelopes and was done by a researcher who was not involved in the drug administration or assessment. Blinding and randomization was done by a researcher who was not involved in the management of the babies.

Neonates in both the groups received phototherapy. The phototherapy devices were the same in both groups and calibrated for each patient. Single surface phototherapy was provided in both groups using a Brilliance PRO Phoenix device equipped with 9 LED bulbs at a distance of 25 cm from the body surface, and at a minimum radiation intensity of 30 μW/cm^2/nm. In addition to phototherapy, the Zinc group received 5 mg elemental zinc i.e., 0.25 mL (syrup containing 20 mg/mL zinc sulfate; Dr Reddy's Laboratories limited). Placebo group received 0.25 mL solution (22.5 g sucrose added to 450 mL distilled water (5% sucrose) and placed in the percolator by the hospital pharmacy). The placebo and zinc sulfate bottles were identical in volume, color, appearance, and packaging. A syringe was used for oral administration. Zinc and placebo syrups were coded and blinded to the participants, investigator, and statistician until the analysis was completed. Nurses administered the drug upon the researcher's prescription. It was explained to guardians that we would discontinue the medication and provide appropriate treatment if any adverse effects like retching, vomiting, abdominal distension, diarrhea, skin rash, and irritability occur. As our study participants were term neonates, we provided breast milk and spoon feeds on demand during phototherapy. Hence, we administered intermittent phototherapy as per unit policy.

A checklist was used to gather information about the infant, including the type of drug used and bilirubin levels. The enrolled neonates were assessed twice daily. The intervention continued until the fifth day. Phototherapy was discontinued when the bilirubin level decreased to levels below the phototherapy range as per American Academy of Pediatrics (AAP) guidelines. Serum total and indirect bilirubin levels were monitored before the intervention and at the onset of phototherapy, and at 24 hour, 48 hour, 72 hour and 96 hour of intervention, and thereafter as per requirement. The duration of treatment was calculated from the day of commencement to the end of phototherapy. The rate of reduction of serum total and indirect bilirubin levels, duration of phototherapy, and length of hospital stay were recorded for the zinc and placebo groups. We also solicited and recorded adverse effects like vomiting, skin rash, diarrhea, and excessive cry between two groups.

Statistical analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 24. Chi-square test was applied to check the significance of association between two attributes. Moreover, data analysis was performed using the independent sample *t* test, repeated measures of ANOVA, and post hoc test. *P* values of <0.05 were considered statistically significant, and analysis was based on intention to treat.

RESULTS

During the study period, 296 neonates who were admitted to our tertiary care NICU with jaundice were assessed clinically for eligibility. Among these, 190 neonates were excluded (83 were preterm, 10 had direct hyperbilirubinemia, 76 had severe sepsis, 8 required mechanical ventilation and 13 refused consent). We randomly allocated 106 neonates to receive zinc (*n*=53) or placebo (*n*=53) with phototherapy. One patient in study group was discharged against medical advice on day 3 of treatment after randomization and analysis was based on intention to treat. **Fig. 1** shows the flow of study participants. Both the groups were comparable for birth weight, gestational age, gender, mode of feeding, mode of delivery, age at intervention, and initial laboratory parameters (**Table I**).

There was a significant difference between the mean change in bilirubin levels The mean (SD) total serum

Table I Baseline Characteristics of Study Participants

Parameters	*Zinc group (n=53)*	*Placebo group (n=53)*
Age at enrolment (h)[a]	92.705 (0.15)	87.85 (34.89)
Onset of jaundice after birth (h)[a]	65.8 (29.1)	55.8 (24.4)
Female gender	27 (51)	23 (43)
Normal vaginal delivery	42 (79)	33 (62)
Exclusive breastfeeding	35 (66)	23 (43)
Birthweight (g)[a]	2809 (326.74)	2755 (363.78)
DCT positive	6.5.66	8.7.55%
Reticulocyte count (%)[a]	2.69 (1.4)	2.49 (1.5)
Hemoglobin (g/dL)[a]	15.01 (1.60)	14.8 (1.13)

Values in no. (%) or [a]mean (SD). DCT: direct Coomb test.

bilirubin levels in zinc and placebo groups were 15.3 (2.85) vs 17.1 (2.21) mg/dL (Mean difference (MD) 1.74; $P<0.001$) at 24 hour; 11.7 (4.46) vs 14.62 (3.83) mg/dL (MD 2.89; $P<0.001$) at 48 hour; 6.7 (4.77) vs 9.5 (3.70) mg/dL (MD 2.79; $P=0.001$) at 72 hour; and 5.1 (3.95) vs 6.5 (3.70) mg/dL (MD 1.49; $P=0.045$) after 72 hours, respectively. The mean bilirubin decreased from 19.11 to 5.06 µg/dL in the zinc group, and from 18.57 to 6.55 µg/dL in the control group **(Fig. 2)**

The mean (SD) duration of phototherapy required in the zinc group was less than the placebo [53.42 (19.62) vs 71.41 (19.43) hour; $P<0.001$], while there was no significant difference in the two groups in terms of mean (SD) duration of hospital stay [81.05 (19.43) vs 86.25 (20.02) hour; $P= 0.227$].

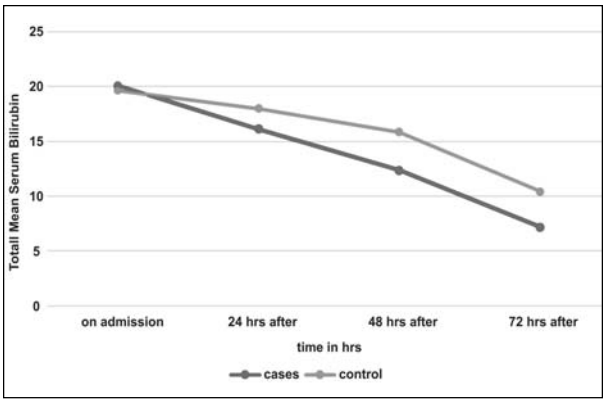

Fig. 2 Comparison of total mean serum bilirubin level of the neonates in the zinc and placebo groups.

There were no significant side effects in either group, and only one patient had vomiting on the third day of treatment in the zinc group, which improved subsequently.

DISCUSSION

The present study demonstrated that zinc supplementation at a dose of 5 mg/day (RDA) for 5 days, along with phototherapy, can significantly reduce total serum bilirubin levels in term neonates. The duration of phototherapy was also less in neonates who received zinc compared to the placebo group. None of the neonates had any significant side effects of zinc sulfate syrup.

Many previous studies support the results obtained in the present trial [3,6,8,9]. Mendez-Sanchez, et al. [3] gave single

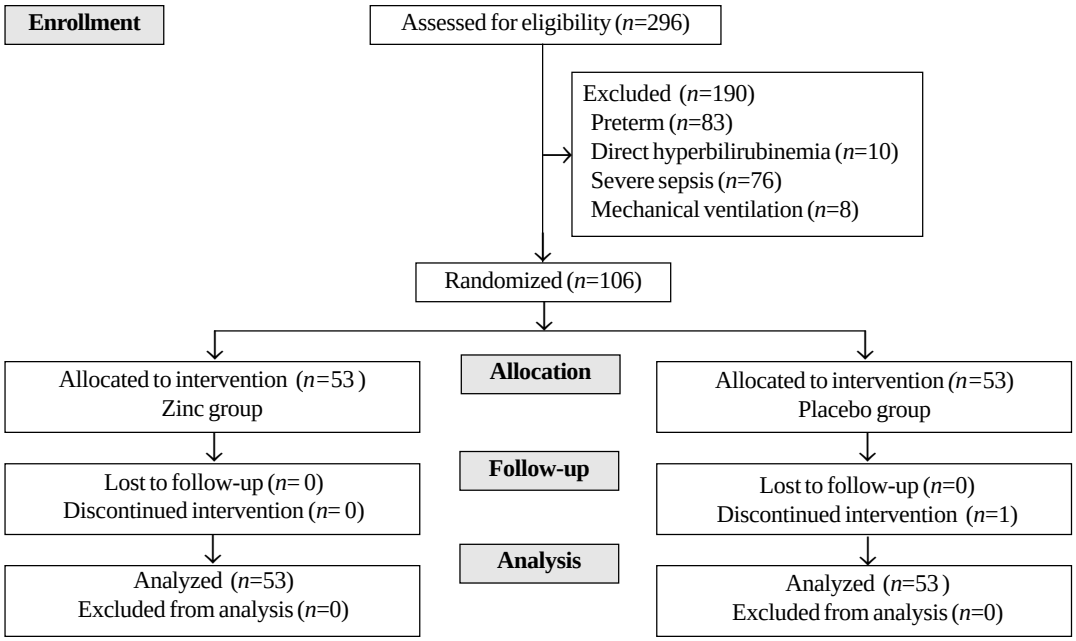

Fig. 1 Flow of participants in the study.

Table II Serum Bilirubin Levels at Admission and at Various Time Intervals After Intervention

Parameters	*Zinc group*	*Placebo group*	*MD (effect size)*	*P value*
At admission	19.11 (2.160)	18.57 (2.144)	0.54	0.195
At 24 hr of intervention	15.34 (2.854)	17.083 (2.213)	1.74	<0.001
At 48 hr of intervention	11.731 (4.461)	14.620 (3.829)	2.889	<0.001
At 72 hr of intervention	6.691 (4.773)	9.485 (3.704)	2.794	0.001
At 96 hr of intervention	5.066 (3.95)	6.555 (3.7042)	1.489	0.046

Values in mean (SD).

dose oral zinc sulphate at 100 mg daily for 7 days to adult, patients with chronic form of Gilbert syndrome. They showed a significant decrease in serum bilirubin levels after 24 hours in their subjects. In a randomized controlled trial conducted by Hashemian, et al. [8], where the therapeutic effect of zinc sulfate on neonatal hyperbilirubinemia in term neonates was evaluated, mean total serum bilirubin levels were significantly lower in the zinc group. Similarly, a recent randomized controlled trial [6] showed that the use of zinc sulphate syrup in preterm neonates with indirect hyperbilirubinemia significantly reduced serum bilirubin levels within 48 hours of treatment. Two other trials showed similar results [9,10]. On the other hand, there are many studies conducted for prophylactic zinc use in neonatal jaundice with inconsistent results [1,7,11-13].

Some studies [2,4,14] do not support the results of our study, with one showing effect of oral zinc on hyperbilirubinemia on LBW premature neonates being significant only at 24 hour after treatment. The cause of the discrepancy between these mentioned studies and the present study might be the gestational age of participants, zinc dosage, delayed release of zinc to reach the active area, and small sample size in this study.

Previous studies have either found no effect of oral zinc on phototherapy duration [4,5], or have shown shorter duration with zinc supplementation [1,8,12]. The reduced duration of phototherapy may be attributed to the fact that prolonged use is associated with diarrhea and a decrease in the enterohepatic cycle, which can result in a decrease in serum bilirubin levels. A systematic review and meta-analysis by Yang, et al. [15] also showed zinc sulfate resulted in significantly decreased duration of phototherapy.

The limitations of the study were that it included only term neonates with uncomplicated jaundice, thereby excluding neonates at high risk of hyperbilirubinemia. Additionally, we could not measure serum zinc levels before and after intervention.

In view of the positive results obtained from oral zinc on the reduction of serum bilirubin in term neonates in this study, further studies with different dosages and formulations of zinc, and more precise laboratory studies (zinc level), including neonates with complicated jaundice are recommended.

Acknowledgement: Dr Prashant Patil, Ex-Professor of Pediatrics, GMC Aurangabad, for his valuable guidance and support.
Ethic clearance: IEC-Government Medical College, Aurangabad; No. 426/2017, dated Oct 23, 2017.
Contributors: THM: data collection, data analysis and interpretation, drafting the article; SMM: conception and design of the work, supervised the study, revived literature and critical revision of the article; PKG: data interpretation and drafting the article: NR: data analysis interpretation and drafting of manuscript; PK, TJ, SP: critical revision of article. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.

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WHAT IS ALREADY KNOWN?

- In animal models and adult human studies, oral zinc has been used for hyperbilirubinemia with inconsistent results.

WHAT THIS STUDY ADDS?

- Oral zinc sulphate supplementation at a dose of 5 mg once a day along with phototherapy can significantly reduce total and indirect serum bilirubin levels, and also help in reducing the total duration of phototherapy required in the term neonates with hyperbilirubinemia.

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NOTICE FOR ANNUAL GENERAL BODY MEETING OF INDIAN ACADEMY OF PEDIATRICS

Notice is hereby given that the Annual General Body Meeting of Indian Academy of Pediatrics for 2024 is scheduled to be held on 26th January, 2024, during 61st IAP Pedicon at Lulu Bolgatty International Convention Centre, Grand Hyatt, Kochi (Kerala) from 5:00 PM onwards, to consider the following agenda:

AGENDA

1. Welcome note and information of Executive Board Members 2024.
2. Obituary.
3. Confirmation of the minutes of the Annual General Body Meeting held on 21st February, 2023 at Gandhinagar (Gujarat).
4. Business arising out of the minutes.
5. Consideration and adoption of Annual Report of the Society.
6. Consideration and adoption of the audited Statement of Accounts for the year ended 31st March, 2023, and the Budget for the year 2024-2025.
7. Appointment of Auditors and fixing their remuneration for 2024-25.
8. Appointment of Honorary Legal Advisor for 2024-25.
9. Consideration of matters related to IAP Election for 2025.
10. Matters related to 62nd National Conference (IAP Pedicon 2025).
11. Any other business, notice of which has been circulated with the agenda.
12. Any other business of which 30 days' notice has been given to the Secretary General in writing.
13. Any other business with the permission of the chair.

Note:

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

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

Kindly make it convenient to attend the meeting.

With kind regards,

Dr Upendra Kinjawadekar President, IAP 2023	Dr GV Basavaraja President, IAP 2024	Dr Vineet K Saxena Secretary General, 2022 & 2023

Place: Navi Mumbai
Date: November 02, 2023

RESEARCH PAPER

Accuracy of Advanced Pediatric Life Support Intubation Depth Formula in Indian Children Aged 1 to 12 Years

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Objective: To evaluate the accuracy of the Advanced Pediatric Life Support (APLS) endotracheal tube (ET) depth formula in Indian children aged 1 to 12 years. **Methods:** We enrolled 86 children aged 1-12 years requiring intubation and ventilation. The ET depth was determined using the APLS formula, and chest *X*-rays were utilized to evaluate 'appropriate ET depth (accuracy)' based on 'vertebral level criteria' and 'safe distance between ET tip and carina.' **Results:** Out of 86 cases, none had bronchial intubation. An accuracy of 37.2% (32 cases) was observed, with 57% (49 cases) showing deep placement. Among deep placements, 11 met 'vertebral level criteria' but not 'safe distance criteria.' Redefining deep placement based solely on 'safe distance criteria,' resulted in 50% accuracy. **Conclusion:** APLS formula effectively prevents bronchial intubation in Indian children, but tends to overestimate ET depth (50% cases) when considering the 'safe distance between ET tip and carina.'

Keywords: *Chest X-ray, Endotracheal tube depth, Safe distance.*

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Endotracheal intubation is a life-saving procedure commonly performed in the emergency and intensive care settings. Appropriate depth placement of the endotracheal tube (ET) in mid-trachea is important. If the ET is placed too shallow, it can cause accidental extubation and injury to the vocal cords and subglottis [1]. Placing too deep can result in endobronchial intubation, increasing the risk of barotrauma and pneumothorax of intubated lung; and atelectasis and collapse of the opposite lung [1,2]. In addition, neck movements during patient handling can also affect the placement of the ET, causing it to move downwards and upward with neck flexion and extension, respectively [3]. In children, the placement of the ET requires even more precision due to varying tracheal lengths [4].

Several formulas are used to estimate the depth of ET placement, such as the Advanced Pediatric Life Support (APLS) formula [5-7]. Among these, the APLS formula is most commonly used in the pediatric emergency and intensive care; although, its accuracy has not been tested in Indian children. After intubation, the placement of ET is confirmed through clinical methods [8]; although, a chest *X*-ray is the gold standard for confirming the exact position of the ET tip in the trachea [9].

Studies evaluating the accuracy of the APLS-ET depth formula are limited in literature and have shown inconsistent results, with most being retrospective in nature. This study aimed to evaluate the accuracy of the APLS ET depth formula as measured by 'appropriate ET depth placement' in Indian children aged 1 to 12 years.

METHODS

This analytical cross-sectional study was conducted in the pediatric intensive care unit (PICU) of a tertiary care center between November, 2019 and August, 2021, with the study protocol approved by the institution's ethics committee. Informed consent and assent, was collected from participants or their guardians in accordance with ethical guidelines. The study population comprised children aged 1 to 12 years who required intubation and mechanical ventilation for various medical conditions. Children with known or suspected airway, vertebral, facial, or chest wall anomalies, skeletal dysplasia, short-necked syndromes (such as Down syndrome or Noonan syndrome), dysmorphism, and poor *X*-ray image quality were excluded from the study. The primary outcome measure for the accuracy of the APLS depth formula was 'appropriate ET depth placement.'

The study utilized the following definitions and formulas. The APLS formula used to estimate ET depth was [5]: "Distance between ET tip and angle of mouth (cm) = Age (years)/2 + 12." 'Appropriate ET depth placement' was

defined as ET tip placed in the mid-trachea and at a safe distance away from the carina. 'Mid-trachea position' spanned from the interspace between the first and second thoracic vertebrae (T1-T2 interspace) to the second and third thoracic vertebrae (T2-T3 interspace) [7]. The 'safe distance between ET tip and carina' was derived from a linear correlation between 'ET descent on neck flexion' and age, using the formula: "Safe distance between ET tip and carina (mm) = 0.83 × Age (years) + 9.3" [3]. To prevent endobronchial intubation or ET impingement on the carina during inadvertent neck flexion movements while handling sick patients, it is important to maintain this distance. 'Shallow ET' placement' was defined as ET tip positioned above the T1-T2 interspace, while 'Deep ET placement' was defined as ET tip positioned below the T2-T3 interspace or ET tip to carina distance less than the safe distance.

After intubation, the ET depth was placed according to the APLS formula [5], and the corresponding ET depth mark was positioned at the right angle of the mouth. Prompt visual inspection and auscultation of the chest were done to ensure accurate tracheal placement. Instances of bronchial intubation, identified by unilateral absent air entry resolved upon ET withdrawal, were classified as 'deep ET placement.' Post-intubation, a bedside supine digital chest *X*-ray (AP view) was obtained using a portable *X*-ray machine. The ET depth mark at the angle of the mouth was rechecked at the time of the *X*-ray to rule out any ET displacement between the time of intubation and the time of imaging.

Precautions were taken during the *X*-ray including a supine position (with the bed fully horizontal), neutral and centered neck position, computed radiography (CR) plate placed to capture the chest and lower cervical spine, *X*-ray beam positioned perpendicular to the patient, and *X*-ray exposure given during the inspiratory phase of the ventilator breath. Confirmation of the neutral neck position relied on the lower mandible border lying between cervical vertebrae 4 to 6 (C4-C6) [7]. The CR system (AGFA 85-X CR Digitizer) and Radiant Dicom viewer were used to analyze the *X*-ray images on a computer. Parameters, including the distance between the ET tip and the carina, ET tip relation to the vertebral column, and outer diameter (OD) of the ET, were measured to the nearest 0.1 mm. Three readings were taken for each parameter by three different observers, and the average was used for analysis.

To determine the 'actual distance between the ET tip and the carina,' first, the ratio of the OD of the ET (seen on the CR image) to the actual OD of ET (mentioned on the ET pack) was calculated to eliminate any parallax error caused by the spread of *X*-rays. The formula used to determine the actual distance was: "Actual distance between ET tip and carina (in mm) = (Actual ET OD) / (ET OD on CR) x (ET tip to carina distance on CR)." Based on this distance and the ET tip's position in relation to the vertebral column, ET placements were categorized as appropriate, shallow, or deep according to the definitions provided.

The minimum sample size for this study was estimated using the formula: $n = (z)^2 \times p \times (1-p)/d^2$. In a previous study by Zhou, et al. [10], the accuracy of the APLS formula was found to be 66.28%. Taking prevalence (p) as 0.662 from this study, with 10% absolute precision, 95% confidence level, and 0.05 as critical alpha, the calculated sample size was 86.

Statistical analysis: The study data included both continuous and categorical variables. To analyze these variables, descriptive statistics were used, including the mean, standard deviation (SD), range for continuous data, and frequency with percentage and proportions for categorical variables.

RESULTS

A total of 104 children were screened, of which two were excluded (1 with Down syndrome and 1 with dysmorphism). Sixteen more participants were excluded later due to poor visualization of the ET tip and carina on the *X*-ray. The final analysis included a total of 86 subjects. The baseline characteristics and indications for intubation are listed in **Table I**. All subjects on the *X*-ray had neutral position of the neck. ET tip position was found to be in the mid-trachea in 36 (41.8%) cases and in the low trachea in 45 (52.3%), as defined by vertebral level. The accuracy of the APLS formula (% of cases with appropriate ET depth placement) was found to be 37.2% (95% CI 27.02%-48.3%) (**Table II**). Deep ET placement was observed in 49 (57%) cases. Among the 49 subjects with 'deep ET

Table I Baseline Characteristics of the Study Population (*N*=86)

Characteristics	*Value*
Age (y)[a]	6.6 (3.9)
Males	50 (58.1)
Weight (kg) [a]	20.3 (9.5)
Supine length (cm)[a]	107.8 (24.6)
Cuffed endotracheal tube	58 (67.4)
Indications of intubation	
Altered sensorium	24 (27.9)
Respiratory failure/distress	32 (37.3)
Septic shock with MODS	14 (16.3)
MIS-C	6 (6.9)
Dengue shock with MODS	5 (5.8)
Diabetic ketoacidosis	5 (5.8)

Values in no. (%) or [a]mean (SD). MODS: multi-organ dysfunction syndrome; MIS-C: multisystem inflammatory syndrome in children following coronavirus disease.

Table II Accuracy of Advanced Pediatric Life Support-Endotracheal Tube (APLS-ET) Depth Formula Based on 'Vertebral and Safe Distance Criteria' vs 'Only Safe Distance Criteria' (*N*=86)

ET depth placement	*No. (%)*
Both 'vertebral level' and 'safe distance criteria'	
Appropriate[a]	32 (37.2)
Deep	49 (57.0)
Shallow	5 (5.8)
Only 'safe distance criteria'	
Appropriate[b]	43 (50.0)
Deep	38 (44.2)
Shallow	5 (5.8)

ET: endotracheal tube. [a]Appropriate ET depth: ET tip level at T1-T2/T2/T2-T3 plus ET tip to carina distance more than safe distance [safe distance (mm)= 0.83×age (years)+9.3]. [b]Appropriate ET depth: ET tip level at or below T1-T2 plus ET tip to carina distance more than safe distance [safe distance (mm)=0.83×age(years)+9.3].

placement', 11 fulfilled only the vertebral level criteria, but not the safe distance criteria. After adopting safe distance criteria alone for deep ET placement, the results showed appropriate depth in 43 (50% accuracy) and deep placement in 38 (44.2%) cases. None of our subjects had bronchial intubation.

DISCUSSION

In this study, we investigated the accuracy of the APLS-ET depth formula in Indian children. The results indicated a low accuracy rate of 37.2% for the formula, primarily due to inaccurate deep placements.

Notably, among our 11 cases despite being classified as 'deep placements' based on 'vertebral level criteria' [7], a 'safe distance between the ET tip and carina' was maintained, indicating that these cases were actually safe from all the hazards of deep placement, even on inadvertent neck flexion movements. Thus, adding 'vertebral level criteria' to the definition of deep placement, yielded no additional meaningful significance. Using the 'safe distance criteria' alone as the basis for defining deep ET placement, we found the accuracy of the APLS formula to be 50%, though still lower than the results of prior studies ranging from 66-73% [10-13]. Volsko, et al. [14] observed malpositioned ET in 73% cases, the majority of malpositions being deep placements. However, their deep placement criterion (<1 cm ET tip to carina distance) [14] was less than the safe distance criteria derived from the age formula [3]. Neunhoeffer, et al. [13] reported 27% malposition cases among 79 children intubated using the APLS depth formula, with their deep placement criterion also falling short of the safe distance criteria [13]. Another retrospective study [12] revealed 67.9% accuracy for the APLS-ET depth formula with most malpositions being deep [12]. However, their definition of appropriate ET depth relied on vertebral level criteria without considering the safe distance from the carina. Contrary to the above studies, Lau, et al. [15] found that the APLS depth formula under-estimated optimal depth by 1 cm in children aged 1 to 15 years. However, their study lacked clarity regarding the chosen criteria for appropriate ET depth. Differences in our results compared to the aforementioned studies may be attributed to their retrospective nature and inadequate consideration of 'safe distance criteria.' These limitations could introduce confounding variables such as improper neck positioning during *X*-rays or displacement of the ET between the time of fixation and imaging. In our study, we mitigated these concerns by reconfirming the ET depth mark during *X*-rays and maintaining a neutral neck position.

Zhou, et al. [10] compared APLS accuracy with a 'middle finger length' method using bronchoscopy in 86 children aged 4 to 14 years. The APLS formula yielded 66.3% accuracy, primarily identifying proximal/shallow mal-positions. However, their chosen deep placement criterion (<0.5 cm ET tip to carina distance) was short of the safe distance criteria, potentially explaining the limited number of deep placements detected. Koshy, et al. [11] estimated 72.7% accuracy of the APLS formula for Indian children aged 2 to 12 years based on a pre-operative chest *X*-ray method. However, this estimate was derived without direct observations and relied on a small sample size.

Being conducted in a single center with a relatively small sample of critically ill children, the generalizability of our findings may be limited. Furthermore, we did not assess the distance from the upper border of the ET cuff to the vocal cords in cases of cuffed ET intubations. This measurement is vital for identifying potential risks of vocal cord or subglottic injuries with shallow ET placements; however, it requires measuring tracheal length using bronchoscopy or other methods that may not be feasible in critically ill children.

In conclusion, the APLS formula effectively guards against bronchial intubation in Indian children aged 1 to 12 years, assuming their neck remains neutrally positioned. However, it tends to overestimate ET depth in approximately 50% of cases, when considering the 'safe distance criteria' to compensate for ET movements during neck flexion. Thus, it is important to verify the ET tip's position through early post-intubation *X*-rays and make necessary adjustments as required. Subsequent research with larger sample sizes is needed to validate our findings as well as to assess the 'upper border of ET cuff to vocal cords distance' for a more comprehensive evaluation of this formula.

Ethical clearance: Institutional Ethics Committee, ABVIMS & Dr RML Hospital, New Delhi; No. IEC/ABVIMS/RMLH714/19, dated Oct 22, 2019.

WHAT THIS STUDY ADDS?

- The Advanced Pediatric Life Support (APLS) intubation depth formula effectively guards against bronchial intubation in Indian children aged 1-12 years; however, it tends to overestimate endotracheal tube depth in approximately half the cases.

Contributors: VK: conceived the idea; SA, VK: conceptualized the study and devised its design; SA, MG, K: collected the data; BP, SB: analyzed and interpreted the data and provided critical inputs; VK, BP, SB: supervised data collection and helped in the conduct of the study; SA, MG, K: drafted the manuscript. VK, BP, SB: critically reviewed and revised the manuscript. All the authors read and approved the final manuscript, and agree to be accountable for all aspects of the study.
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RESEARCH PAPER

Establishing Linguistic Equivalency of the Marathi Translation of the Ages and Stages Questionnaires, Third Edition (ASQ-3)

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Objective: This study aims to establish linguistic equivalence of the Marathi translation of the Ages and Stages Questionnaires-Third Edition (ASQ-3) in an urban setting of India. **Methods**: All items of the ASQ-3 were translated and back translated by translators from a non-medical background, piloted on 40 families and reviewed by an expert panel. The final version, adjusted for linguistic equivalence, was tested on 111 bilingual parents recruited to complete questionnaires about their children in both English and Marathi. Intraclass correlation coefficient (ICC), a measure of reliability, were calculated between responses in both languages for each domain of the ASQ-3. **Results**: ICC for each of the five domains were communication: 0.77; gross motor: 0.88; fine motor: 0.80; problem solving: 0.84; personal-social: 0.84. There were no statistically significant differences between Marathi and English questionnaires. **Conclusion**: This Marathi translation of the ASQ-3 was linguistically equivalent to the English version, and can be utilized for developmental screening with Marathi-speaking families.

Keywords: *Assessment, Development, Parents, Screening, Surveillance.*

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The Ages and Stages Questionnaires, third edition is a parent-completed developmental screening tool, developed to identify a child's strengths, areas to monitor, and areas that may be at risk for delay [1]. It is a widely used and recommended tool for developmental screening of children worldwide [2,3].

The ASQ-3 has 21 questionnaires or age intervals, covering 1 month to 5.5 years. Each interval has 30 scored items and 6-9 open-ended questions. For each age interval, statistically derived cutoffs are distinct for the five domains covered (communication, gross motor, fine motor, problem-solving, and personal social). Each item is scored with 10 points for 'yes,' 5 for 'sometimes,' and 0 for 'not yet.' Professionals can calculate the total domain score in 2-3 minutes and follow the instructions provided for further action. ASQ-3 requires respondents to observe the children in everyday routines or play to respond to the items. If respondents are unsure of the child's ability, they are allowed time to try the tasks with the child thus reducing the chances of having faulty recall or insufficient knowledge of their child's development [1].

Though the ASQ-3 has been developed in a high-income country, it is in use in 23 low and low- and middle-income countries (LMICs) with 16 translations [4]. In India, Hindi translations of limited age intervals have been used in two studies [5,6]. Of all Indian languages, only Bengali and Kanada translations are available for use [7]. A variety of methods were used for translations and cultural adaptation of the ASQ-3 around the world, according to the recent review of published studies [8]. Back translations, which involve word-for-word exchanges, may not accurately convey the tone or intention of the original text. Linguistic equivalence is necessary to maintain the integrity of the item while keeping the language at a low reading level and in a parent-friendly tone [9,10]. We describe and discuss the process of building linguistic equivalency of the ASQ-3 in Marathi as an integral first step of the cross-cultural adaptation process for this screening tool. The aim of this study is to have a linguistically equivalent version of the ASQ-3 in Marathi for use in our pediatric outpatient department, primarily serving urban Marathi-speaking families.

METHODS

This cross-sectional observational study, approved by the institutional ethics committee, was conducted in a large-city based tertiary care medical college and hospital in Maharashtra, from December, 2019 to December, 2021.

We received permission for translation from the ASQ-3 publisher, Brookes Publishing, who provided an Excel sheet with all the items of ASQ-3 and instructions for the process of translation and adaptation. All these items were forward translated to Marathi and back-translated to English by

different senior translators from a non-medical background. A representative of the Ages and Stages International Research Group (ASIR) reviewed the translation file with the first author.

This first version was pilot tested on 40 parents recruited from our pediatric outpatient department during their well-baby visits. A researcher, trained and experienced with the ASQ-3, asked them for feedback about the ease of reading and understanding the tasks listed. After the parents responded to the Marathi ASQ-3, we discussed how applicable the items were to their children. With input from the parents and the team's clinical judgment, changes were made to improve language equivalence. For example, there were mismatches for similar words like 'reach', 'hold' and 'grab' or intention of items such as 'does your child' instead of 'can your child.' Marathi words for 'squatting' and 'problem solving' were of a higher reading level and words like 'cheerio' and 'snowman' do not have direct translations. A speech language pathologist provided alternatives for complex words such as 'gurgling' and 'cooing.' In addition, we corrected an item where the translation resulted in the opposite meaning, causing an unintended lower score for a particular skill. No items were adapted for culture or environment at this time. Several iterations of the Marathi version were required before the author team and ASIR representative approved the translation.

Parents who were bilingual (Marathi and English) were requested to complete both the Marathi and English ASQ-3 to determine if they were equivalent. The responses of the parents were then compared for consistency [11]. In the absence of comparative publications, the sample size was arbitrarily chosen to include all intervals with a target sample size of 100 with at least four participants in 20 of the 21 age intervals. The 9-month and 10-month intervals have the same items and were not tested separately.

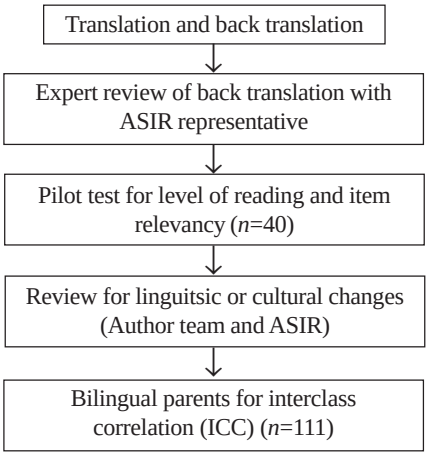
Recruitment methods during the pandemic included phone calls, the use of social media, and in-person during visits at the hospital's pediatric outpatient center. A registration form that included information regarding the study protocols and required participants to check off a box for informed consent was shared over text messages. The ASQ-3 age calculator was used to identify the appropriate age interval for each child. Adjusted age was used for children under age two years in cases of prematurity. Demographic information such as education and family income but excluding geographical location was collected. Kuppuswamy classification system was used to identify socioeconomic levels of the sample [12]. Parents were asked to fill out forms within two weeks of receiving the questionnaires.

Statistical analysis: Microsoft Excel was used to collate item-level data for both questionnaires. All data were coded and analyzed using Statistical Package for Social Sciences Software, version 25. An intraclass correlation coefficient (ICC) single measure value analysis was

Table I Distribution of Study Participants According to ASQ-3 Age Intervals (*N*=152)

Interval	*Age range covered*	*No.(%)*
2-mo	1 mo 0 d to 2 mo 30 d	7 (6.3)
4-mo	3 mo 0 days to 4 mo 30 days	6 (5.4)
6-mo	5 mo 0 d to 6 mo 3 d	5 (4.5)
8-mo	7 mo 0 days to 8 mo 30 d	7 (6.3)
10-mo	9 mo 0 d to 10 months 30 d	7 (6.3)
12-mo	11 mo 0 d to 12 mo 30 d	5 (4.5)
14-mo	13 mo 0 d to 14 mo 30 d	5 (4.5)
16-mo	15 mo 0 d to 16mo 30 d	5 (4.5)
18-mo	17 months 0 d to 18 mo 30 d	6 (5.4)
20-mo	19 mo 0 d to 20 mo 30 d	5 (4.5)
22-mo	21 mo 0 d to 22 mo 30 d	4 (3.6)
24-mo	23 mo 0 d to 25 mo 15 d	5 (4.5)
27-mo	25 mo 16 d to 28 mo 15 d	5 (4.5)
30-mo	28 mo 16 d to 31 mo 15 d	3 (2.7)
33-mo	31 mo 16 d to 34 mo 15 d	4 (3.6)
36-mo	34 mo 16 d to 38 mo 30 d	8 (7.2)
42-mo	39 mo 0 d to 44 mo 30d	4 (3.6)
48-mo	45 mo 0 d to 50 mo 30 d	5 (4.5)
56-mo	51 mo 0 d to 56 mo 30 d	8 (7.2)
60-mo	57 mo 0 d to 66 mo 0 d	7 (6.3)

ASQ:ages and stages questionnaires.



ASQ-3: ages and stages questionnaires Third Edition; ASIR: ages and stages international research group.

Fig.1 Study flow of ASQ-3 Marathi translation.

performed between responses in English and Marathi for each domain rather than age interval since some items repeat across multiple intervals.

RESULTS

A total of 152 parents registered, of which 111 (73%) returned the completed English and Marathi questionnaires and demographic forms. The remaining 41(27%) parents either failed to fill out the questionnaires entirely or did not respond within the stipulated time (**Fig.1**). **Table I** shows the distribution of participants according to the ASQ-3 age intervals. Most respondents were mothers (81%) of middle- and upper-class socioeconomic status. Education level of all respondents, except for one (Grade 12th completed) were graduates or above. Seventy five percent of the children were born preterm.

Table II shows intraclass correlation coefficient (ICC) for each of the five domains of the ASQ-3. The strong correlation of 0.77 to 0.88 between the English and Marathi questionnaire scores in all domains indicates that the Marathi version of the ASQ-3 worked well in the population tested.

DISCUSSION

India's linguistic diversity makes translation complex, as seen in studies that made linguistic adaptations to address the differences in the Spanish language as spoken in Peru vs Chile [8]. Our investigation for equivalence focused on the population encountered within our clinical setting viz., Marathi-speaking families from the city or nearby towns. In our setting, the Marathi version of the ASQ-3 performed well, as indicated by the strong correlation between the scores of the English and Marathi questionnaires in all domains.

Parents' feedback during piloting was critical in determining the applicability (cultural adaptation) of the items to the population. During the piloting, parents discussed the cultural suitability of some items i.e., using forks while eating, using a mirror for play with infants and the expectation of independence in self-help skills [6]. While social norms and taboos may be customary, parents stated that they seek other sources of information and tend to move away from beliefs that may be barriers to their children's development. In urbanized India, many families are also choosing to send their children to play-schools as early as two years old, where independence in skills is encouraged and expected sooner.

Parent observations integrated into developmental screening can add critical value to the surveillance process and corroborate screening outcomes [13,14]. While there may be concerns about the reliability of parent reports in LMICs due to lack of awareness of child development, the functional nature of the ASQ-3 items offers parents and caregivers the opportunity to interact before responding rather than relying on knowledge of milestones or recall. As models of developmental care move towards being family-centric, the bi-directionality of the ASQ-3 presents an opportunity for parent education and anticipatory guidance for appropriate play and interactions [15]. Using the Marathi questionnaires made routine screening possible and accessible to more families without disruptions or adding time to the visits in our practice.

The limitation of the sample population demographics, particularly its lack of heterogeneity in geographical region and parents' high education status, made it difficult to explore culturally sensitive items for adaptation such as zipping a jacket or coping Roman letters or numbers. Future research on the Marathi ASQ-3 should focus on validating and determining psychometric properties, including comparing cutoffs for the Marathi-speaking population.

Table II Interclass Correlation Coefficient (ICC) of the Five Domains of the Marathi Translation of ASQ-3

Domain	*ICC (95% CI)*
Communication	0.776 (0.664-0.847)
Gross Motor	0.882 (0.830-0.923)
Fine Motor	0.801(0.700-0.864)
Problem solving	0.846 (0.771-0.897)
Personal social	0.845(0.723-0.874)
Total scores	0.88 (0.821-0.919)

ASQ-3: ages and stages questionnaires-3. All P<0.001.

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Ethical clearance: Ethics Committee at Bharati Vidyapeeth Medical College; No. BVDUMC/IEC/03, dated June 30, 2021.
Contributors: PP: Conceptualized the study idea, coordinated with Ages and Stages International Research Group and Brookes Publishing, implementation of study methodology, data collection and organization, manuscript writing; NM: Data collection, reviewing results and manuscript review; GO: Formulation of research methodology, data interpretation and manuscript review; KP: Data Analysis and manuscript review.
Funding: None; *Competing interests*: None stated.

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WHAT THIS STUDY ADDS?

- The linguistic equivalence of the Marathi translation of the Ages and Stages Questionnaires third edition (ASQ-3) is strong and can be used with Marathi-speaking families for developmental screening.

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RESEARCH PAPER

Serum Micronutrients and Antioxidant Levels in Children With Transfusion-Dependent Thalassemia

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Objectives: To estimate serum zinc, copper, magnesium and antioxidant levels in children with transfusion-dependent thalassemia (TDT). **Methods**: Cross-sectional study, enrolling children with TDT aged 3-14 years and age-matched healthy children without thalassemia. Serum zinc, copper, magnesium and total antioxidant capacity were estimated by direct colorimetric method and ELISA, respectively. **Results**: 72 children (24 females; mean (SD) age 8.5 (3.2) years) were enrolled. Mean (SD) values of micronutrients in the study group and control group children were: serum zinc [89.4 (26.9) vs 93.5 (41.6) mg/dL; *P*=0.496], copper [118.3 (36.6) vs 123.3 (29.8) mg/L; *P*=0.133], magnesium [1.9 (0.3) vs 2.0 (0.2) mg/dL; *P*=0.015]. Total oxidant capacity level was not different in both the groups [median (range) 124.8 (16.0-501.7) vs 146.8 (14.0-641.7) mg/mL; *P*=0.605]. 24 (33%) children with TDT had low serum zinc levels (<65 mg/dL), and 31 (43%) had high serum copper levels (≥121 mg/L). **Conclusions**: Children with TDT were found to have significantly lower magnesium levels compared to healthy children.

Keywords: *Free radical damage, Growth, Nutrition, Oxidation.*

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Micronutrients and antioxidants have been studied in transfusion-dependent thalassemia (TDT) to understand the pathophysiology of end organ damage [1-3]. Previous studies have indicated that oxidative stress in patients with TDT is caused by the alteration in serum trace elements and antioxidant levels [4,5]. Zinc, copper and magnesium are few of the important microelements having multiple roles at cellular level reducing the free iron induced cellular damage. Apart from the known chelating effect of desferrioxamine on zinc, no other chelators have any proven effect on these micronutrients. As the findings of previous studies on various micronutrients and antioxidants in children with TDT have not shown uniform results globally [1-6], we planned to study micronutrient and antioxidant levels among children with TDT in this region.

METHODS

This cross-sectional study was conducted at the thalassemia day care centre of a tertiary care pediatric hospital, between November, 2020 and October, 2021. All children with TDT aged 3-14 years, who were registered at our centre and receiving regular blood transfusions and chelation were enrolled.

Children with TDT who had poor compliance to transfusion, less than six months of transfusion duration, taking zinc or multivitamin supplementation during the last 3 months were excluded. The study was approved by the institutional ethics committee, and an informed consent was obtained from parents and assent was taken from children older than 7 years. Healthy controls were taken from children visiting hospital's outpatient department either for routine immunization or for minor illnesses like upper respiratory infection. Those who had taken multivitamin or zinc supplementation at any time in last three months were excluded from the study. Detailed history and examination were done for all enrolled children. Children were asked to come after overnight fasting, and 4 mL of venous blood was collected (2 mL each for complete blood count, and for estimation of zinc, copper, magnesium, and antioxidant levels). Serum zinc and copper were estimated by direct colorimetric method with Diasys reagent and magnesium by xylidyl blue method (Beckman Coulter AU 680 biochemistry analyzer). Serum total antioxidant level was estimated by double antibody sandwich ELISA technique (Qaybee-Bio life sciences total antioxidant capacity kit). We measured the total antioxidant level in blood and body fluids (total antioxidant capacity, T-AOC); however, individual antioxidants were not analyzed separately. The normal level of serum zinc, copper and magnesium were defined as 65-118 mg/dL, 63.7-140.12 µg/dL and 1.8-2.5 mg/dL, respectively [7-9].

Statistical analysis: Data were entered in a Microsoft Excel sheet and analyzed using Statistical Package for Social Sciences (SPSS) Version 25.0 for windows. Student *t* test was used to compare differences between two means. Chi-square test or Fisher exact test were used for comparing categorical variables. *P* value <0.05 was taken as significant.

RESULTS

Eighty-five children with TDT were screened, out of which 72 aged 3-14 years [mean (SD) age 8.5 (3.2) years; 24 females] were included as study group and matched 83 healthy children were enrolled as controls [mean (SD) age 8.6 (2.8) years; 49 females]. Comparison of baseline parameters of children with TDT and healthy controls is shown in **Table I** and **Table II**.

Children with TDT had lower serum zinc, copper, magnesium and antioxidant levels compared to healthy children, but the difference was statistically significant only for serum magnesium levels. 33% of the children with TDT had low serum zinc levels (*P*=0.003), while 43% had high serum copper levels (*P*=0.337). Around 22% of our study population was magnesium deficient (**Table II**). The antioxidant level was comparatively higher in TDT patient of age <5 years but not statistically significant.

There was no significant correlation between zinc and ferritin level or frequency of transfusion. The mean body weight and height were significantly lower among TDT patients with low zinc level (*P*=0.020 and *P*=0.021), which indicates that children of TDT with poor nutritional status had low zinc level. Serum copper value did not have any correlation with above mentioned parameters. The mean body weight and height were significantly higher among TDT children with hypermagnesemia (*P*=0.042 and *P*=0.010, respectively). Mean magnesium value had no correlation with height, weight or ferritin value. There was no correlation between anthropometric parameters including weight, height, BMI and antioxidant status in cases. The VLDL (very low density lipoprotein) and TG (triglyceride) level were negatively correlated with antioxidant level of children with TDT, where high VLDL level was seen with decreasing antioxidant level (RR -0.244; *P*=0.039).

Table I Baseline Characteristics of Children With Transfusion-Dependent Thalassemia

Parameters	*Outcome*
Age at diagnosis (mo)	11.8 (1.5)
Age at first transfusion (months)	11.4 (1.4)
Number of transfusions/y	17.5 (3.9)
Ferritin level (µg/L)[a]	1500 (123-8543)
Duration of chelation	
Deferasirox, *n*=72	68.6 (37.9)
Deferiprone, *n*= 57	17.1 (9.5)

Values in mean (SD or [a] median (range).

DISCUSSION

In this study involving 72 children with TDT, serum zinc, copper, magnesium and antioxidant levels were compared to healthy children.

Similar to our results, another Indian study of 35 thalassemia major patients, found 65% patients were zinc deficient [10]. A study from Egypt evaluated the prevalence of zinc deficiency in TDT patients where 98% were found to be zinc deficient [11]. On the contrary, low zinc level in only 2.6 % patients [3], and no zinc deficiency [12] in TDT have also been reported. Copper deficiency has been infrequently reported in TDT [2,15], and one study reported excess copper levels in up to 20% children [13]. Most of the studies on zinc level in TDT children showed low levels while few studies showed normal levels, and copper level was normal or elevated in most of the similar studies. Studies on magnesium are too less for predicting a trend in children with TDT.

The findings of our study on zinc and copper correlate with many of the similar studies done previously on TDT children, but the low magnesium value in children with TDT has been uncommonly reported, as very few studies have looked at the magnesium levels of these patients.

Table II Serum Levels of the Study Variables in Children With Transfusion-Dependent Thalassemia and Controls

Parameter	*Case (n=72)*	*Control (n=83)*
Age (y)	8.5 (3.2)	8.6 (2.8)
Weight (kg)[c]	23.1 (7.0)	26.4 (8.5)
Height (cm)	124.7 (1.3)	127.4 (18.3)
Body mass index (kg/m^2)[d]	14.6 (1.3)	15.7 (2.0)
Serum zinc (ug/dL)	89.4 (26.9)	93.5 (41.6)
Low (<65 µg/dL)[a,c]	24 (33.3)	41 (49.4)
High (>118 µg/dL)[a,c]	9 (12.5)	19 (22.9)
Serum copper (µg/L)	118.3 (36.6)	123.3 (29.8)
Low (<51 µg/L)[a]	1 (1.4)	0
High (>121 ìg/L)[a]	31 (43.1)	43 (51.8)
Serum magnesium (mg/dL)[c]	1.9 (0.3)	2.0 (0.2)
Hypomagnesemia (<1.8 mg/dL)[a]	16 (22.2)	12 (14.5)
Hypermagnesemia (>2.5 mg/dL)[a]	2 (2.8)	2 (2.4)
Total antioxidant status[b]	124.8 (16.0-501.7)	146.8 (14.0-641.7)

Value in mean (SD), [a] no. (%) or [b] median (range). [c]P<0.05 ; [d]P<0.001.

WHAT THIS STUDY ADDS?

- Children with transfusion-dependent thalassemia had lower magnesium levels than children without thalassemia.

The study has certain limitations including lack of detailed dietary evaluation, and not studying the effect of supplementation of the studied micronutrients. Lower than expected hemoglobin in children with TDT can be explained by the inability to maintain 3-4 weekly transfusion policy during the pandemic due to lack of blood donors, and inability to reach the hospital.

No significant differences were found between serum zinc, copper and anti-oxidant levels between children with TDT and healthy controls; though, serum magnesium levels were significantly lower in these with TDT. The pathophysiological basis for this difference, and its clinical implications, still need to be demonstrated.

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Contributors: SR: conceptualized the study, did literature review, drafted the manuscript; YV: screened patients and collected data; DS: supervised the study, helped in drafting manuscript; SS: supervised all biochemical testing and tabulating the results; MK: supervized, provided inputs in drafting. All authors contributed in the final preparation of the manuscript.

Ethic clearance: IEC, Chacha Nehru Bal Chikitsalaya; No. 85/16263, dated Nov 28, 2020.

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RESEARCH PAPER

Spirometry in Children at Six Months After SARS-CoV-2 Infection: A Single-Center Study

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Objective: To study the spirometry parameters of children six months after severe acute coronavirus 2 (SARS-CoV-2) infection. **Methods**: This single center descriptive study enrolled children aged 7-18 years after 6 months of SARS-CoV-2 infection. A detailed interval history and clinical examination was recorded. Spirometry was performed and best of the three attempts was taken into consideration to measure forced vital capacity (FVC) and forced expiratory volume 1 second (FEV1). **Results**: A convenience sample of 40 (21 boys) children was enrolled, median (IQR) age 13 (10.75, 17) years. Twelve (30%) children had abnormal spirometry with low FVC (<80%); 10/12 (83.3%) had FEV_1<80%. Children who were underweight had higher odds of having abnormal spirometry [OR (95% CI) 5.13 (1.19, 22.11); *P*=0.028]. There was no significant association of abnormal spirometry with age, sex, severity of initial infection and oxygen requirement during the initial infection (*P*>0.05). **Conclusion**: Abnormal spirometry results were observed in one-third children post-SARS-CoV-2 infection at six months follow-up.

Keywords: *Complications. Follow-up, FEV_1, FVC, Pulmonary sequelae.*

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Children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were mostly reported to be asymptomatic, and among those who were symptomatic, most had mild infection. Similar to SARS, a histopathological progression was seen in coronavirus disease 2019 (COVID-19) pneumonia after a few weeks with intra-alveolar and interstitial fibrin deposition and chronic inflammatory infiltrates [1]. Coronavirus infection can directly promote lung fibrosis as the nucleocapsid protein of SARS-CoV-1 is known to promote and enhance transforming growth factor-beta (TGF-β) signaling, which is a powerful pro-fibrotic signal. SARS-CoV-2 may also exhibit similar property and induce long term lung changes [2].

SARS-CoV-1 and Middle East Respiratory Syndrome (MERS), which are similar to SARS-CoV-2, are known to cause pulmonary sequelae, leading to pulmonary function impairment ranging over months to years [3]. The long term effects on pulmonary function in COVID-19 pediatric survivors have not been studied widely. Therefore, we studied the spirometry parameters in children with SARS-CoV-2 infection, and the associated risk factors.

METHODS

This descriptive study was performed in children diagnosed with SARS-CoV-2 infection in the Department of Pediatrics of a tertiary care public hospital in Delhi from June, 2020 to October, 2021. Permission was taken from the institutional ethics committee before the start of the study. Children aged 7 to 18 years who were positive for SARS-CoV-2 infection, either by reverse transcriptase-polymerase chain reaction (RT-PCR) or rapid antigen test, and previously hospitalized for SARS-CoV-2 were enrolled. Any child with chronic respiratory diseases like cystic fibrosis, interstitial lung diseases and asthma; pre-existing neuromuscular disorders like muscle dystrophies and spinal cord injury that may affect pulmonary function tests; pre-existing conditions that may affect pulmonary function test like lung surgery, known sequelae of pulmonary tuberculosis, kyphosis, scoliosis and chest wall deformities; neurodevelopmental disorders, where poor cognitive ability may hinder performing the pulmonary function test; and those not residing in Delhi-NCR or unwilling to return for follow-up were excluded.

The eligible subjects were identified by two methods viz., screening the hospital records of patients hospitalized from June to December, 2020, and prospectively from inpatient records of those with COVID-19 from January to October, 2021 (**Fig.1**). They were screened and contact details were noted. Their parents were contacted telephonically and requested to follow-up after six months of discharge for enrolment in the study. They were informed

about the date of follow-up visit, one month prior to the visit, and again within one week of follow-up date, if they missed the visit. At the routine follow-up visit, children who satisfied the inclusion and exclusion criteria were enrolled into the study, after informed written consent from the parents and assent from children more than 7 years of age.

The primary outcome variables were measures of lung function on pulmonary function test viz., forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and ratio of FEV1 and FVC.

The earlier reported proportion of adult patients with SARS-CoV-2 infection with pulmonary sequelae was 25.5% [4]. The calculated sample size for similar sample proportion with 10% margin of error and 95% confidence level was 73. We planned a sample size of convenience of at least 40 children considering the expected number of pediatric inpatients.

The symptoms at presentation, relevant demographic and clinical details, baseline investigations if any, duration of hospital stay and course during hospital stay were noted from the hospital records. A detailed clinical examination was performed. Blood investigations and imaging were not done in all patients as per the guidelines in force during the pandemic, and investigations were performed if clinically indicated based on disease severity. A structured form was used to record the clinical details, results of laboratory investigations including chest *X*-ray, duration of hospital stay, oxygen requirement, treatment received, and outcome.

At the follow-up visit, the participants were asked about the resolution of respiratory symptoms, and current medical issues, if any. A general physical examination and systemic examination were done. Anthropometry parameters were noted, standard deviations were calculated using Indian Academy of Pediatrics charts for height and weight, and centiles for BMI.

Pulmonary function test (PFT) was carried out according to the spirometry guidelines given by American Thoracic Society/European Respiratory Society [5,6], and Schiller SP-260 PC spirometer (Schiller Healthcare India Pvt. Ltd.) was used. A single trained respiratory technician performed all the tests. The obtained results were assessed for acceptability and repeatability [5]. The measured values were recorded and compared with predicted values. The best of the three attempts was taken into consideration. The best of FVC was taken into account and FEV1/ FVC of the best attempt was calculated. Children who were unable to perform the manoeuvres of pulmonary function test after five attempts were excluded from the study. Any child with an acute systemic illness at the time of spirometry was asked to revisit the hospital after resolution within two weeks period. After the test, child was subjected to 6 minutes' walk test and pulmonary function test was repeated immediately (data not included).

Predicted values of FVC, FEV1/FVC, and FEV1 given by Knudson [7] based on age, sex and height were used in the software to calculate the percentage of predicted values. FVC <80% of predicted, and FEV1/FVC <90% in below 11 years and <75% above 12 years of age was considered abnormal [8, 9]. As the lower limits of normal were not available, cutoff percentages were taken [9]. Total lung capacity could not be assessed at the study center, and therefore a reduced FVC with normal or increased FEV1/ FVC was considered to be suggestive of lung restriction [6].

Statistical analysis: Categorical data (sex, demographic

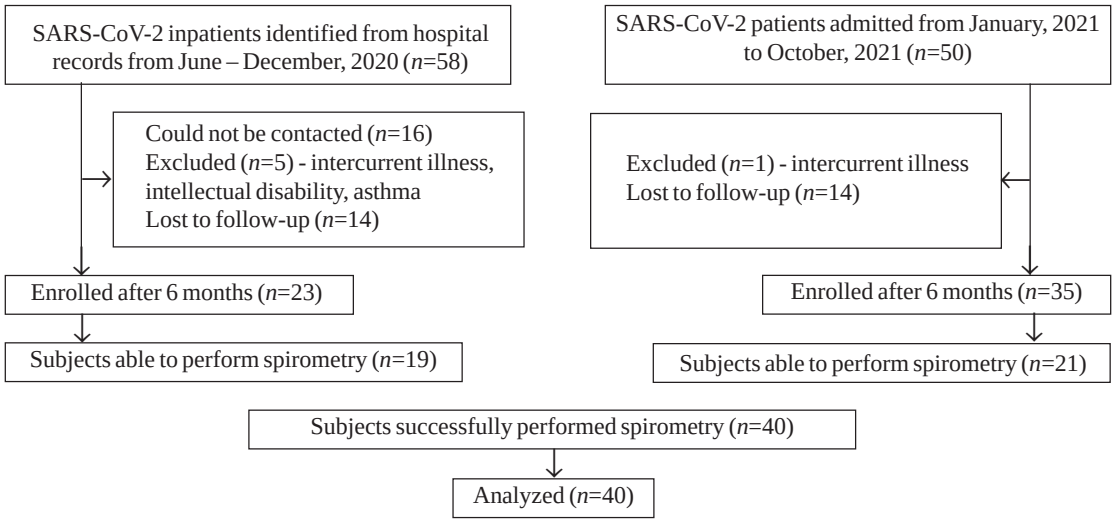

Fig. 1 Study flow chart.

and clinical features) are presented as proportions and continuous variables (age, anthropometry, PFT values) are presented as median (IQR). All analyses were done using Epi Info software. The risk of pulmonary dysfunction was compared for patients with different risk factors by univariate analysis using odds ratio (OR) with 95% CI. *P* value <0.05 was considered statistically significant.

RESULTS

The study enrolled 40 patients after spirometry on follow-up of 6 months. The study flowchart is shown in **Fig. 1**. The baseline characteristics of the study subjects are shown in **Table I**. The median (IQR) age of the study cohort was 13 (10.75, 17) years, weight and height *z*-scores were - 0.25 (-1.0, +0.33) and -0.43 (-0.79, -0.4), respectively.

Of the 40 children evaluated, 12 (30%) had FVC<80%, 10 (25%) had FEV1<80% and two children had isolated decrease in FVC. All children had normal FEV1/FVC ratio. There was no statistically significant association of age, gender, severity, *X*-ray findings and abnormal spirometry in children (**Table II**). The odds of abnormal spirometry on follow-up were higher for underweight children as compared to normal weight children [OR (95% CI) 5.13 (1.19, 22.11); *P*=0.028].

Table I Baseline Characteristics of Children With SARS-CoV-2 Infection (*N*=40)

Variable	*No. (%)*
Age, y	
7-12	18 (45)
13-18	22 (55)
Male sex	21 (52.5)
COVID symptoms[a]	
Fever	31 (78)
Vomiting	13 (33)
Headache	11 (28)
Cough	11 (28)
Hematological parameters[a]	
Neutrophilia	3 (11.5)
Neutropenia	3 (11.5)
Lymphocytosis	4 (15.3)
Lymphopenia	4 (15.3)
Thrombocytopenia	9 (34)
Chest *X*-ray findings[a] (*n*=21)	
No abnormality	14 (66.7)
Ground glass opacities	5 (23.8)
Pleural effusion	2 (9)
Disease severity[b]	
Asymptomatic	5 (12.5)
Mild	20 (50)
Moderate	11 (27.5)
Severe	4 (10)
Oxygen requirement[a]	
High flow nasal cannula	4 (10)
Venturi mask	1 (2.5)
Nasal prongs	1 (2.5)

[a]Parameters during acute COVID; [b]As per Indian Council of Medical Research classification [20]. COVID: coronavirus disease.

DISCUSSION

In this single-center descriptive study, approximately one-third children with SARS-CoV-2 infection were found to have abnormal spirometry parameters at six months follow-up. All of the children with abnormal parameters may be suggestive of restrictive ventilator defect, as FVC was low and FEV1/FVC was normal. Underweight was the only risk factor significantly associated with the abnormal spirometry on univariate analysis.

A recent study reported abnormal spirometry in 23% and 10%, at 3 and 6 months of follow-up, respectively [10]. Another study from the US reported abnormal spirometry in 10% of the subjects [11]. A relatively lower proportion of spirometry abnormalities in comparison to the present study could be because the majority of patients in their study cohort were outpatients with mild disease, and competitive athletes. On the contrary, no abnormal spirometry was seen on follow-up in two other studies [12,13], probably as they enrolled only mildly symptomatic and asymptomatic children.

Table II Factors Associated With Abnormal Spirometry in Children Six Months After SARS-CoV-2 Infection

Variable	*Pulmonary dysfunction, n/N (%)*
Age	
7-12 y	8/18 (44)
13-18 y	4/22 (18.1)
Male sex	6/21 (28.5)
Weight[a]	
Normal	5/25 (20)
Underweight	7/12 (58)
Obese	0/3
Disease severity	
Asymptomatic	0/5
Mild	7/20 (35)
Moderate	3/11 (27.2)
Severe	2/4 (50)
Oxygen requirement	2/6 (33)
Chest *X*-ray findings	
Normal	10/14 (71)
Ground glass opacities	2/5 (40)
Pleural effusion	1/2 (50)

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

WHAT THIS STUDY ADDS?

- Children may have abnormal spirometry results after six months of SARS-CoV-2 infection.

The mechanism behind post-COVID lung injury is still a matter of debate. A prolonged pro-inflammatory response related to SARS-CoV-2 infection can provoke an atypical response of the immune system and mast cells, promoting a cascade of events affecting the respiratory and immune systems [14]. SARS-CoV-2 can induce pulmonary fibrosis by promoting the upregulation of pro-fibrotic signaling molecules, including transforming growth factorbeta (TGF-β), leading to lung fibrosis and interstitial remodelling [15]. The abnormal spirometry may be suggestive of restrictive ventilator type in this study, which is similar to adult studies [16]. The majority of the children enrolled in the earlier pediatric studies were asthmatics, which could have accounted for the predominance of an obstructive pattern on PFT at follow-up [10,11].

We found underweight children to have higher odds of abnormal spirometry. An association of both underweight and obesity with severity of COVID-19 disease has previously been reported in adults [17]. However, no such association was seen in pediatric studies [10-13]. The occurrence of abnormal spirometry was not significantly associated with severity of the initial infection in the present study, similar to a previous report [18].

The small sample size in this study was a result of designation of the institute as an exclusive COVID-facility that limited attendance of recovered patients for follow-up at the institute. The predicted normal spirometry values used in the software in this study were based on cutoffs as per an earlier study conducted in the USA [10]. The use of Caucasian prediction equations may result in poor agreement with Indian equation in most height and age categories among both sexes, resulting in misinterpretation of spirometry data. Details of concomitant infections were not collected. Additionally, the baseline lung function parameters of the participants in the study were not available. More sensitive investigations like plethysmography and gas exchange for total lung capacity measurement could have been done for evaluation of the pulmonary function, though these are meant for research settings and not routinely available for clinical use.

To conclude, a high proportion of children (higher in underweight) recovered with SARS-CoV-infection demonstrated abnormal spirometry at six months follow-up. The occurrence of asymptomatic changes in lung function on spirometry needs to be confirmed with larger studies and longer follow-up, to elucidate the pathophysiology of pulmonary sequelae in pediatric SARS-CoV 2 infection.

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Contributors: PS: enrolled patients and did the outcome assessment, and assisted in study planning and statistical analysis; DM: conceptualized and planned the study, did the statistical analysis, and finalized the manuscript; AA: provided intellectual inputs regarding conduct of the study and manuscript preparation; DK: assisted in planning the study, outcome assessment, and did the initial manuscript preparation. All authors approved the final manuscript.
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Indian Academy of Pediatrics Revised Guidelines on Evaluation, Prevention and Management of Childhood Obesity

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Justification: The last guidelines for pediatric obesity were released in 2004 by Indian Academy of Pediatrics (IAP). Since then, there has been an alarming increase in prevalence and a significant shift in our understanding in the pathogenesis, risk factors, evaluation, and management of pediatric obesity and its complications. Thus, it was decided to revise and update the previous recommendations.

Objectives: To review the existing literature on the burden of childhood obesity and its underlying etiology and risk factors. To recommend evaluation of childhood obesity and suggest optimum prevention and management strategies of childhood obesity.

Process: The following IAP chapters (Pediatric and Adolescent Endocrinology, Infant and Young Child feeding, Nutrition, Non-Communicable Disease and Adolescent Health Academy) were invited to nominate members to become part of the writing committee. The Committee held discussions on various aspects of childhood obesity through online meetings between February and August, 2023. Recommendations were then formulated, which were analyzed, revised and approved by all members of the Committee.

Recommendations: Exogenous or primary obesity accounts for the majority of cases of childhood obesity. It is important to differentiate it from endogenous or secondary obesity as evaluation and management changes depending on the cause. In Indian, in children under 5 years of age, weight for length/height using WHO charts, and in children 5-18 years, BMI using IAP 2015 charts is used to diagnose overweight and obesity. Waist circumference should be routinely measured in all overweight and obese children and plotted on India specific charts, as it is a key measure of cardio-metabolic risk. Routine evaluation for endocrine causes is not recommended, except in short and obese children with additional diagnostic clues. All obese children more than ten years old should be evaluated for comorbidities like hypertension, dyslipidemia, hyperglycemia and non-alcoholic fatty liver disease/metabolic dysfunction associated steatotic liver disease (NAFLD/ MASLD). Prevention and management of childhood obesity mainly involves healthy diet practices, daily moderate to vigorous physical activity and reduced screen time. Pharmacotherapy may be offered as an addition to lifestyle interventions only in cases of class 3 obesity or if there are any life-threatening comorbidities. Finally, surgical management may be offered in children older than 12 years of age with class 2 obesity and associated comorbidities or class 3 obesity with/without comorbidities, only after failure of a proper trial of intense lifestyle modifications and pharmacotherapy for at least 6 months.

Keywords: *Comorbidities, Overweight, Metabolic syndrome.*

Childhood obesity has emerged as an important public health problem in India as well as other countries in the world. In 2017, it was estimated that more than 14.4 million children in India were obese, the second highest rate in the world, only behind China [1]. In addition to the prevalence, the severity of obesity is also showing an alarming rise, which was significantly worsened by the restrictions implemented during the COVID-19 pandemic.

PROCESS

In February, 2023, the executive board of Indian Academy of Pediatrics (IAP) established a writing committee chaired by the president of IAP to formulate recommendations on obesity in Indian children. The following IAP chapters (Pediatric and Adolescent Endocrinology, Infant and Young Child Feeding, Nutrition, Non-Communicable Disease and Adolescent Health Academy) contributed to the guidelines, as members of these chapters are routinely involved in the care of children with obesity. Five sub-committees were assembled to carry out a detailed review of literature. These sub-committees then prepared the first draft of recommendations by June, 2023. These recommendations were then deliberated upon and revised by the sub-committee members. The second draft was put together, based on all the suggestions, and resent to all members. A National Consultative meeting was held on July 14, 2023 on digital platform (Zoom) where all the reviews were discussed, and the deliberations among experts provided the direction to frame the recommendations. Evidence was assessed and graded following the method used by the American Academy of Pediatrics (AAP) guidelines [2]. The final document was put together by the Writing Committee after a number of revisions and was approved by the Executive Board of IAP.

RECOMMENDATIONS

1. Recognition of Childhood Obesity as a Chronic Disease and Need for Updated Guidelines for Indian Children and Adolescents

The issue of pediatric obesity, once considered a problem in only high-income countries, has now reached epidemic proportions even in middle and low-income countries, including urban slums and rural areas. In the last few years, various reputed medical bodies, including the American Association of Clinical Endocrinology (AACE), Pediatric Endocrine Society (PES) and very recently, the American Academy of Pediatrics (AAP) and the Endocrine Society of India (ESI) have recognized obesity as a chronic disease [3-6]. There is now enough proof that childhood obesity tracks into adulthood, negatively affecting physical and psychological health [7]. Hence, pediatricians and health care providers (HCPs) in India should recognize and treat pediatric obesity as "a chronic disease characterized by excess or dysfunctional body fat (adiposity) which impairs health leading to long term morbidity and even early mortality." Hence, a need was felt to revise and update the previous guidelines [8].

Recommendation 1.0

Pediatricians and HCPs should recognize and treat pediatric obesity as a chronic disease characterized by excess or dysfunctional body fat (adiposity), which impairs health, leading to long-term morbidity and early mortality. (*Evidence level B, Recommendation level moderate*).

2. Prevalence of Childhood Obesity

Prevalence of infantile obesity: Data on prevalence of infantile obesity is scarce in world literature, because the focus on association of early life factors with later obesity is relatively recent. National Family Health Survey 5 (NFHS 5) data from India reported 3.4% of children below five years to be overweight (4.2% in urban areas) with an increase of almost 50% from 2.1% in NFHS 4 [9]. In the United States (US), the prevalence of obesity was found to be 16% during infancy [10]

Prevalence of childhood and adolescent obesity: The prevalence of childhood obesity quoted in various studies is as high as 40% to up to 24 times rise in the past 2-3 decades [11].The prevalence varies with the definitions and criteria selected for evaluation [12]. With a global prevalence of 18%, about 200 million school children are estimated to be overweight/obese worldwide [13].

The prevalence of overweight in the comprehensive national nutrition survey (CNNS) of 2016-18, in children between 5-9 years of age and adolescents, was 4% and 5%, respectively. In the same survey, the prevalence of obesity in children aged 5-9 years and adolescents was only 1% [14]. This is in contrast to studies conducted across various parts of India that report a prevalence of 3% to 24.7% for overweight and 1.5% to 14% for obesity among adolescents; this difference could be due to the varying socioeconomic class in studies across India. Pooled data from a meta-analysis of 52 Indian studies reveals that the combined prevalence of overweight and obesity has increased from 16.3% (2001-2005) to 19.3% (after 2010). In the meta-analysis, a higher incidence of overweight/obesity was seen among boys, urban population, higher socioeconomic strata and North Indian population [13].

Recommendation 2.0

The rising prevalence of infantile, childhood and adolescent obesity in India (including the rural population) needs to be addressed urgently by all the stakeholders (HCPs, school

authorities, national medical bodies and policy makers) involved in the management and prevention of pediatric obesity.
(*Evidence level A, Recommendation level strong*)

3. Etiology and Risk Factors of Childhood Obesity

Infantile Obesity

Maternal factors

Maternal preconception BMI ≥30 kg/m^2, excessive gestational weight gain, and gestational diabetes mellitus increase the risk of infantile obesity. Small for gestational age infants at birth, due to maternal factors like tobacco use, gestational hypertension (PIH) and insufficient maternal weight gain often show an inappropriate rapid catch up weight gain in the postnatal period or for the first 2 years of life and are also at higher risk for obesity in childhood [15].

Nutritional factors

These arise mainly from faulty feeding patterns which includes overfeeding, bottle feeding, exposure to formula feeds with added sugars, junk food, etc. Parental eating behaviour is a crucial determinant of the infant feeding practices [16]. Early addition of sugar sweetened beverages and fruit juices leads to four- to fivefold higher odds of obesity even in infants exclusively breastfed till 6 months of age. If the duration of exclusive breastfeeding is less than 6 months, the risk of obesity is 6- to 12-fold higher [15,17].

Genetic factors

Genetic obesity must be suspected in any infant and child under 5 years of age with severe obesity [4]. Genetic obesity can be polygenic, monogenic or syndromic.

Childhood and Adolescent Obesity

Obesity in children and adolescents is multifactorial and usually involves an interplay of factors such as genetic predisposition, behavioural and cultural practices and environmental influences causing an imbalance where energy intake exceeds expenditure [5].

Family and home factors

- Eating practices**:** Eating habits like high-energy diets, eating fewer fruits and vegetables, eating a lot of meat, frequent dining out, eating fast foods and ultra-processed foods, snacking, and consuming beverages with added sugar and eating quickly has a positive correlation with the development of obesity and overweight [18].
- Screen time: Children who are involved in sedentary activities, such as watching television, playing video games and using computers or mobile phones are at higher risk of developing obesity [19].

Environmental factors

Obesogenic environment refers to a setting, such as a home, school and community, "that encourages weight gain and is not supportive of weight loss." [20]. Physical environment indicators (residential density, access to green spaces, public transport, cycle lanes in urban areas, and sidewalks) and food environmental factors (like access to convenience stores, grocery stores, fast-food restaurants, online food delivery apps and fruit and vegetable markets) have evidence of association with obesity [21].

Policy level factors

- Online and T.V advertising of HFSS (High in Fat, Salt and Sugar) foods aimed at children promotes short-term consumption of energy-dense and nutrient-poor foods leading to childhood obesity [22].
- Food labeling policies - There is enough evidence to support that good and responsible food labeling can reduce the burden of childhood obesity by guiding the customers to buy the right/healthy foods by influencing consumer behaviors [23].

Individual factors

These could be prenatal, lifestyle related, endocrine related, genetic or due to other factors as enumerated in **Box I.**

A practical way to classify childhood obesity is exogenous/primary/lifestyle obesity and secondary/endogenous obesity. Exogenous obesity accounts for the majority of the cases of childhood obesity (>90%), whereas secondary causes account for <10% of the cases (endocrine causes account for <1% of all cases) [24,25].

Recommendation 3.0

Exogenous or primary obesity accounts for the majority of cases of childhood obesity. It is important to differentiate it from endogenous or secondary obesity as evaluation and management changes depending on the cause. (*Evidence level X, recommendation strong*)

4. Evaluation of Childhood Obesity

A. Clinical Evaluation (history and physical examination)

A detailed history and examination are essential to identify the etiology of obesity, associated comorbidities and to plan supporting laboratory evaluation and structured management strategies for sustained weight loss [4,25] (**Table I** and **Box II**). Red flags in identifying pathological or secondary causes of childhood obesity are enumerated in **Box III.**

Recommendation 4.0

4.1 Every overweight and obese child should have a detailed

Box I Causes of Childhood Obesity

Exogenous or primary obesity (>90%)

- Parental factors (The chance of obesity in a child if only one parent is obese is 40% and this increases to 80% chance if both parents are obese)
- Prenatal factors (Maternal nutrition or body mass index, maternal gestational diabetes mellitus, excessive weight gain in pregnancy, placental dysfunction and intrauterine growth restriction)
- Lifestyle factors (physical inactivity, poor sleep hygiene and excess screen time)
- Dietary factors (Parental eating behaviour, overfeeding, exposure to formula feeds, prolonged bottle-feeding, excess quantity of processed or packaged foods, trans fats, JUNCS food, carbonated or sweet beverages, nocturnal snacking)
- Environmental and policy level factors (easy accessibility to supermarkets, paucity of public grounds and gardens, commercials for HFSS (High in Fat, Salt and Sugar) foods

Endogenous or secondary causes of childhood obesity (<10%)

Endocrine (Hypothyroidism, Cushing syndrome, Growth hormone deficiency, Pseudohypoparathyroidism)

Monogenic disorders (Melanocortin-4 receptor haploinsufficiency, Leptin or leptin-receptor deficiency, Proopriomelanocortin deficiency, Prohormone Convertase-1 deficiency, etc)

Syndromes (Prader–Willi, Bardet–Biedl, Alstrom, Cohen, etc)

Neurological/hypothalamic causes (Space occupying lesions including craniopharyngioma, glioma, hamartoma, histiocytosis; infective causes comprising tuberculosis or meningo-encephalitis; brain surgery or radiotherapy; trauma; ROHHAD {Rapid onset obesity, hypothalamic dysregulation, hypoventilation, and autonomic dysregulation})

Drug induced (Glucocorticoids, Antiepileptics, Antipsychotics, Sulfonylureas)

Psychological (Depressive disorders, eating disorders such as binge eating)

Miscellaneous causes: Emotional deprivation, neglect or abuse, single overprotective parent; children and young people with special health care needs (developmental and physical disabilities); children with autism spectrum disorder / attention deficit hyperactivity disorder)

M*odified from Khadilkar V, et al. Evaluation of children and adolescents with obesity. Indian J Pediatr. 2021;88:1214-1221)*

Table I Clinical Examination of an Overweight or Obese Child

Parameters	*Etiology/comorbidity*
Anthropometry	Weight, height, body mass index, mid-parental height, watch for changing centiles upwards Plot on growth chart
Body fat distribution	Waist circumference
Pubertal staging (sexual maturity rating)	
Lipomastia and buried penis	Simple obesity
Micropenis (hypogonadism), undescended testis	Prader-Willi syndrome
Delayed/precocious puberty	Hypothalamic/pituitary lesions
Moon facies, buffalo hump	Cushing syndrome (exogenous or endogenous)
Blood pressure	Compare with age/sex/height appropriate references
Skin examination	Acanthosis nigricans - insulin resistance acne, hirsutism - PCOS
	Violaceous stria - Cushing syndrome
	Xanthelasma, skin tags - dyslipidemia
	Intertrigo
Hair	Dry, brittle- hypothyroidism
	Red hair – monogenic (POMC mutation)
Genetic syndromes (dysmorphism)	
Small hands and feet	Albright hereditary osteodystrophy
Polydactyly, retinitis pigmentosa	Bardet-Biedl syndrome
Skeletal complaints like bowing of legs, limp, of hip motion	Slipped capital femoral epiphysis, genu valgum, tibia vara, limited range fractures
Hepatomegaly	Non alcoholic fatty liver disease

Box II Evaluation of an Overweight or Obese Child Based on History and Possible Etiology/Comorbidity

Dietary history

Diet rich in carbohydrate/ fat/ energy dense foods

Lack of breastfeeding and early introduction of complementary feed

Increased consumption of JUNCS (junk foods, ultra-processed foods- nova Classification 4, Nutritionally inappropriate foods, caffeinated/ colored/ carbonated foods/ beverages and sugar-sweetened food and beverages)

Large portion size, snacking

Physical activity

Decreased physical activity or sedentary habits

Increased non- academic screen time

Irregular sleep duration

Birth history

Birth weight, intrauterine growth restriction, post-natal events

Antenatal

Maternal pregnancy overweight/gestational diabetes/hypertension

Menstrual history

Menstrual irregularity and hirsutism- Polycystic ovarian syndrome

Family history

Obesity and associated complications like hypertension, heart disease/eating habits/behavioral pattern

Development history

Attainment of milestones/ current school performance/ developmental disabilities (chromosomal/genetic syndromes)

Drug intake: Corticosteroids, Olanzapine, risperidone, antiepileptics like valproate, gabapentin

Psychological assessment

Eating disorder, anxiety, depression, self-esteem, readiness and ability for behavior change, peer relationship, bullying

Hypothalamic obesity- CNS infection, trauma, radiation, mass

Headache, vomiting, visual disturbances

Shortness of breath, exercise intolerance: Asthma

Acne and hirsutism: Polycystic ovarian syndrome

Snoring, sleep disruption, morning headaches, day-time somnolence: Obstructive sleep apnea

Hip, knee or back pain: Slipped capital femoral epiphyses

Abdominal pain: Gastroesophageal reflux, constipation, gall bladder disease, non-alcoholic fatty liver disease

Recurrent headache: Pseudotumor cerebri

history and physical examination including specific measurements such as BMI, waist circumference and blood pressure, to identify etiology and associated comorbidities. (*Evidence level B, Recommendation level strong*)

Box III Red Flags for Pathological Obesity

Early onset obesity - very rapid gain in weight in first few years

Short stature for age or mid parental height/ poor linear growth

Hyperphagia–non-discriminatory

Dysmorphism

Associated features, e.g., developmental delay, vision abnormalities, behavioral problems

History of steroid intake

Hypogonadism

B. Defining overweight and obesity using BMI (5-18 year old) and weight for length/height (under 5 year old) on age appropriate growth charts

BMI is the most used tool in clinical practice for screening, diagnosing and grading overweight and obesity. It is easy to use, inexpensive and in most cases, strongly correlates with the standard methods of measuring body fat such as Dual-energy *X*-ray absorptiometry (DXA) [26]. The advantage of BMI is that it is not only used for classifying weight status and associated health risk, but it is also useful to follow a child or adolescent's weight trajectory over time, particularly in response to individualized treatment or public health measures [27].

Traditionally, the BMI cut-offs used by Centre for Disease control (CDC) and WHO for overweight and

obesity in children 5-18 years are ≥85th percentile (≥ +1SD) and ≥95th percentile (≥+2 SD), respectively [4,5,28]. These cut-offs coincide with the adult cut-offs for overweight and obesity of BMI 25 kg/m^2 and 30 kg/m^2, respectively. The Asian population tends to have adiposity and increased cardio-metabolic risk at lower BMI, hence the International Obesity Task Force (IOTF) and WHO have suggested lower cut-offs to define overweight and obesity in Asian children [29,30]. The IAP charts for BMI devised in 2015 follow the WHO and IOTF suggested cutoffs, where the 23 adult equivalent is used to define overweight and 27 adult equivalent is used to define obesity [31]. Numerous studies have demonstrated the advantages and utility of IAP charts as compared to the WHO charts in Indian children [32].

In the recently released PES as well as the AAP guidelines for childhood obesity, the classes of severe obesity have been redefined as follows [4,5]: Class 2 obesity: ≥120% to < 140% of 95th percentile or BMI ≥35 kg/m2 to < 40kg/m2 whichever is lower based on age and gender; and, Class 3 obesity: ≥140% of the 95th percentile or BMI ≥40 kg/m2 whichever is lower based on age and gender.

Web Table I and **II** and **Web Fig. 1** and **2** show the percentiles for extended IAP BMI charts including class 2 and 3 obesity based on 120% and 140% of the IAP obesity cutoff values of 27 adult equivalent, respectively. These extended charts need further validation but may be useful in deciding treatment options and monitoring response to therapy.

In a busy pediatric outpatient department (OPD), BMI calculation takes time and often gets looked over. To overcome this, IAP has recently published the pediatrician-friendly growth charts which contain a quick screening BMI tool for 8 -18 year old children, embedded in the growth chart itself [33]. This tool eliminates the need for calculation as weight can be plotted against the height directly on the tool. The drawback of this tool is that a child at the extreme ends of height-for-age could be incorrectly classified. Hence, if a child is found to be abnormal on the BMI tool, his/ her BMI should be verified on IAP BMI charts.

In children between 2-5 years of age, country specific BMI charts are used to diagnose overweight and obesity [4,5]. However, IAP growth charts are not available for children under 5 years of age. Hence, in children under 5 years of age, IAP recommends WHO weight for height/length charts to diagnose overweight and obesity. Overweight is defined as weight-for-length/height ≥2 standard deviation (SD) (≥97th percentile) but less than + 3 SD (<99.9th percentile) and obesity as values ≥3 SD (≥ 99.9th percentile) on the WHO charts [34].

In children under 5 years, growth monitoring should be done at every vaccine visit (or at least 6 monthly after first birthday). In children greater than 5 years, BMI calculation and plotting should be done at least annually [35].

Recommendation 4.0

4.2 In 5-18 years old Indian children, BMI should be used to diagnose overweight and obesity. The IAP 2015 BMI charts should be used for plotting the BMI in Indian children. (*Evidence level B, Recommendation level moderate*)

4.3 BMI cutoffs (on IAP 2015 BMI charts) of 23rd adult equivalent should be used to define overweight and 27th adult equivalent should be used to define obesity in Indian children and adolescents aged 5-18 years.
(*Evidence level B, Recommendation level moderate*)

4.4 In Indian children under 5 years of age, weight for length/ height using WHO charts should be usedto diagnose overweight and obesity. A child whose weight-for-length/height ≥+2 SD (≥97th percentile) but less than + 3 SD (<99.9th percentile) is diagnosed as overweight and value ≥3 SD (≥99.9th percentile) is diagnosed as obese.
(*Evidence level B, Recommendation level moderate*)

4.5 In children under 5 years weight for length/ height plotting should be done at every vaccine visit or at least 6 monthly (after 1st birthday). In children greater than 5 years, BMI plotting should be at least annually.
(*Evidence level X, Recommendation level strong*)

C. Utility of emerging measures of adiposity in overweight and obese children

The BMI, although useful, has some limitations. BMI does not directly assess body composition (and hence fat content) and therefore has low sensitivity for detecting excess adiposity (around 50%). BMI is not equally valid across gender, age groups (hence the use of Z-scores in children) and race or ethnicities [36]. BMI cannot differentiate between lean and fat mass. BMI alone is an insufficient marker of abdominal adiposity and hence can fail to fully detect cardio-metabolic risk [37]. In fact, in 25% of cases, normal BMI is compatible with excess body fat, which is very commonly seen in the Asian population [31]. In such individuals, waist circumference (WC) is a simple measure of adiposity which is not difficult to standardize and apply clinically. The combination of BMI and WC, thus identifies a high-risk obesity phenotype superior to either parameter alone [37].

WC is an important predictor of visceral adiposity. It is strongly associated with metabolic syndrome, all-cause and cardiovascular morbidity and mortality with or without adjustment for BMI [38,39]. WC is measured horizontally in a standing child just above the lateral border of the right ileum with a stretch-resistant tape at the end of normal

expiration [40]. Like BMI, country-specific growth charts should be used for plotting WC. Traditionally, WC above the 90th percentile is used as a cut-off for identifying central adiposity and children who are at risk of developing metabolic syndrome [41]. A multicentre, large-scale trial has shown that a WC cut-off above the 70th centile may be more suitable in screening and identifying Indian children at risk for metabolic syndrome [42]. However, more Indian studies are required to validate these WC cutoffs.

In a busy clinical setting, it is sometimes difficult to measure WC, as the physical landmarks for measurement of WC are not always clear in overweight and obese children. Recently, measures such as wrist circumference are being used to identify children with metabolic risk as they are easier to measure and more socially acceptable. India-specific wrist circumference percentiles have been published in the past and like WC, 70th percentile is used as the cutoff to screen hypertension [43]. However, more Indian studies on overweight and obese children are necessary to validate the cutoffs.

Among the various methods used for analysis of body composition, dual-energy *X*-ray absorptiometry (DXA) has the highest sensitivity and specificity in detecting body fat in the pediatric population [44]. Due to its accuracy, speed, low radiation dose and ease of use, DXA has now become one of the most commonly used standards for measuring body composition in the children. However, due to it being expensive, requirement of trained operators and lack of standardization due to different machines and software available, its current use is limited more for research purposes in the Indian scenario. Bioelectrical impedance analysis (BIA) although less accurate than DXA is routinely used for body composition analysis in the field/ clinical settings due to ease of use, portability, easy availability and relatively low cost [45].

Recommendation 4.0

4.6 Waist circumference should be routinely measured in all overweight and obese children and plotted on India specific charts, as it is a key measure of cardio-metabolic risk. (*Evidence level B, Recommendation level strong*)

4.7 In Indian children, waist circumference greater than 70th percentile can be used as a cutoff for identifying children with central adiposity who are at a risk of developing metabolic syndrome.
(*Evidence level C, Recommendation level weak*)

D. Laboratory evaluation in childhood obesity

The goal of laboratory evaluation is to screen for associated comorbidities and MS. Since exogenous obesity is the most prevalent type of pediatric obesity, testing for secondary causes should only be done in presence of clues on the history and examination.

Endocrine disorders are suspected in children with obesity who also have short stature or poor growth velocity and the presence of additional diagnostic clues [4,5] (**Box IV**). In obese children, thyroid function tests should be carefully interpreted. Mild elevation of TSH with normal or mildly elevated free T3, T4 does not indicate hypothyroidism. The mild TSH elevation is due to peripheral resistance to thyroid hormone as well as due to increased hypothalamic TRH drive caused by increased leptin levels [46].

In south-east Asia, due to the increased prevalence of consanguineous marriages, genetic disorders could be the etiology in 30% of morbidly obese individuals [47]. They present with early or rapid onset obesity with hyperphagia as the defining symptom. Genetic diagnosis is important for prognosis, therapeutic management and counseling. The threshold for genetic testing should be lower in the presence of consanguinity, early-onset obesity (<5 years of age), dysmorphism, developmental delay, growth retardation, congenital abnormalities, vision abnormalities and hormone deficiencies [48].

Recommendation 4.0

4.8 The committee recommends against routine evaluation for endocrine cause except in short and obese children with additional diagnostic clues.

(*Evidence level C, Recommendation level moderate*)

4.9 Genetic testing should be only recommended for early or rapid onset obesity (<5 years of age) with hyperphagia, clinical pointers and/or family history of suspected syndromic obesity.
(*Evidence level B, Recommendation level moderate*)

Box IV Suspected Etiology and Laboratory Evaluation of Pediatric Obesity

Exogenous obesity: Fasting lipid profile, alanine aminotransferase (ALT), renal function tests, fasting blood glucose, oral glucose tolerance test, glycosylated hemoglobin (if indicated)

Hypothyroidism: TSH, free thyroxine

Cushing syndrome: Serum or salivary cortisol (11 PM), dexamethasone suppression test, 24-hour urine-free cortisol test

Growth hormone deficiency: Bone age, Insulin-like growth factor-1, Insulin-like growth factor binding protein-3, growth hormone stimulation test

Pseudohypoparathyroidism: Calcium, phosphorus, parathyroid hormone, *X*-ray hand

Genetic or monogenic obesity: Specific genetic test (advised by a specialist)

Hypothalamic and pituitary disease: Magnetic resonance imaging (MRI) of brain

E. Metabolic syndrome in Indian children

MS in adults is diagnosed by the presence of at least 3 out of the 5 risk factors: central adiposity, elevated blood pressure, hyperglycemia, elevated triglycerides and reduced high-density lipoprotein cholesterol (HDL-C). But there is still no consensus for the definition for MS in children [49,50]. The prevalence of MS is 13.6% in overweight and 46.4% in obese Indian children aged 10-18 years [51].

As per International Diabetes Federation (IDF), MS can be diagnosed in children aged 10-16 years with the following criteria: presence of abdominal obesity (defined by waist circumference (WC) ≥90th centile for age, gender and ethnicity) with ≥2 of the following: Triglycerides ≥150 mg/dl, HDL-cholesterol ≥40 mg/dl, fasting blood glucose ≥ 100 mg/dl and systolic blood pressure ≥130 mm of Hg; Diastolic blood pressure ≤85 mm of Hg (≥95th centile adjusted for age, height and gender) [52].

This definition fails to define MS in children <10 years of age (screening advised if WC ≥90th centile for age, gender and ethnicity). IDF advocates the use of adult cut-offs for adolescents >16 years of age. As discussed earlier, it is important to note that Indian population is likely to develop MS at lower BMI and WC; thus ≥70th percentile for screening may be more appropriate [42].

F. Comorbidity screening

Pediatric obesity is associated with an increased prevalence of dyslipidemia. Due to high prevalence, NHLBI (National Heart, Lung and Blood Institute) and AHA (American Heart Association) recommend universal screening for dyslipidemia at 9-11 years of age and then at 17-21 years of age with a non-fasting lipid sample which if abnormal will need confirmation on a fasting lipid sample [41,53] (**Table II**). Due to the higher prevalence of dyslipidemia in overweight and obese children, a fasting lipid sample is recommended for screening [41].

Obesity is an independent risk factor for the development of pre-diabetes and type 2 diabetes (T2D), which is being increasingly seen in children younger than 10 years. ADA recommends screening for diabetes in children at 10 years of age or pubertal onset, whichever is earlier, in the presence of risk factors and earlier in the presence of symptoms [54]. It is evaluated by fasting blood glucose or oral glucose challenge test. In the absence of unequivocal hyperglycemia, the diagnosis is confirmed if 2 different tests are above threshold or a single test is above the threshold on 2 separate occasions. Pre-diabetes is defined as fasting plasma glucose between 100-125 mg/dL or 2 hour plasma glucose on oral glucose tolerance test (OGTT) between 140-199 mg/dL. Diabetes is defined as fasting plasma glucose ≥126 mg/dL or 2 hour plasma glucose on OGTT ≥200 mg/dL. HbA1c is not commonly recommended for the diagnosis of T2D in children due to racial-ethnic variations [55]. Measurement of insulin to detect insulin resistance is not recommended due to lack of standardized assay and increased variability of the results in non-obese and obese children [4,56].

Non-alcoholic fatty liver disease (NAFLD) also known as metabolic dysfunction associated steatotic liver disease (MASLD) is the most common chronic liver disease with prevalence as high as 34% in obese children [57]. The risk factors for MASLD include Asian ethnicity, male gender, > 10 years of age, positive family history, pre-diabetes or DM, OSA and dyslipidemia. Alanine aminotransferase (ALT) is the screening test (normal <26 U/L in males and <22 U/L in females as per liver SAFETY (Screening ALT for Elevation in Today's Youth) study even though it correlates poorly with disease severity [58]. It is recommended to evaluate for other liver pathology in the presence of ALT >2 times the sex-specific upper limit of normal. Additional diagnostic evaluation of the liver (ultrasonography, FibroScan, MRI) may be needed if ALT >80 U/L. It is recommended to screen all obese and overweight children ≥9 years of age with risk factors for MASLD [59].

Children and adolescents with obesity are at a higher risk for hypertension with a prevalence of 5-30%.The 2017, AAP guidelines on childhood hypertension recommend screening of all children from 3 years of age [60]. Elevated BP is defined as BP percentile ≥90th to < 95th for age and gender, stage 1 hypertension is defined as ≥95th to <95th percentile +12mmHg or 130/80 to 139/89 mm Hg (whichever is lower) and stage 2 hypertension is defined as ≥95th percentile +12mm Hg or ≥140/90 mm Hg (whichever is lower). Indian children's blood pressure reference percentiles are available and should be used for evaluation [61].

Table II Cutoffs for Lipid Levels Among Children

Serum lipids	*Acceptable, mg/dL*	*Borderline, mg/dL*	*Abnormal, mg/dL*
Total cholesterol	<170	170-199	≥200
LDL cholesterol	<110	110-129	≥130
Non-HDL cholesterol	<120	120-144	≥145
Triglycerides			
0-9 y	<75	75-99	≥100
10-19 y	<90	90-129	≥130
HDL cholesterol	>45	40-45	<40

LDL: low-density lipoprotein; HDL: high-density lipoprotein. Modified from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128 Suppl 5:S213-56.

There is an increased prevalence of obstructive sleep apnea (OSA) in obese children (45% in obese children vs 9% in non-obese children) [62]. It is to be screened using a polysomnogram (gold standard diagnostic test) based on presence of supporting history and examination.

Obese adolescent girls are at increased risk of developing PCOS with prevalence of 3-11% [63]. It is difficult to diagnose during the first three post-menarcheal years due to lack of consensus on diagnostic criteria and presence of physiological menstrual abnormalities and mild hyperandrogenism. The diagnosis of PCOS in an adolescent girl should be made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of irregular menstrual cycles along with dysfunction of ovulation [64]. Polycystic ovarian morphology on ultrasound alone is not reliable to diagnose adolescents because multifollicular ovaries are a feature of normal puberty that subsides with the onset of regular menstrual cycles.

There is 32% more risk of developing depression in obese children as compared to non-obese children and it has a significant impact on obesity management [65].It is also important to evaluate musculoskeletal disorders due to their high association with obesity [66]. Idiopathic intracranial hypertension is commonly associated with obesity, especially in adolescent girls (3.5 times the risk than non-obese population) and presents with headaches, tinnitus or visual changes [67].

Recommendation 4.0

4.10 All obese children ≥10 years (irrespective of risk factors) and obese children aged 2-10 years (if risk factors like positive family history of obesity, dyslipidemia, premature coronary artery disease, diabetes or hypertension are present), or waist circumference greater than 70th percentile, should be evaluated for hypertension, dyslipidemia, hyperglycemia, MASLD and other comorbidities.
(*Evidence level B, Recommendation level moderate*)

4.11 All overweight children ≥10 years of age should be evaluated for hypertension, dyslipidemia, hyperglycemia, MASLD and other comorbidities in presence of risk factors or waist circumference greater than 70th percentile. (*Evidence level B, Recommendation level moderate*)

5. Prevention of Childhood Obesity

A. Dietary role in the prevention of childhood obesity

Preventive strategies in infancy [68]:

- Promotion of healthy maternal nutrition and weight status at reproductive age and during pregnancy
- Optimal infant feeding practices
  - Exclusive breastfeeding till six months of age.
  - Continue breastfeeding till 2 years and beyond.
  - Avoid formula feed. If mother's milk is not available, pasteurised donor human milk (if available) is better than formula
  - Fresh home-made complementary foods starting at 6 months
  - Avoid extra sugar (first two years of life) and low salt (first year)
  - Avoid sugar-sweetened beverages (SSB) and packed fruit juices.
  - Avoid packaged food.
  - Avoid forced feeding, promote responsive feeding
  - No bottle feeding
- Careful, regular monitoring of infant growth to detect early excessive weight gain.

Preventive strategies in children and adolescents: Parents/ caregivers should provide a healthy eating environment, set meal timings and routine for the child. The diet should be a blend of diverse food groups to provide sufficient energy, protein, fats, micronutrients and vitamins in optimal proportions [69]. Use of recommended dietary allowances (RDA) and the estimated average requirements (EAR) including the Tolerable Upper Limits, published by National Institute of Nutrition, ICMR, 2020 for macro-nutrients and micronutrients is recommended [70]. Children with obesity are more prone to develop iron deficiency with or without anemia. Therefore, active screening and treatment of anemia is recommended in obese children. Many children are likely to have other deficiencies, like vitamin B 12, zinc, vitamin D, etc.,which need to be addressed.

Foods should routinely be prepared with low salt, little or no added solid fats/trans-fat and free sugars should be restricted to <5% of total energy intake, especially in beverages [71]. Beyond 2 years, adequate consumption of dietary fiber is encouraged by eating a variety of fiber-rich fruits, vegetables, cereals, and whole-grain products. The consumption of JUNCS (Junk foods- high in fat, high in salt, high in sugar with very low nutrients, ultra-processed foods-Nova Classification 4, nutritionally inappropriate foods, caffeinated/colored/carbonated foods/beverages, and sugar-sweetened food and beverages) should be avoided in children and adolescents [72]. Whole fruit intake should be encouraged over fruit juice as the latter has high sugar content, lacks fiber and provides no nutritional advantage. Freshly cooked home food is preferred over packaged/ processed foods as the latter results in higher consumption of

calories, salt, free sugar and saturated fats. The habit of liberal water intake should be cultivated over colas, sugar-sweetened beverages, fruit juices/drinks at home and school.

Parents should adopt an authoritative (i.e., by setting examples) rather than authoritarian approach towards development of healthy eating habits among children. They should recognize and respond to the child's hunger and satiety cues and avoid overfeeding and forced-feeding. Children are encouraged to develop self-regulation of over-feeding skills to regulate their meal intake (portion size) [73,74]. They can involve children in food shopping and meal preparation and entrust them with the responsibility for healthy cooking and eating practices as they get older. Threatening, bribing or forceful attempts to make children eat and finish their meals makes them insensitive to hunger and satiety cues, thereby resulting in overeating. The intake of food and beverages while watching TV/ screen should be strongly discouraged. Food should never be a part of reward or punishment to a child.

Schools are viewed as an essential setting for intervening in children's obesity-related behavior. Teaching staff can significantly facilitate and contribute to delivery of the intervention, increasing its sustainability. School events/ fetes/programs should not be sponsored by manufacturers of unhealthy foods/drinks.

The AAP Clinical Decision Support 10 chart recommends the pneumonic '5-2-1-0' rule for prevention of obesity among children. This '5-2-1-0' rule translates to consumption of at least 5 servings of fruits and vegetables each day, limit screen time < 2 hours per day, participation in 1 hour of physical activity every day (moderate to vigorous physical exercise every day) and no intake or 0 intake of sugar-sweetened beverages daily [75].

Recommendation 5.0

5.1 Prevention of childhood obesity should start by promoting healthy maternal weight in the prenatal period, smoking cessation before pregnancy, appropriate gestational weight gain and diet, exclusive breastfeeding in the first 6 months, ensuring appropriate weight gain in infancy and transition to balanced home-made complementary foods, avoid salt (first year of life) and extra sugar (first two years of life), avoiding packaged foods and forced feeding. (*Evidence level B, Recommendation level strong*)

5.2 Childhood nutrition should have a balanced diet, healthy eating pattern and behaviour. Child's diet should be a blend of diverse food groups to provide sufficient energy, protein, fats, micronutrients and vitamins in optimal proportions. (*Evidence level A, Recommendation level strozng*)

5.3 Appropriate portion sizes should be offered to children depending upon the child's age and the energy density of the food. (*Evidence level C, Recommendation level moderate*).

5.4 It is recommended to avoid the consumption of JUNCS food and beverages in children and adolescents. (*Evidence level B, Recommendation level strong*)

B. Role of physical activity/exercise in prevention of pediatric obesity

Physical activity and or exercise is an essential conjunct to a healthy diet for the prevention of obesity in children. Exercise reduces visceral adipose tissue, promotes increased muscle mass, independently reduces the risk for cardio-metabolic complications, improves motor and cognitive development, psychosocial well-being, skeletal health and overall risk of mortality [76].

Infants are encouraged to remain active throughout the day through activities like reaching and grasping, pulling and pushing, and floor play (including crawling) in a safe and supervised environment. Favorable health outcomes are associated with 30 minutes/day of prone position (tummy time) in young infants. Toddlers and preschoolers should engage in varied physical activities as per their developmental age, that is spread across the day (at least 180 minutes a day). They should not be restrained for more than 1 hour (e.g., in prams/strollers, high chairs, or strapped on a caregiver's back) [77].

Older children and adolescents should regularly engage in both aerobic and anaerobic exercises to maintain good health and strengthen their muscles and bones. An average of at least 60 minutes of moderate to vigorous physical activity spread throughout the day is recommended for children and adolescents (5-17 years) [78]. High-intensity interval training/ resistance exercises (20 minutes in a day) should be incorporated at least 3 times a week to strengthen their muscles and bones [79]. Besides planned exercise, children should actively participate in daily chores, sports, recreational work, and team play. The activities should be age-appropriate, enjoyable, sustainable, and well-aligned with family dynamics and the child's daily routine. Safe play areas should be identified in all communities for children, especially for those belonging to low socioeconomic strata. The school curriculum should also incorporate 30 minutes of exercise schedule every day.

There is evidence to support an association of inadequate and poor-quality sleep with the risk of overweight and obesity in children. Recommended sleep duration by age is: 0-5 years – at least 11 hours, 5-10 years – at least 10 hours, 10 years and above – at least 9 hours [80].

Recommendation 5.0

5.5 Age-appropriate, moderate to vigorous physical activity for at least 60 minutes per day, should be recommended for

the prevention of obesity in older children and adolescents (5-17 years).
(*Evidence level B, Recommendation level moderate*)

5.6 Infants, toddlers and preschoolers should be encouraged to remain active throughout the day through age-appropriate activities and play.
(*Evidence level B, Recommendation level moderate*)

5.7 Sleep hygiene should be followed for getting recommended age-appropriate good quality sleep to decrease likelihood of developing childhood obesity.
(*Evidence level B, Recommendation level moderate*)

C. Role of screen time in the prevention of pediatric obesity

Sedentary behavior, which comprises predominantly recreational screen time (time spent watching television, computer and smart phone usage) in children is likely to track from preschool years to preadolescent age and to young adulthood and is positively associated with obesity. The combined effect of reducing recreational screen time (<2 hours) and increasing moderate to vigorous physical activity (>60 minutes) per day, brings down the odds of being overweight/obese by three to fourfold [81]. A review of 13 studies found moderately strong evidence for associations between screen time and adiposity. The effects of increasing screen time go beyond physical morbidities and affect development, mental health and quality of life [19].

As a part of its strategy on Ending Childhood Obesity WHO released its recommendations on screen time for under 5 children in 2019 [82]. It recommends no screen time for children under 1 year of age and not more than 1 hour for under 5 years of age. The Indian Academy of Pediatrics has published comprehensive recommendations on 'Screen Time and Digital Wellness in Infants, Children and Adolescents' as well as Parental Guidelines on screen time [83]. The recommended screen time is zero up to 2 years, maximum 1 hour from 2-5 years and 2 hours from 5-10 years, the lesser the better. Children in the 10-18 age group is advised to balance screen time with other age-specific developmental goals. This includes recreational screen time as well as time spent on screen to complete educational assignments at home or school. Screen time should be mainly for the purpose of education and studying. Recreational screen time should be kept to bare minimum.

Recommendation 5.0

5.8 The recommended screen time is no screen time up to 2 years, maximum 1 hour from 1-5 years and 2 hours from 5-10 years, the lesser the better. The 10-18 age group is advised to balance screen time with other age specific developmental goals.
(*Evidence level A, Recommendation strong*)

6. Management of Childhood Obesity

A. Principles of management of pediatric obesity

The goals of treating childhood and adolescent obesity are to decrease adiposity, alleviate related physical and psychosocial comorbidities, halt the progression to chronic illnesses and support longterm weight maintenance. The management should have a multimodal approach that includes various healthy lifestyle modifications like dietary advice, regular physical activities, behavioral interventions aiming at modifying eating behaviors, decreasing sedentary behaviors and encouraging sleep routines, medications, and surgical options (only if indicated) [4,5,74].

To effectively treat obesity, behavioral support programs must be family-centered and developmentally appropriate. For instance, treatment for children may be primarily parent-based, whereas teenagers may need more self-direction [84]. Studies have shown that family-based therapies were helpful in reducing child weight by a moderate to large effect. Furthermore, family-based interventions that resulted in both short- and long-term weight loss in children were more likely to focus on both parental and family weight management in addition to the children [85].

Motivational interviewing (MI) is a patient-centered counseling strategy, which acknowledges and attends to a patient's needs [86]. This strategy encourages a patient's personal motivation for development, in contrast to the more conventional model in which a clinician prescribes behavior adjustment. Prospective studies on MI have revealed that the technique improves weight status as compared to control systems. The findings revealed a greater decrease in BMI percentile or BMI *Z* score and a lesser increase in BMI [87].

The American Academy of Pediatrics (AAP) previously had suggested a stage-based approach for pediatric weight management to tackle obesity at different ages with varying levels of severity [75,88].

Recommendation 6.0

6.1 The initial management of pediatric obesity is lifestyle modification at the primary HCP level. If this fails to produce results after 6 months, the management is transferred to a multidisciplinary team for multimodal approach. This will involve caregivers including parents, family and school, HCPs or pediatricians, pediatric specialists for comorbidities like endocrinologists/pulmonologists, psychologists or counselors and dieticians in the prevention, management and follow-up care of overweight and obese children.
(*Evidence level X, Recommendation level strong*)

B. Dietary management of obesity

Dietary management in infantile obesity: It is important to strike a delicate balance between allowing the infant's

nutrient needs for optimal growth and development while at the same time not allowing excessive weight gain. This can be achieved as follows- Premature initiation of complementary foods is linked with increased BMI and hence complementary feeding must be started only after 6 months of exclusive breastfeeding. Standard infant feeding recommendations of IAP must be followed with special emphasis on avoiding sugar-sweetened beverages and junk food [68,72]. In contrast, in genetic (monogenic and syndromic) obesity, the physiological hunger-satiety feedback is not intact. Hence standard nutritional counseling may not be effective. The energy intake in such cases will have to be individualized based on activity level and behavior.

Ensure responsive feeding wherein the caregiver recognizes the hunger cues, engages, and encourages self-feeding in an age-appropriate manner. Forced-feeding must be avoided at all ages. In genetic obesity, due to hyperphagia, the management must focus on controlling access to food and reducing food preoccupation. Caregivers must be counseled that this may lead to temper tantrums, outbursts etc.

Dietary management in obese children and adolescents: The goal is towards weight maintenance rather than weight loss in children; unless in severe obesity where gradual weight loss is recommended [89]. Calorie restriction is not usually recommended before 6 years of age and increasing physical activity and weight maintenance are more rewarding.

Weight maintenance for 1-2 years will reduce excess weight-for-height (approx. 20%) in a growing child. A healthy diet based on the Traffic Light/Stop Light diet is an acceptable, feasible and sustainable intervention for weight management in overweight and obese children [90]. An alternative approach towards a healthy and balanced diet is based on the principles of MyPlate (USDA *choose-myplate.gov/* ICMR-NIN My plate) which can be adapted to different food cultures and ethnicities.

For the management of children with severe obesity and/or those with comorbidities or complications, a gradual weight loss is recommended (0.5 kg per month for 2-5 years and 1 kg per week for older children and adolescents) [91]. Intervention trials using varied dietary strategies for intensive weight management in children or youth/adults with severe obesity have yielded inconsistent results in reducing BMI. These dietary strategies were based on modifying the macronutrient content [92,93] and/or the quality of carbohydrate [94,95] or caloric restriction like very low energy diets (VLED) [96,97], protein-sparing modified fast [98,99] or a low-carbohydrate diet [101,102]. Though there is sufficient evidence to support safety of energy-restricted diets, it should be prescribed only under close supervision and intensive monitoring [98,99]. Potential risk for disordered eating behaviours, growth impairment, loss of lean body mass and micronutrient deficiency remains a concern in adopting these strategies.

There is no 'one size fits all' approach. Therefore, the diet plan should be individualised taking into consideration the age, pubertal status, rate of growth, BMI percentile, associated comorbidities, family preferences and socio-economic status.

Recommendation 6.0

6.2 Interventions for children and adolescents with obesity should aim at weight maintenance initially using healthy dietary practices and behaviors that are culturally acceptable, affordable, and ensure long-term compliance.
(*Evidence level B, Recommendation level strong*)

6.3 Children with severe obesity and or with comorbidities can be considered for energy-restricted supervised intensive dietary interventions (e.g., very low- carbohydrate diets, very low-energy diets and lower glycemic index diets) to achieve gradual weight loss.
(*Evidence level C, Recommendation level weak*)

6.4 Dietary intervention should be an individualised family-based approach on individual needs, preferences, and medical conditions which optimises outcomes for children and adolescents with severe obesity and or cardiometabolic complications.
(*Evidence level B, Recommendation level strong*)

C. Role of physical activity/exercise in the management of pediatric obesity

Exercise intervention in overweight and obese children should be tailored to the age, gender, preference, socio-economic status and fitness level of a child. Barriers that limit the participation of children in physical activities should also be identified and addressed adequately before any intervention. A quick evaluation of the child for any disability, which may hinder the physical activity e.g., slipped capital femoral epiphyses (SCFE) should be done, before guiding the physical activity.

Moderate to vigorous aerobic activity at least 60 min per day along with resistance exercise (at least 20 min over 3 days/week) are effective interventions for decreasing body weight, body mass index, and fat mass in children with obesity [102]. The combination of aerobic exercise and strength training has synergistic effects. A goal setting approach is suggested to gradually build up the child's physical activity to recommended level. Goals should be individualized for each child.

Non-weight-bearing activities like recumbent and stationary cycling, rowing ergometry and swimming are

recommended for children with severe obesity. Gradually, focus is shifted towards activities that promote core stability, posture, gait and cardiorespiratory endurance. Bone-strengthening activities like jumping and skipping are introduced later and continued at least three times per week. A targeted and gradual increase in time and intensity of activities is recommended in a stepwise fashion.

Recommendation 6.0

6.5 Exercise intervention in obese children should be tailored as per the age, gender, preference, socioeconomic status and disability or fitness level of a child. A combination of aerobic and strength training exercises is recommended for the management of children with obesity.
(*Evidence level B, Recommendation level moderate*)

D. Pharmacological management of childhood obesity

Pharmacotherapy options are offered only in adolescents over the age of 12 years, after a significant well focused lifestyle modification program has not yielded results or when an associated comorbidity warrants it [5]. Drugs approved for children are very limited and lack long-term safety and efficacy data (**Table III**) [103]. The drug therapy is termed ineffective if it fails to safely reduce BMI by 5% over 12 weeks of consistent use [4]. As the drugs have a differential effect on different comorbidities, the choice often depends on the associated comorbidity profile. They are not recommended as monotherapy and are always prescribed along with a comprehensive lifestyle modification program. A systematic review evaluating weight loss medications in adolescents found a modest weight reduction with pharmacotherapy with short or no post-intervention follow-up [103,104].

Glucagon-like peptide-1 (GLP-1) analogues have been recently approved by the Food and Drug administration for long-term treatment of obesity in children aged ≥12 years. In recently published data, Liraglutide showed a modest weight loss as compared to placebo and lifestyle therapy alone (absolute change in weight was -4.50 kg [95% CI -7.17 to -1.84] at end of 56 weeks, mean (SD) starting weight in liraglutide group being 99.3 (19.7) kg [105,106]. Its use may be limited by the need for daily subcutaneous injections and the rebound weight gain after stopping therapy. Another GLP-1 analogue, Semaglutide, resulted in significant weight loss as compared to placebo and lifestyle modification alone (absolute change in weight was -17.7 kg [95% CI -21.8 to -13.7] at end of 68 weeks, mean starting weight being 107.5 (24.5) kg [107]. It is used as a once-a-week subcutaneous injection. Orlistat produces a modest weight loss (reduces BMI by 0.5-1.5 kg/m2) with significant gastrointestinal side effects with increased discontinuation rates. A recent study showed improvement in dyslipidemia but with minimal benefit on BMI reduction and hypertension [108]. Metformin produced <5% weight loss when used along with lifestyle modification. Due to this, it may be used in obese adolescents who are diabetic or prediabetic [109]

Recommendation 6.0

6.6 Adjunct use of pharmacotherapy to a comprehensive lifestyle modification program may be recommended in adolescents ≥12 years of age having class 2 obesity with immediate or life-threatening comorbidities or class 3 obesity with or without comorbidities.
(*Grade B, Moderate recommendation*)

E. Surgical management of pediatric obesity

Severe obesity (class 2 and 3 obesity) presents with a significant risk of comorbidities and early mortality. Due to the significantly lesser success of intensive lifestyle and medical management in weight reduction, surgical weight loss options are being increasingly used.

It may be offered to children older than 12 with [5,110] Class 2 obesity with significant comorbidities (T2DM, MASLD, OSA, Blount disease, slipped capital femoral epiphyses, gastro-esophageal reflux disease, idiopathic intracranial hypertension, dyslipidemia, hypertension, disease-associated depression, etc.), and Class 3 obesity with or without comorbidities.

Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most used procedures. Minor complications (up-to 15%) and a few major complications (up to 8%) may be seen in the postoperative period. Nearly 25% may need a follow-up procedure [111,112]. SG is the more commonly used simpler procedure and is associated with fewer complications. RYGB is associated with an increased risk of anastomotic leakage, small bowel obstruction, cholelithiasis and micronutrient deficiency. Teen-LABS study has shown comparable outcomes of SG and RYGB with significant improvement in BMI and cardiovascular risk factors [113-115].

Micronutrient supplementation and adherence to comprehensive lifestyle changes post-surgery are needed for sustained long-term effects. All patients need to undergo a psychological assessment before surgery. It is contraindicated in the presence of a treatable cause of obesity, substance abuse, chronic medical illness, psychiatric illness, cognitive state that impairs compliance to post-operative regimens and inability to comprehend the risk/ benefits of the surgery. Completion of puberty or growth is no longer a contraindication to bariatric surgery. It is to be preferably done in a centre of excellence with facilities for post-operative management [110,111].

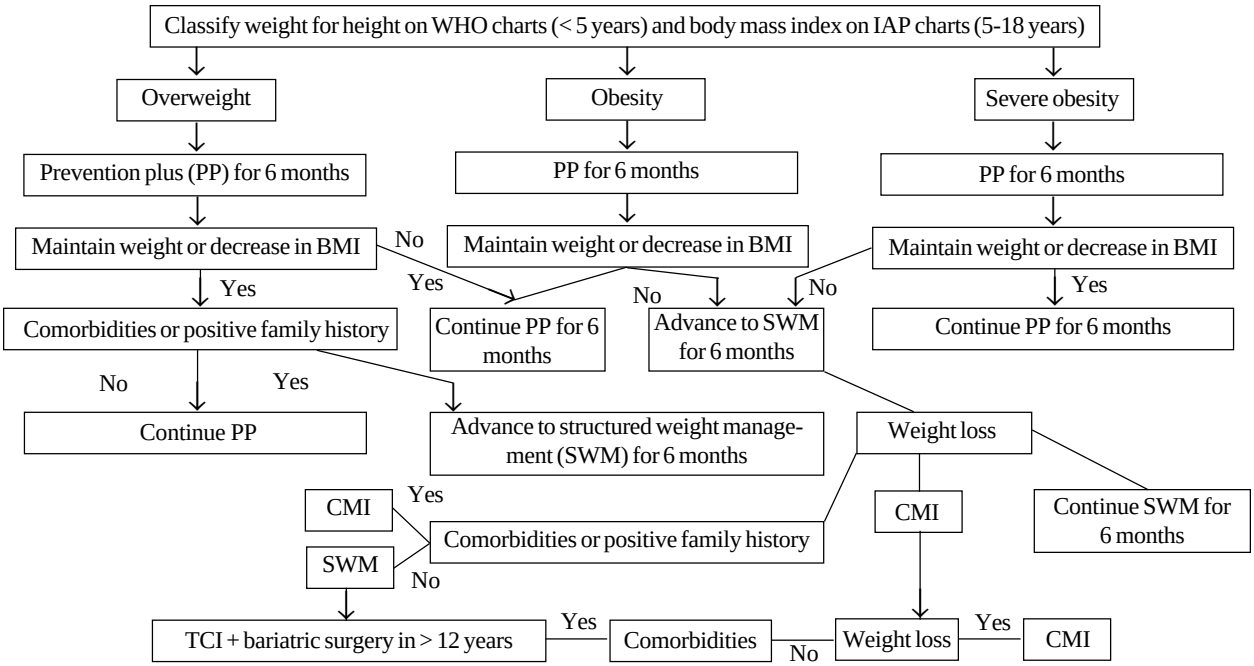
Table III Drugs Used for Treatment of Obesity

Drug and dosage	*Approval*	*Mechanism of action*	*Side effects*
Orlistat (120 mg PO TID)	FDA approved for obesity in ≥12 y of age	Gastrointestinal lipase inhibitor	Steatorrhea, abdominal cramps, fecal incontinence, flatulence, fat soluble vitamins deficiency
Liraglutide (2.4-3 mg/d SC)	FDA approved for obesity with or without type 2 diabetes in children ≥12 y of age	Glucagon like peptide-1 analogue which decreases gastric emptying, appetite suppressant	Vomiting, Nausea, abdominal Pain, diarrhea, constipation, dyspepsia, increased risk of medullary cell thyroid carcinoma (family history of MEN2 positive)
Semaglutide (2.4 mg/week, SC)	FDA approved for obesity in children ≥12 y of age	Glucagon like peptide-1 which decreases gastric emptying, appetite suppressant	Headache, abdominal pain, nausea, vomisting, diarrhea, gall stones, low blood pressure, rash
Phentermine (7.5mg-37.5mg PO)	FDA approved for short term use (12 weeks) in ≥16 y of age	Nor-epinephrine reuptake inhibitor	Hypertension, dizziness, headache, tremor, dry mouth, stomach-ache,Insomnia, tachycardia, constipation, diarrhea, vomiting, anxiety, restless
Topiramate (25-100 mg PO BID)	FDA approved for binge eating disorder ≥18y of age	Carbonic anhydrase inhibitor and suppress appetite centrally	Cognitive slowingTeratogenic
Metformin (250-1000 mg PO BD)	Not approved for treatment of obesity. Approved for ≥10 y of age for treatment of Type 2 diabetes. Adjunct use to prevent weight gain in girls with polycysctic ovarian syndrome and on antipsychotic medication	Reduces hepatic glucose production, decreases intestinal absorption of glucose & increases peripheral insulin sensitivity	GI complaints, nausea/vomiting, vitamin B12, diarrhea, bloating deficiency, lactic acidosis (rare)
Octreotide (5-15 ug/kg/day SC (divided in TID)	Not approved for treatment of obesity. Used in hypothalamic obesity		Gallstones, diarrhea, edema, abdominal cramps, nausea, bloating, reduction in thyroxine concentration Decreased growth hormone with normal IGF1
Leptin (Titration of doses to serum levels, SC)	Not approved Used only for leptin deficiency		Local reactions, headache, abdominal pain
Growth hormone (1-3 mg/m2 SC daily)	Not approved for obesity. FDA approved only in Prader Willi syndrome for linear growth		Edema, carpal tunnel syndrome
Melanocortin 4 Receptor agonist (Setmelanotide) (1-3 mg daily SC)	FDA approved in ≥6-year-olds with POMC deficiency, pro-protein subtilisin or kexin type 1 deficiency. and leptin receptor deficiency		Injection site reaction, nausea
Lisdexamfetamine	Not approved for treatment of obesity Used in binge eating disorder		Dry mouth, insomnia, tachycardia, constipation, anxiety

Recommendation 6.0

6.7 Surgical management may be offered in children older than 12 years of age with class 2 obesity and associated comorbidities or class 3 obesity with/without comorbidities only after failure of a proper trial of intense lifestyle modifications and pharmacotherapy for at least 6 months. (*Grade C, Moderate recommendation*)

A simplified algorithm in the management of childhood exogenous overweight and obesity (accounting for > 90% of cases) has been illustrated in **Fig. 1**.



CMI: Comprehensive multidisciplinary intervention. TCI: Tertiary care intervention.

Fig.1 Simplified algorithm for management of childhood exogenous overweight and obesity.

CONCLUSION

Pediatricians should recognize and treat pediatric obesity as a chronic disease. Exogenous or primary obesity is responsible for the majority of cases of childhood obesity. In Indian children under 5 years of age, weight for length/height using WHO charts and in children 5-18 years, BMI using IAP 2015 charts is used to diagnose overweight and obesity. Cutoffs for class 2 and class 3 obesity have been defined based on the IAP BMI charts. Waist circumference should be routinely measured in all overweight and obese children as it is a key measure of cardiometabolic risk. Routine evaluation for endocrine cause is only recommended in short and obese children with additional diagnostic clues. All obese children ≥10 years should be evaluated for comorbidities like hypertension, dyslipidemia, hyperglycemia and NAFLD (MASLD). Prevention and management of childhood obesity is primarily based on healthy diet, physical exercise and reduction in screen time. The prevention and management of pediatric obesity requires a multimodal staged approach involving caregivers including parents, family and school, HCPs or pediatricians, pediatric specialists, psychologists, counselors and nutritionists.

Contributors: All authors were part of the National Consultative Committee that formulated these guidelines. VK, NS and UK conceived the design and prepared the agenda. AB, SG, AG, KS and PS reviewed the literature for each section in detail and wrote the first draft of the respective sections. AA, SB, SC, JC, KE, RK, SM, HS, AS and ST moderated the draft recommendations of each respective section and provided critical inputs. RH was the invited expert who provided critical inputs for revision and participated in discussions VK, NS, UK and VS provided their inputs in the guidelines, participated in discussions and manuscript editing. All authors approved the final version

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Web Table I Extended Indian Academy of Pediatrics (IAP) Body Mass Index (BMI) Chart Percentiles for Girls Aged 5-18 Years

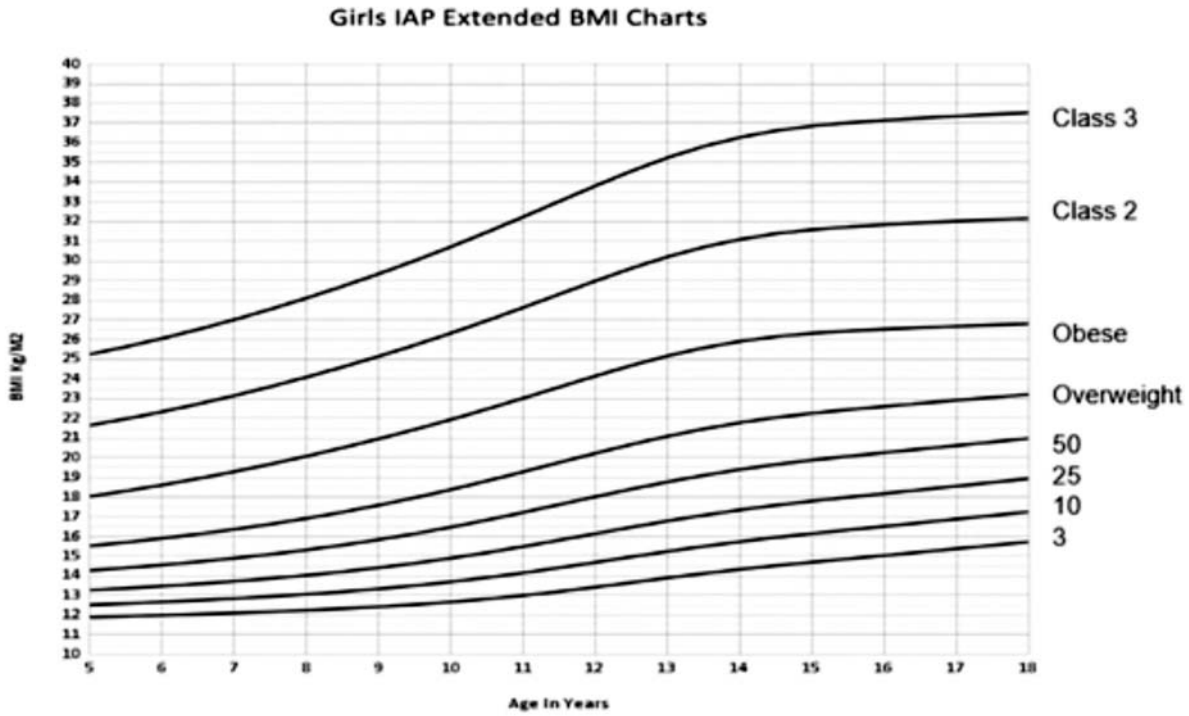
Age (y)	*3rd*	*10th*	*25th*	*50th*	*Overweight (23 adult equivalent)*	*Obesity (27 adult equivalent)*	*Class 2 obesity (≥120% to <140% of 27 adult equivalent)*	*Class 3 obesity (≥140% of 27 adult equivalent)*
5	11.9	12.5	13.3	14.3	15.5	18.0	21.6	25.2
5.5	11.9	12.6	13.4	14.4	15.7	18.3	22.0	25.6
6	12.0	12.7	13.5	14.5	15.9	18.6	22.3	26.1
6.5	12.1	12.8	13.6	14.7	16.1	18.9	22.7	26.5
7	12.1	12.8	13.7	14.9	16.4	19.3	23.1	27.0
7.5	12.2	12.9	13.9	15.1	16.6	19.7	23.6	27.5
8	12.3	13.1	14.0	15.3	16.9	20.1	24.1	28.1
8.5	12.3	13.2	14.2	15.6	17.2	20.5	24.6	28.7
9	12.4	13.3	14.4	15.8	17.6	21.0	25.1	29.3
9.5	12.5	13.5	14.6	16.1	18.0	21.4	25.7	30.0
10	12.7	13.7	14.9	16.5	18.4	21.9	26.3	30.7
10.5	12.8	13.9	15.2	16.8	18.8	22.5	27.0	31.5
11	13.0	14.1	15.5	17.2	19.3	23.0	27.6	32.2
11.5	13.2	14.4	15.8	17.6	19.8	23.6	28.3	33.0
12	13.4	14.7	16.1	18.0	20.2	24.1	29.0	33.8
12.5	13.7	15.0	16.5	18.4	20.7	24.7	29.6	34.6
13	13.9	15.2	16.8	18.8	21.1	25.2	30.2	35.2
13.5	14.1	15.5	17.1	19.1	21.5	25.6	30.7	35.8
14	14.3	15.7	17.3	19.4	21.8	25.9	31.1	36.3
14.5	14.5	16.0	17.6	19.7	22.0	26.2	31.4	36.6
15	14.7	16.1	17.8	19.9	22.3	26.3	31.6	36.8
15.5	14.9	16.3	18.0	20.1	22.4	26.4	31.7	37.0
16	15.0	16.5	18.2	20.3	22.6	26.5	31.8	37.1
16.5	15.2	16.7	18.4	20.4	22.8	26.6	31.9	37.3
17	15.4	16.9	18.6	20.6	22.9	26.7	32.0	37.3
17.5	15.5	17.1	18.7	20.8	23.1	26.7	32.1	37.4
18	15.7	17.3	18.9	21.0	23.2	26.8	32.2	37.5

Unpublished data.

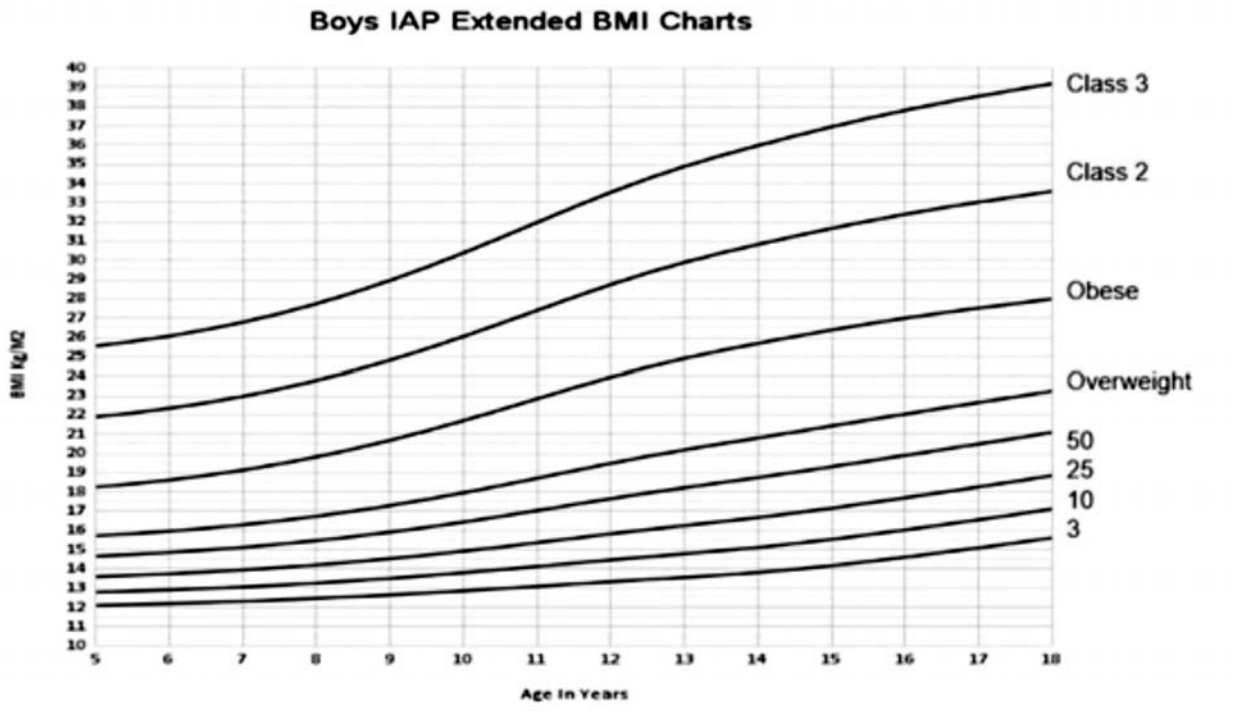
Web Table II Extended Indian Academy of Pediatrics (IAP) Body Mass Index (BMI) Chart Percentiles for Boys Aged 5-18 Years

Age (y)	*3rd*	*10th*	*25th*	*50th*	*Overweight (23 adult equivalent)*	*Obesity (27 adult equivalent)*	*Class 2 obesity (≥120% to <140% of 27 adult equivalent)*	*Class 3 obesity (≥140% of 27 adult equivalent)*
5	12.1	12.8	13.6	14.7	15.7	18.3	21.9	25.6
5.5	12.2	12.9	13.7	14.8	15.8	18.4	22.1	25.8
6	12.2	12.9	13.7	14.9	16.0	18.6	22.3	26.1
6.5	12.3	13.0	13.8	15.0	16.1	18.9	22.6	26.4
7	12.3	13.1	13.9	15.1	16.3	19.1	23.0	26.8
7.5	12.4	13.2	14.1	15.3	16.5	19.5	23.3	27.2
8	12.5	13.3	14.2	15.5	16.7	19.8	23.8	27.8
8.5	12.6	13.4	14.4	15.7	17.0	20.2	24.3	28.3
9	12.7	13.5	14.5	15.9	17.3	20.7	24.8	29.0
9.5	12.8	13.7	14.7	16.2	17.6	21.2	25.4	29.7
10	12.9	13.8	14.9	16.4	18.0	21.7	26.1	30.4
10.5	13.0	14.0	15.1	16.7	18.3	22.3	26.7	31.2
11	13.1	14.1	15.4	17.0	18.7	22.8	27.4	32.0
11.5	13.2	14.3	15.6	17.3	19.1	23.4	28.1	32.8
12	13.3	14.5	15.8	17.7	19.5	24.0	28.7	33.5
12.5	13.5	14.6	16.0	17.9	19.8	24.5	29.4	34.2
13	13.6	14.8	16.3	18.2	20.2	24.9	29.9	34.9
13.5	13.7	14.9	16.5	18.5	20.5	25.3	30.4	35.5
14	13.8	15.1	16.7	18.7	20.8	25.7	30.8	36.0
14.5	14.0	15.3	16.9	19.0	21.1	26.0	31.3	36.5
15	14.2	15.5	17.2	19.3	21.4	26.4	31.7	36.9
15.5	14.4	15.8	17.4	19.6	21.7	26.7	32.0	37.4
16	14.6	16.0	17.7	19.9	22.0	27.0	32.4	37.8
16.5	14.9	16.3	18.0	20.2	22.4	27.3	32.7	38.2
17	15.1	16.6	18.3	20.5	22.6	27.5	33.0	38.5
17.5	15.4	16.8	18.6	20.8	22.9	27.8	33.3	38.9
18	15.6	17.1	18.9	21.1	23.2	28.0	33.6	39.2

Unpublished data.



Web Fig. 1 Extended Indian Academy of Pediatrics (IAP) body mass index (BMI) chart for 5-18 years girls.



Web Fig.2 Extended Indian Academy of Pediatrics (IAP) body mass index (BMI) chart for 5-18 years boys.

Childhood Cancer in India: Miles to Go Before We Sleep!

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Once regarded as incurable, thanks to the advances in diagnostics and treatment, childhood cancer is now treatable with excellent outcomes and a good quality of life. We, herein, revisit two articles pertaining to childhood cancer published five decades ago and analyze the strides made in the manage-ment of childhood cancer in India since then [1,2].

THE PAST

In 1973, Pratap, et al. [1] described the epidemiology of 162 malignant childhood neoplasms in the repository of a tertiary center in Kanpur, India, over a decade [1]. Out of 7,857 cases of malignant neoplasms documented in the institutional surgico-pathological records, childhood cancer cases comprised 2.06%, with a male preponderance. Lymphoma was reported as the commonest pediatric malignancy and was classified into three groups viz., lymphosarcoma, reticulum cell sarcoma and Hodgkin disease, a classification based on histomorphological characteristics alone. Other cancers reported were retino-blastoma, Ewing sarcoma, osteogenic sarcoma, teratoma, orchidoblastoma, embryonal rhabdomyosarcoma, melanotic progonoma and neuroblastoma.

In the same issue of *the journal*, Rohatgi, et al. [2] described a series of fifteen infants who presented with an abdominal lump and were variously diagnosed as neuroblastoma, Wilms tumor, rhabdomyosarcoma, choledochal cyst and mesenteric cyst, following surgical exploration. The diagnostic aids used included clinical examination, conventional radiographic methods and microscopic examination.

The advent of ultrasonography around that time made it possible to not only localize abdominal masses but also objectively describe its size and consistency (solid or cystic) in a safe and non-invasive manner without ionizing radiation exposure. Unfortunately, ultrasonic evaluation was not used in both these studies as the access to ultrasound came much later in the 1980s in India, and even so the availability was restricted to select hospitals and was viewed with skepti-cism by doctors and patients alike [3]. In the absence of advanced diagnostic modalities, the prognostic factors for most cancers were largely based on few broad parameters like the age of the child, site of the primary tumor and the degree of differentiation of the tumor. Therapeutic options for children with abdominal neoplasms were limited to one or two modalities; and a limited armamentarium of chemotherapeutic drugs were available.

THE PRESENT

Since then, the picture of childhood cancer in India has totally metamorphosed, thanks to the availability of trained manpower and state-of-the-art diagnostics and therapeutics. The Pediatric Hematology Oncology (PHO) Chapter of the Indian Academy of Pediatrics (IAP), since its genesis in 1987, has been a steady and sure force behind the growth of pediatric oncology in India. The National Training Project of the Practical Pediatric Oncology Program (NTP-PPO), a collaboration between the International Society of Pediatric Oncology (SIOP) and the PHO chapter, was instrumental in nurturing specialist personnel equipped to diagnose and treat children with cancers. The starting of academic programs like fellowship courses in pediatric hematology oncology under the aegis of the National Board of Examinations and IAP, along with National Medical Council recognized 3-year Doctorate of Medicine (DM) courses in pediatric oncology,

have played a huge role in supporting the advancements in pediatric cancer in India.

Over the years, there has been a tremendous growth in the laboratory techniques and diagnostic modalities of cancer in India. Easy availability of basic blood tests, including complete blood counts and peripheral smear examination, and imaging modalities like ultrasound, computed tomographic scan and magnetic resonance imag-ing has significantly reduced the lag time in the diagnosis of cancer. Functional imaging modalities including positron emission tomography (PET) scans have revolutionized cancer care by aiding the diagnosis of malignancy, staging, tumor characterization, response assessment and survei-llance. From a mere 16 centers performing PET scans in India in 2008, there has been an exponential growth in centers performing functional imaging [4,5]. Advancements in immunophenotyping including detection of minimal residual disease by flowcytometry, cytogenetic analysis, molecular workup (like BCR-ABL testing) by fluorescence situ hybridization (FISH) or polymerase chain reaction (PCR) techniques, and karyotyping of malignant cells have fostered better outcomes for childhood leukemia by assign-ing patients to treatment groups based on risk assignment [6]. Likewise, molecular tests for solid tumors like N-MYC amplification for neuroblastoma and EWS-FLI1 and EWS-ERG gene fusions for Ewing sarcoma by next generation sequencing (NGS) have helped ease diagnostic challenges for round cell tumors [7]. Determining chromosomal translocations in certain solid malignancies including brain tumors are now used for prognostication and therapy modification based on risk stratified treatment approaches. Availability of safe and effective intravenous sedative drugs have further eased the diagnostic procedures for children with cancer. Together, these advances have contributed to a paradigm shift in cancer management with a substantial reduction in cost and time facilitating early diagnosis and accurate staging.

Risk stratified treatment based on clinical and biological parameters including early response to treatment is now the essence of pediatric oncology treatment. Various cytogenetic and molecular analyses (discussed above) along with other patient variables are routinely used to determine the stage of disease or assign it to protocol-based therapy. Response to the first few chemotherapy cycles is regarded as the most important predictor of long-term chance of cure in a majority of diseases and this also ameliorates the toxic effects of therapy in good risk patients and intensifies treatment in high-risk disease [8]. Treatment of acute lymphoblastic leukemia is a classic example of this evolution. Previously high-dose craniospinal radiotherapy was an integral part of treatment, which was associated with significant long-term toxicities and moderate outcomes. In 1982, triple intrathecal therapy substituted prophylactic cranial radiotherapy in some patients and by 2009 systemic and intrathecal chemotherapy eliminated the need for prophylactic radiotherapy in all children and the survival rate jumped to nearly 90% [9,10]. Hematopoietic stem cell transplant (HSCT) services in India have rapidly evolved over the last few decades; a lot of children are benefited each year with matched, unrelated or haploidentical family donors for various oncological and other metabolic/genetic disorders [11]. Targeted therapy like dasatinib and arsenic trioxide, and monoclonal antibodies like rituximab and gemtuzumab have also emerged as effective treatment strategies for various childhood cancers.

Multidisciplinary care, ensuring participation of treating pediatric oncologists, radiation oncologists, onco-surgeons, nuclear medicine specialists etc., have played a pivotal role in ensuring optimal therapeutic outcomes for these children. Limb salvage surgeries for bone cancers, advanced surgical procedures for brain tumors and precision radiation therapy techniques (albeit the limited availability of proton therapy in India) have contributed in better outcomes with improved quality of life [12]. A lot has also changed in the supportive care available to these children over the last 50 years. From an era of whole blood transfusions, we have moved to ready availability of safe blood component products including apheresis, leukodepleted and irradiated blood products [13]. Pediatric intensive care support, improved infection control practices, use of effective anti-microbial therapy and availability of long term central venous access devices have given the much-needed edge to cancer care.

Alongside, development of regional networks like the Indian Pediatric Hematology Oncology Group (INPHOG) through its research focus has aided identification of indigenous causes of treatment failure for childhood cancer, and has helped strategize mechanisms to improve care and outcomes of pediatric cancer [14,15]. Various nongovernmental organizations like Cankids, Jiv Daya and Leukemia Crusaders, to name a few, have played a crucial role in knitting the missing threads, providing drugs, diagnostics, psychological and other support to families of children with cancer [16]. Their efforts at reducing abandonment, providing holistic care in resource limited settings and ensuring continuity of care during the COVID-19 pandemic has opened new avenues in social and healthcare partnerships.

THE FUTURE

Although the remarkable progress made in childhood cancer is laudable, a lot more is desired. The disparity in access to cancer care between various geographical regions in a vast country like ours, between public and private healthcare sectors, and gender-based discrimination needs to be addressed. There is a need to tackle problems of malnutrition and absence of proper support structure, which is likely

to offset any survival advantage offered by the use of standard cancer treatment protocols. There is also a need to strengthen data collection and develop population-based cancer registries which will help collect the actual burden and incidence of cancer in India. Use of artificial intelligence technology and telemedicine can also help reduce regional disparities in cancer services in India, and serve as useful tools lest another pandemic breaks out. Advancements in cancer treatment like immunotherapy including chimeric antigen receptor T cell (CAR-T) therapy, bispecific T-cell engager antibodies, targeted therapy, proton therapy and gene therapy are on the anvil offering hope for refractory and relapsed disease [17,18]. With improving survival, developing specialized, comprehensive, multidisciplinary follow-up programs to address at least some of the needs of these childhood cancer survivors is the need of the hour and the way forward.

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European Consensus Guidelines on the Management of Respiratory Distress Syndrome, 2022 : What is New?

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We present a summary of the European Consensus guidelines on management of respiratory distress syndrome, which were released in 2022, and compare these with the current National Neonatology Forum of India guidelines, and discuss the feasibility of their application in the Indian settings.

Keywords: *Antenatal, Continuous positive airway pressure, Steroids, Surfactant.*

Respiratory distress is the commonest morbidity in preterm neonates that warrants neonatal intensive care (NICU) admission. Management of respiratory distress syndrome (RDS) is not only limited to respiratory pathology, but it is a continuum of care starting right from prenatal period till discharge from the NICU. RDS in preterm neonates and its multipronged management is one of the most researched realms of preterm care. The European Society of Pediatric Research (ESPR) and Union of European Neonatal and Perinatal Societies (UNEPS) have been formulating guidelines for management of respiratory distress in preterm neonates for the past two decades, and recently the sixth version of guidelines has been published [1], which is an update of the previous version [2]. **Table I** and **Table II** provides a summary of the comparison between the 2019 and 2022 guidelines.

Prenatal and Delivery Room Management

Antenatal steroids are the cornerstone for prevention of complications of prematurity. Recommendations for administration of steroids from lower limit of viability (22 weeks) to 34 weeks remain the same; however, in women in spontaneous preterm labor after 34 weeks, steroid treatment is controversial and not advisable. In women with a singleton pregnancy and a short cervix in mid-pregnancy or previous preterm birth, vaginal progesterone therapy should be used. Other recommendations include preference for T-piece over bag and mask, and when delayed cord clamping is not feasible, considering umbilical cord milking in infants with gestational age more than 28 weeks.

The search for most appropriate interface for delivery room continuous positive airway pressure (CPAP) remains. Concerns are raised for application of PAP with face mask as face mask application is likely to induce apnea via the trigeminocardiac reflex in spontaneously breathing infants. Hyperthermia should be avoided, especially when using caps and cling wrap along with thermal mattresses.

Neonatal Intensive Care Management

Timely surfactant therapy remains the mainstay of treatment for preterm neonates with clinical evidence of worsening RDS. The threshold for initial dose of surfactant is FiO2 of 0.30, but the level of evidence is downgraded in the current update [1]. The evidence is stronger now for surfactant administration in neonates less than 30 weeks gestation, who need intubation in delivery room for stabilization. Less-invasive surfactant administration (LISA) remains the method of choice for surfactant administration with more evidence in favor of long-term benefits with this methods, compared to intubation-surfactant-extubation (INSURE). The threshold for repeat surfactant, type, and dose of surfactants are summarized in **Table I** and **Table II**.

CPAP or synchronized non-invasive positive pressure ventilation (NIPPV) should be started from birth in all babies at risk of RDS, such as those less than 30 weeks of gestation who do not need intubation for stabilization. CPAP continues to have advantages over other modes of non-invasive respiratory support (NRS) because of its ease of administration and monitoring.

Heated humidified high flow oxygen with nasal cannula (HHFNC) can be used as an alternative to CPAP for some babies, with the advantage of less nasal trauma, provided centers have access to CPAP or NIPPV for those failing this mode. Role of mechanical ventilation, as in previous guidelines, is restricted to those neonates with severe RDS who do not respond to initial surfactant therapy and NRS.

Table I New Recommendation/Changes in Recommendations in the 2022 Update of European Consensus Guidelines on RDS

Recommendation	*2019 update*	*2022 update*
Short cervix in mid pregnancy or previous preterm, vaginal progesterone treatment to increase gestational age at delivery	None	New recommendation
Umbilical cord milking as an alternative to DCC, if DCC is not possible	None	Only in infants with gestational age >28 wk since increased risk of IVH (B2)
LMA use for surfactant	Size of LMA limits its use.	LMA may be used for more mature infants >1.0 kg (B2)
Protocols for ROP screening in preterm neonates	None	New recommendation
Role of synchronized NIPPV	CPAP (A1) was the preferred mode	New recommendation on synchronized NIPPV comparable to CPAP (A1) CPAP or (s) NIPPV should be started from birth in all babies at risk of RDS, such as those <30 wk of gestation who do not need intubation for stabilization (A1).
Further escalation of CPAP/NIPPV	PEEP can be individualised depending on clinical condition, perfusion, and oxy-genation (D2)	New recommendation Ability to escalate to NIPPV can reduce the need for ventilation in some infants (A1)
HHHFNC	During weaning, can be used as alternative to CPAP in some babies (B2)	Alternative to CPAP in some babies with advantage of less nasal trauma, provided centers have access to CPAP or NIPPV (B2)
Initial CPAP pressure	Spontaneous breathing neonate to be stabilised with CPAP of at least 6 cm H20 via masks or nasal prongs (B1)	5 to 6 cm H20 but no strong evidence to recommend. Expert opinion to start at 6 cm H20 (D2)
Routine sustained inflation	SAIL trial stopped early due to excess deaths in the intervention group Do not use since no long-term benefit (B1)	No evidence of benefit but evidence of harm in infants with gestational age less than 28 wk
Oxygen use: Initial FiO2 0.30 for babies < 28 weeks, 021 to 0.30 for 28 to 31 weeks and 0.21 for 32 weeks and above	Level of evidence B1	Level of evidence downgraded to B2
Threshold for first dose of surfactant	Suggested protocol to treat at FiO2 of 0.30 on CPAP pressure of at least 6 cm H20 (A1)Occasions where surfactant can be given in delivery suite is when intubation is needed for stabilization (A1)	Rescue surfactant should be given early in the course of disease (A1) *Suggested protocol same but level of evidence downgraded (B2)* and use of lung ultrasound to assess need of surfactant. If a preterm baby <30 wk of gestation requires intubation for stabilisation, they should be given surfactant (A2)
Role of inhaled budesonide	Can be considered for infants at very high risk of BPD (A2)	Not mentioned

Use of lung protective ventilatory modes (volume targeted ventilation, VTV) is recommended [1]. In neonates who need ventilation, considering extubation at higher CPAP pressure of 7 to 9 cm H20 or NIPPV will improve the chances of success [1].

The role of postnatal steroids (low dose dexamethasone regimen described in DART trial and low dose prophylactic hydrocortisone) have been adopted by a few neonatal centers to improve perinatal outcome and their use is applicable to select group neonates at high risk of BPD. In the supportive management strategies for RDS, restrictive policy of blood transfusion now has stronger evidence [4,5]. In neonates who need a higher dose of caffeine, rather than a rapid hike in dose, there should be a gradual increase in maintenance dose of caffeine from 5 to 8 mg per kg per day over several weeks to maintain the therapeutic effect and to minimize the adverse effects of high dose caffeine like seizures or cerebellar

Table II Recommendations With Change in Level of Evidence (Upgraded) in the 2022 Update of European Consensus Guidelines on Repiratory Distress Syndrome

Recommendation	*2019 update*	*2022 update*
CPAP for spontaneously breathing neonates	Level of evidence B1	Level of evidence changed from B1 to A1
T -piece device vs bag and mask as resuscitation device	Gentle pressures with 20 to 25 cm H20 PIP to be used for persistently apneic or bradycardia babies but no mention of T-piece resuscitation device	T -piece devices to be used rather than bag and mask (B1)
Babies who require intubation for stabilisation should be given surfactant	Level of evidence B1	Level of evidence changed from B1 to A2 If a preterm neonate < 30 wk gestation requires intubation for stabilisation, they should be given surfactant (A2)
Method of surfactant administration: LISA vs INSURE	Level of evidence B2 for LISA as preferred method	Level of evidence for LISA changed from B2 to A1
Surfactant in late preterm and early term	Not mentioned	No recommendation could be due to heterogeneity of the existing data.
Permissive hypercapnia	While weaning MV, can tolerate moderate hypercarbia provided pH is above 7.22 (B2)	Addition: Avoid PCO2 < 7 kPa (35 mm Hg) when on MV to reduce brain injury (C1)
Parenteral nutrition	To be started at birth. Amino acids at 1 to 2 g/kg quickly increase to 2.5 to 3.5 g/kg/d (C2) Lipids 1 to 2 g per kg on d 1 and quickly to 4 g per kg (C2)	The level of evidence for amino acids is now B2
Antibiotics use	No level of evidence mentioned	In infants with RDS, start judiciously and stop when sepsis is ruled out (D1)
Pharmacological closure of PDA	No level of evidence on use of paracetamol	PCM preferred when there is thrombocytopenia or renal concerns (B2)
Thresholds for red blood cell transfusions	Severe cardiopulmonary disease (Hct 36% or Hb 12g/dL) Oxygen dependent (11g/dL or Hct 30%) Stable infants beyond 2 wk (7g/dL or Hct 25%) (C2)	Level of evidence now A2

LISA: Less-invasive surfactant administration, INSURE: Intubation-surfactant-extubation, PDA: patent ductus arteriousus, PCM:paracetamol.

hemorrhage. The use of inhaled nitric oxide may have a role in limited situations like preterm infants with a history of mid-trimester oligohydramnios, birth asphyxia, and documented pulmonary hypertension with severe respiratory distress.

Implications for Practice

The European 2023 recommendations [1], in many aspects, remain unchanged compared to 2019 [2], but there are some key considerations about their implication in clinical practice in Indian context. Recently, in 2021-22, National Neonatology Forum of India (NNF) [6,7] has also formulated context specific evidence based clinical practice guidelines on various aspects of respiratory distress management.

The NNF guidelines acknowledge the limitations of clinical practice in Indian context and hence advocate cautious use of surfactant, CPAP and synchronized NIPPV, only in units where adequate logistics for monitoring and escalation of treatment in case deterioration is present. Notable is that NNF provides a more precise guide for considering a higher threshold (PEEP/MAP ≥7 cm H2O and FiO2 >0.4) for invasive or non-invasive ventilation and a lower threshold (any MV and FiO2 >0.30) for RDS plus asphyxia or sepsis.

Indian NNF guidelines, unlike European guidelines, do not recommend the use of laryngeal mask airway (LMA) for surfactant therapy and use of HHHFNC in neonates at risk of RDS. Both the guidelines acknowledge the lack of a well-fitting interface for CPAP and NIPPV, with lesser nasal trauma [6]. Amongst the existing interfaces, leaks are common with both nasal prongs and masks but somewhat less with prongs.

In the light of these guidelines, it remains to be remembered that many Indian neonatal units are still resource limited with shortage of infrastructure and lack of skilled manpower to perform the procedures and operate the more sophisticated equipment like synchronized NIPPV. Implementation of many recommendations like use of T-piece resuscitator, achieving the target oxygen saturations in delivery rooms, application of delivery room CPAP, administration of surfactant by LISA/MIST would be a challenge in Indian scenario. This is important considering the reports that only 50% of medical colleges and district hospitals have air-oxygen blenders (95% CI 41.4% to 60.9%) and staff trained in the use of CPAP is present in 56% (95% CI 45.8% to 65.8%) of hospitals [7]. Point of care lung ultrasound is gaining popularity for diagnosis of respiratory pathology in neonates, however, again considering the cost and expertise required, using clinical scoring such as Silverman Anderman Score may be a better option to assess the severity of RDS in centers with lack of expertise in lung ultrasonography. With respiratory circuits reported to be reused in 53.8% (95% CI 42.3% to 63.9%) of hospitals [5], the transition from CPAP to HHHFNC (and vice versa) can be a demanding clinical practice in some of the resource-constrained Indian units.

Hence, clinicians should prioritize the context specific implementation and gain skill in sophisticated procedures, and technology-driven decision making may prove to be beneficial in clinical management in the future.

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Pediatric Renal Rickets at a Tertiary Center

We report clinical and etiological profile of 19 children (10 males) with renal rickets managed in the years 2021-2022. Median (IQR) age of presentation was 60 (18-96) months. The commonest cause was renal tubular acidosis (*n*=8). Genetic analysis revealed the diagnosis in 83% subjects (5 out of 6 tested).

Keywords: *Hypophosphatemic rickets, Renal tubular acidosis, Vitamin D*

The reported etiology of renal rickets have been renal tubular acidosis (RTA), chronic kidney disease (CKD), hypophosphatemic rickets, vitamin D dependent rickets (VDDR), chronic liver disease and malabsorption [1,2]. Hypophosphatemic rickets is the commonest form of renal rickets reported in the Western population [3]. A pragmatic and protocol based approach is required to address the diagnosis and therapeutic aspects of this challenging disorder [4]. There is a paucity of recent data from Indian centres on renal rickets. We, therefore, report our observation on cases of renal rickets.

This was a retrospective case record analysis over a period of two years from January, 2021 to December, 2022. Data of all cases of diagnosed renal rickets i.e., RTA (proximal and distal), chronic kidney disease with rickets, hypophosphatemic rickets and VDDR were included in study. The protocol of the study was approved by institutional ethics committee. The clinical features, biochemical investigations, radiological feature and response to therapy were noted. In addition, results of genetic analysis performed in six children was also noted. The diagnosis of RTA, CKD, VDDR and hypophosphatemic ricket was made as per standard [1]. The investigation results noted included complete blood count, kidney function test, liver function test, arterial blood gas, serum calcium, phosphate, alkaline phosphatase, urine microscopy, urine calcium/ creatinine ratio, *X*-ray bilateral wrist, and ultrasonography of kidney, ureter and bladder. Vitamin D levels (25-OH Vitamin D, 1,25 $(OH)_2$ vitamin D3) were performed in VDDR to establish its diagnosis. Ophthalmological and hearing evaluation was performed, as and when indicated.

The present study included 19 patients (10 males); age group being 3 months to 14 years (median 60 months). Four cases (21.1%) presented during infancy, 5 (26.3%) during 1-5 years and the rest 10 (52.6%) belonged to 6-14 years of age (**Web Table I**).

Failure to thrive, polyuria, polydipsia, were consistently present in all RTA patients. Nephrocalcinosis was present in all dRTA patients. Skeletal deformity (genu valgum) was present in four RTA, three hypophosphatemic and 1 CKD patient, and Parental consanguinity was present in one of 19 patients.

Hypokalemia (serum potassium<3.5 meq/L) was present in 6(75%) RTA patients and metabolic acidosis in all RTA patients (*n*=8) and CKD (*n*=7) patients. Two of the dRTA patients had hemolytic anemia, and of these, one had a pathogenic variant in *SLC4A1*. Of the three pRTA patients, one child was diagnosed as nephropathic cystinosis based on the detection of recurrent pathogenic point variation (c.922G>A (p. Gly308Arg) in exon 11 in *CTNS* gene. He also had diabetes insipidus and hypothyroidism. There were three cases of hypophosphatemic rickets. One girl aged 7 years was found to have pathogenic variation in *PHEX* gene (c.1735G>A; p. Gly579Arg). The child was given treatment as phosphate granules, vitamin D, and oral calcium and showed dramatic response to therapy over two years. One boy aged 14 years had pathogenic variation in *CLCN5* gene (c.473G>A p. Gly158Asp), confirming it to be Dent disease. Cystinosis and Dent disease had features of renal Fanconi syndrome.

A rare form of refractory rickets (vitamin D dependent rickets type 2 A) was diagnosed in a 2-year-old boy, who presented to us with alopecia and rickets. Genetic study showed homozygous splice acceptor variant in exon 7 of *VDR* gene, located on chromosome 12. There were two deaths among this group of 19 patients. One child had nephropathic cystinosis and the other had chronic kidney disease.

The present study was a case record analysis of 19 cases of rickets with renal defects. commonest etiologies were RTA and CKD. The median age of presentation was much less in pRTA than dRTA and CKD. Five dRTA patients had metabolic acidosis, hypokalemia, and medullary nephrocalcinosis. *SLC4A1* variation is known to cause hereditary hemolytic anemia in dRTA patient [5]. Bone disease or rickets is relatively uncommon in dRTA patient, but it was present in two of the five patients [6].

Another form of renal rickets, which presents with knee deformity in adolescents, is hypophosphatemic rickets. Three cases had this form of rickets and 2 revealed genetic variations. This variation as p.Gly88Asp has been previously reported in patients affected with Dent disease [7]. This child had additional findings as hypercalciuria and

proteinuria. Molecular confirmation could not be done in third child.

One child had vitamin D dependent rickets type 2A. Alopecia is present in two-third of cases and it is a marker of disease severity [8]. Alopecia differentiates it from VDDR type 1. Gupta, et al.[9] first reported it in two siblings from India [9]. This child is under treatment with high doses of calcitriol and calcium phosphate. The disease is resistant to treatment with very poor response in cases with alopecia.

RTA and CKD have been the common causes of renal rickets as reported in other Indian series also [10, 11]. We had no patient in category of malabsorption and chronic liver disease, which has been previously reported [12].

The limitations of study are being retrospective case records analysis and restricted genetic analysis. Early pointers for non-nutritional forms of rickets are: growth failure, metabolic acidosis and azotemia. Clinicians should be aware of these pointers for timely diagnosis and management of such cases.

Ethics clearance: Ethical approval was obtained from IEC; No.2023/EC/6177.

Contributors: AS and Sucheta collected the data and AS conceptualized the idea and wrote the manuscript. RG, AA, RP helped in case management and literature search. OPM critically analysed the manuscript.

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Severe Adenovirus Pneumonia Associated With Hemophagocytic Lymphohistiocytosis With Coronary Involvement

Infection-associated hemophagocytic lymphohistiocytosis (HLH) is being increasingly observed in children with severe adenoviral pneumonia in recent reports [1,2]. However, coronary involvement in viral infection associated HLH is rare and most of the previous literature documents cases of Epstein-Barr virus (EBV) associated HLH with coronary involvement [3]. Herein, we report a severe adenovirus-associated HLH with coronary involvement.

This previously healthy 2-year-old boy presented with two weeks history of a febrile illness associated with cold and cough, which was being treated on outpateint basis. He was admitted with us for fever and increasing respiratory rates. His upper respiratory Biofire (rapid respiratory polymerase chain reaction test) was positive for adenovirus. Blood and urine cultures were sterile. He was treated with broncho-dilators and intravenous fluids. However, his fever still persisted. Echocardiography was done on day-5 post admission, which showed significant coronary artery dilatation. The child did not have any clinical features of Kawasaki disease. The child received 2 g/kg intravenous immunoglobulin (IVIG) but developed respiratory distress the next day, and was shifted to the pediatric intensive care unit (PICU).

The patient received heated, humidified high-flow oxygen by nasal cannula (HHHFNC). On auscultation, there was impaired note and bronchial breathing on left lower lobe area. Per abdominal examination revealed hepatosplenomegaly. Chest *X*-ray showed dense consolidation in left lower zone and his C-reactive protein (57 mg/dL) and procalcitonin (31 ng/mL) were high. Patient was treated with injection vancomycin and meropenem. Echocardiography done two days after being shifted to PICU showed dilated left main coronary artery (LMCA) and left anterior descending artery (LAD) with mild mitral regurgitation (MR) and mild left ventricle (LV) systolic dysfunction. The child was started on high dose aspirin and injection methylprednisolone.

As the fever still persisted, work-up to rule out HLH was done, and it showed bicytopenia, hyperferrtinemia and hypertriglyceridemia. Tratment with injection anakinra was started for the child at a dose of 100 mg/day subcutaneously, as the child had not responded to IVIG and methyl-prednisolone.

On fourth day of anakinra, repeat echocardiography showed LVEF 62%, proximal LAD aneurysm with a small thrombus inside, and injection clopidogrel was added to the treatment. His HLH markers started showing improvement but the child continued to remain febrile and HHHFNC dependent (**Table I)**. Anakinra was continued and steroids were changed to intravenous hydrocortisone. The child was not hemodynamically compromised. The patient became afebrile on day 6 of anakinra. High-resolution computed tomography (HRCT) thorax showed near complete collapse/consolidation of left lung, with patchy consolidation in right upper and lower lobes.

After one week of treatment with anakinra, the dose was reduced. The child remained afebrile and he was weaned off HHHFNC after two weeks. Anakinra was stopped after day 10. Whole exome sequencing did not reveal any genetic evidence of primary HLH. Repeat investigations showed decreasing levels of triglycerides, ferritin and aspartate aminotransferase, and rising total leukocyte and platelets.

Table I Trend of Hemophagocytic Lymphohistiocytosis Markers in the Index Child with Adenovirus Pneumonia

Date	*Hemoglobin (g/dL)*	*Total leukocyte count ($\times 10^9$/L)*	*Platelet count ($\times 10^9$/L)*	*Ferritin (µg/L)*	*Fibrinogen (mg/dL)*	*Triglyceride (mg/dL)*	*AST (IU/L)*
Day 1	9.0	3.2	100	4960	-	754	426
Day 6 Anakinra	9.5	3.2	200	2440	-	686	213
Day 9 Anakinra	8.8	3.7	306	757	-	1053	50
Day 11	7.4	9.5	510	317	212	279	28
Day 17	7.9	10.9	480	97	327	67	36

AST: aspartate aminotransferase.

Follow-up echocardiography showed small aneurysm in proximal LAD with possible thrombus in it.

The child was gradually weaned off steroids, and his antibiotics were stopped after a week. The patient was discharged one month post admission. Currently, child is doing well and remains on aspirin since the last six months post discharge.

Adenoviral infections are known to cause secondary HLH, but there is no publication documenting coronary involvement in such cases. On the other hand, EBV-associated secondary HLH has been found to occur with cardiac complications, including coronary involve-ment [3]. In the first published pediatric cases of EB virus associated secondary HLH complicated by coronary artery dilatation [3], the patient also fulfilled the criteria for Kawasaki disease, which was not seen in our patient.

We preferred ankanira over etoposide due to lower sepsis risk and absence of hematological toxicity. There is previous literature documenting use of anakinra as a first line agent in secondary HLH, even in non-rheumatic causes [4,5]. Our observations also suggest that anakinra may be considered for treatment in secondary HLH instead of etoposide with/without dexamethasone. However, in our case, child became afebrile on D6 of anakinra; although, previous literature shows that the average time for anakinra response is within 1-2 days [6].

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Do Pain and Physiological Stress Occur During MIST?

We read with interest the article on pain and physiological stress during minimally invasive surfactant therapy (MIST) in very preterm infants [1]. We seek the following clarifications.

It would have been better if details of success of catheterization in first or second attempt were provided. Newborns who needed a second attempt had hypoxia and/or bradycardia during the first attempt, which may affect neurological status. So, it is possible that due to this event it would affect pain score in next attempt within brief time. We understand that there would be a smaller number of newborns who needed a second attempt. More clarification is needed for where and why the independent *t* test was used and if used, is it a correct test to be applied here where there are no two independent groups?

Due to nature of the study, transient change in heart rate and SpO2 is also likely because of blockage of the airways due to surfactant [2], though less than the intubation-surfactant-extubation (InSurE) technique [3]. This adds to the total score of PIPP-R, which might be misleading. This may be considered as a limitation of utilizing PIPP-R score in this study.

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REPLY

We thank the readers for the interest in our article [1]. We would like to offer the following explanation:

Out of the 23 infants enrolled in the study, only two infants required a second attempt at inserting the catheter. Since the total sample size was very small, we did not analyze the pain scores in these infants separately. But there certainly exists a possibility that the pain scores might be different in infants undergoing a second attempt at MIST, and this may be explored in a larger study. We clarify that the pain scores were analyzed using the paired *t* test.

Tarawneh, et al. [2] reported observing an ETT plug after extubation post INSURE with BLES administered in aliquots, especially in the ELBW infants in their cohort [3]. This ETT plug may indicate major airway blockage. Our cohort consisted of bigger infants, and the thin catheter in MIST does not block the airways as much as the ET tube; however, there exists a possibility of blockage of airways due to surfactant that may cause changes in heart rate and SpO2. As reported previously [3], desaturation and bradycardia happen more often after INSURE compared to MIST. It is difficult to differentiate whether airway obstruction causes the changes in heart rate and SpO2 or the pain. Since these physiological parameters are an integral part of PIPP-R for pain assessment, one cannot disregard these while assigning the PIPP-R score. This could be a limitation of assessing the pain scores with PIPP-R and this aspect needs to be explored in further studies.

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Midline vs Peripherally Inserted Central Catheters

We read with interest the article on safety and outcomes of midline vs peripherally inserted central catheters (PICC) [1]. We would like to highlight and seek clarifications regarding certain aspects of the study:

It has not been mentioned whether the catheter was placed in the dominant or the non-dominant arm. In older children in whom hand dominance has been established, relatively more use and movement of the dominant arm may lead to early dislodgement, local site bleeding, and leakage of the catheter. Similarly, the level of consciousness and activity of the child may also affect these outcomes in a given patient. Hence, inclusion of data on a mental status assessment scale such as Glasgow Coma Scale in the study could have provided useful information.

Since radiological confirmation is not required in case of a midline catheter, the post procedure radiography done in the study could have been avoided in the midline catheter group, thus avoiding unnecessary radiation exposure in these children.

Albumin was the most common drug given through the midline catheters; however, the indication of albumin administration is not mentioned. Since injection Albumin is commonly used in hypercoagulable conditions like burns, AND nephrotic syndrome' these patients may have a higher rate of blockage of the catheter.

We would like to emphasize that though this article has shown comparison of midline catheter vs PICC, only upper limbs have been used for placement of all the catheters in this study. However, PICC placed through saphenous vein has also been shown to be very safe and effective [2]. Further studies may be required, including comparison of outcomes in veins of both upper and lower limbs.

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AUTHORS' REPLY

We would like to thank the readers for their interest in our manuscript. In our study population, selection of vein was based on its caliber determined clinically or by ultrasound screening. We did not consider hand dominance or study this aspect. Also, we studied sick children admitted to PICU, who generally have restricted activity due to their illness, neurological or not. Hence, we think PRISM score is probably more reflective of overall degree of illness, rather than Glasgow Coma Scale (GCS) alone. In fact, as a general observation, we feel that most sick children tend to move the limb with any invasive line lesser, irrespective of hand dominance. While hand dominance may matter in chronic settings (e.g., patient in ward/at home), its relevance in acute pediatric intensive care unit (PICU) setting is doubtful. A randomized controlled trial in 202 adults, which studied the impact of arm selection on incidence of PICC complications, revealed fewer complications on right side compared to left (23% vs 34%; *P*=0.046) irrespective of hand dominance [1]. In a series of 1650 pediatric peripherally inserted central catheters (PICC), catheter site was not found to be a predisposing factor for line fracture/embolization [2]. In our study, 152 right-sided catheters and 113 left-sided catheters were inserted, and the incidence of overall complications was similar in both (22.4% vs 25.6%; *P*=0.39).

At the time of the study, radiographs were routinely done after all line insertion. However, we have moved away from this practice now. While for PICC, radiological confirmation of tip position is important, it is not so for a midline catheter. One can measure the length from proposed insertion site up to axilla and if the length of the planned catheter does not exceed this measurement, radiological exposure can be avoided.

Albumin was administered in 44 patients in the midline group. The indications included underlying gastrointestinal and liver disease (*n*=12, 27%), dengue (*n*=12, 27%), sepsis with shock/MODS (*n*=7, 15.9%), nephrotic syndrome (*n*=5, 11.3%), and others (*n*=8, 18.1%). We did not have any patients with burns in our cohort. The incidence of blockage in the albumin group and non-albumin group did not show any significant differences (9.1% vs 3.4%; *P*=0.139).

Midline catheters are inserted only in upper limb. Hence, we feel it is useful to compare its performance with upper limb PICC. The use of saphenous vein PICC is generally restricted to the neonatal age group. Usually, 24 G catheters are used for this purpose, through which backflow and sampling is not possible. In a retrospective neonatal study

comparing PICC in upper and lower extremity (*n*=374), no significant difference in complications were found [3]. In another neonatal study of 365 PICCs, outcomes of upper and lower extremity PICCs were found to be similar [4].

In older population and adults, use of lower limb PICC is very rare. It is considered only when upper body venous access sites are not available [5,6]. For pediatric difficult venous access, as lower limb PICC gets explored more in the future, further studies in this direction may be planned.

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Topical Cyclopentolate-Induced Systemic Toxicity

A 4-year-old boy presented to the pediatric emergency of our institute with abnormal behavior, restlessness, slurred speech, and difficulty in walking. On detailed history, the mother informed that she had taken him for an ophthalmological examination one hour prior and that cyclopentolate 1% eye drops were instilled thrice at five-minute intervals. He had no complaints of headache, vomiting, abnormal body movements, or breathing difficulty. He was a known case of left congenital nasolacrimal duct obstruction, for which he was recently operated and had gone for his ophthalmology follow-up. At presentation, his heart rate was 100/min, respiratory rate was 26/min, blood pressure was 102/71 mmHg. He had good volume central and peripheral pulses, and SpO_2 was 99% in room air. On examination, he was agitated, disoriented, restless, and had an ataxic gait. His pupils were bilaterally dilated, 4 mm (pharmacologically dilated), and non-reactive. The rest of the systemic examination was unremarkable. A diagnosis of cyclopentolate-induced systemic toxicity was considered. He was managed conservatively and moni-tored for six hours, during which he improved symptomatically and remained hemodynamically stable. 12 hour later, he recovered completely without needing the specific antidote, pyridostigmine and was discharged from hospital.

Cyclopentolate is an anticholinergic (muscarinic antagonist) commonly used for mydriasis and cycloplegia during pediatric ophthalmic procedures. Systemic absorption is through the conjunctiva, nasal mucosa, oropharynx, and digestive system [1-4]. Children are more prone to systemic toxicity due to lower blood volume, lower body mass and immature metabolism [2]. To avoid systemic absorption, the lacrimal sac should be pressed with fingers during the instillation and for 2-3 minutes after. Cyclopentolate-induced systemic toxicity is dose-dependent and can manifest as tachycardia, hypertension, dry mouth, blurred vision, and central nervous system (CNS) manifestations including restlessness, confusion, transient psychotic reactions, hallucinations (visual and auditory), cerebellar signs, and seizures [1,3,4]. CNS manifestations are due to stimulation of higher centres in the cerebrum and medulla. The treatment is mainly symptomatic, and the predominant symptoms resolve spontaneously. Physostigmine is the antidote of choice used only in severe cases, as it can cross the blood-brain barrier [1,2]. The other commonly used mydriatic in pediatric age group is tropicamide 1%. In the index case, the systemic absorption might have increased due to the lacrimal duct procedure, resulting in systemic mani-festations. While cyclopentolate-induced systemic toxicity is rare in children, the treating pediatricians or ophthalmologists should remain vigilant, especially in infants and children, and adhere to appropriate dosing guidelines (one drop of 0.5% for infants and 0.1% for older children of cyclopentolate and one drop after 5 minutes, only if necessary), instillation procedure (pressing

the lacrimal duct), and be aware of the signs and symptoms of toxicity.

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Sublingual Methylcobalamin in Children With Vitamin B12 Deficiency Anemia

We read with interest the recent paper by Saxena, et al. [1] in *the journal*. Vitamin B12 deficiency is common in our country and is an important area for research. We congratulate the authors for studying sublingual B12 therapy in B12 deficiency. We have the following observations on the study:

1. Nine out of 46 children were lost to follow-up, which is almost 20 percent of the participants. Some have suggested that loss of less than 5% leads to little bias, while >20% loss to follow-up poses serious threats to validity [2].
2. Authors have mentioned that the majority of enrolled children were vegetarians (75.7%), with 13.5% non-vegetarians. What was the diet of remaining 11.8% children, and how much non-vegetarian food did the non-vegetarian group take as a proportion of their daily food intake? It is very likely that it was inadequate, as they developed B12 deficiency.
3. Authors have reported that five children (13.5%) had evidence of co-existent iron deficiency at initial presentation [1]. How was iron deficiency established in the study, when there are no test parameters mentioned in results for iron deficiency?
4. We would like to know if tests for other causes of increased homocysteine levels like folate deficiency, hypothyroidism, renal failure, and certain genetic polymorphisms were done. Hypothyroidism is well-known to be associated with lower vitamin B12 levels [3].

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AUTHOR'S RESPONSE

Thank you for your interest in our research paper [1]. We are happy to clarify the issues pointed out by you:

1. The study was carried out during the COVID-19 pandemic (between November, 2020 and April, 2022), and the travel restrictions in force may have contributed to the large attrition in this study.
2. The remaining 10.8% children were ovo-vegetarians [1]. As observed by you, it is not surprising that even non-vegetarian children were deficient in vitamin B12. This was possibly because of only occasional intake of non-vegetarian food in their diets, which may be related to their lower socioeconomic status and/or dietary preferences.
3. We defined iron deficiency based on low serum ferritin

levels (<12 mcg/L in children aged <5 year, < 15 mcg/L in children aged 5-12 year, and <30 mcg/L in the presence of inflammation or infection). These children also received iron and folic acid in addition to sublingual vitamin B12 for treatment.

4. We did not perform genetic polymorphism testing in children with raised homocysteine levels; although, serum folic acid levels, thyroid function tests and renal function tests were carried out in all participants before enrolment. Two children had evidence of co-existent folate deficiency (serum folate <4 ng/mL) and no child had deranged renal functions or hypothyroidism. Moreover, children with chronic diseases or any suspected inborn error of metabolism were excluded.

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NEWS IN BRIEF

India Develops Indigenous CAR T Cell Therapy

It is a historical moment for Indian science. The Central Drugs Standards Control Organisation (CDSCO) has approved an indigenously developed Chimeric Antigen Receptor (CAR) T cell therapy for relapsed/refractory B cell lymphomas and leukemias in October, 2023. CAR T cell therapy in the US costs about Rs 3.3 crore. And India's NEXCAR19, which has been developed by ImmunoACT, will make it available to Indian patients at a minuscule price of INR 30-40 lakhs.

Phase I and II trials were conducted at the Tata Memorial Hospital on 60 patients with a response rate of 70%. Adverse effects like the cytokine release storm and neurological compli-cations were much lower with NEXCAR19 as compared to the CAR T cell therapy available in the US.

In CAR T cell therapy the patients T cells are removed by aphaeresis. The cells are then transferred to a laboratory to genetically modify them to express chimeric antigen receptors against specific targets on the malignant cells. They are multiplied and then reinfused into the patient. Here they attack the cancer cells and have been instrumental in long term remissions, possibly cure, for many untreatable lymphomas and leukemias.

This outstanding success has shot India into the global arena for immunotherapies, which is nothing less than the moon landing by our space scientists!
(*The Indian Express 2 November, 2023*)

Rabies in India

India accounts for 36% of global cases of rabies and 65% of cases in South East Asia. The National Rabies Control Program (NRCP) aims to eliminate rabies by 2030. Rabies is now notifiable in India and attempts to collect real time data have included the Integrated Health Information Platform (IHIP), which uses mobile applications. Prophylactic vaccination for humans and dogs, dog population management and public education are the strategies employed by the NRCP.

A recent report in the Lancet has looked at the trends in India between 2005-2020. The highest incidence is reported from West Bengal (43%), Andhra Pradesh (10%), Maharashtra (8%), and Karnataka and Delhi (7% each). However, there has been a steady decline in incidence from 2.36 to 0.41 per 10 million population. The average annual percentage decline was -11.3%. The major roadblocks have been logistics and funding constraints, and public non-compliance. In certain regions, bats and monkeys may also be reservoirs for the rabies virus and need to be addressed.
(*The Lancet 8 November, 2023*)

The First Chikungunya Vaccine

The first case of chikungunya was reported in 1952 in Tanzania and in November, 2023, the FDA has approved the first effective vaccine against this illness. It is a live attenuated viral vaccine requiring a single dose. Phase III human trials conducted in the US were published in the Lancet in June, 2023. Neutralizing antibodies were seen in 98.9% of the study participants with adverse reactions in 1.6%. Two required hospitalization - one for myalgia and one for SIADH. Intrauterine transmission of chikungunya is known to cause death or disability, and hence the vaccine may be avoided in pregnant women.

This vaccine may be useful in endemic areas, before outbreaks and for travellers to endemic areas. The vaccine will be marketed by the European company Valnev under the name Ixchiq and is approved for persons above 18 years.
(*FDA News Release, 9 November, 2023*)

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CLIPPINGS

Paternal and maternal birth weight and offspring risk of macrosomia at term gestation: A nationwide population study. (Pediatr Perinat Epidemiol. 2023;00: 1-10)

Macrosomia (birth weight ≥4500 g) is important risk factor for delivery complications like shoulder dystocia. Risk factors include previous macrosomic offspring, maternal overweight, diabetes mellitus, and post-term delivery. High maternal birth weight is associated with high offspring birth weight, but whether high birth weight in both parents contributes risk of macrosomia is still unclear. Data from Medical Birth Registry of Norway on all singleton term births during 1967-2017 was used. Primary exposure was parental macrosomia, and outcome was macro-somia in the second generation. Secondary exposure was maternal body mass index (BMI). Data included 647,957 singleton parent-offspring trios born at term. Macrosomia in parents was associated with increased risk of macrosomia in offspring, relative risk both parents were born macrosomic being 6.53 (95% CI 5.31, 8.05), only mother macrosomic 3.37 (95% CI 3.17, 3.57) and only father macrosomic if 2.22 (95% CI 2.12, 2.33).These risks increased by maternal BMI in early pregnancy. If both parents were born macrosomic, 17% infants were macrosomic among mothers with normal BMI. If both parents were macrosomic and mothers were obese, 31% of offspring were macrosomic. Therefore, they concluded that parents' birth weight and maternal BMI are strongly associated with macrosomia in offspring delivered at term gestation.

Prenatal Intravenous Magnesium at 30-34 Weeks' Gestation and Neuro-developmental Outcomes in Offspring: The MAGENTA Randomized Clinical Trial (JAMA. 2023;330:603-14)

Preterm birth is the leading cause of neonatal mortality and morbidity, survivors have higher risk of cerebral palsy (CP). Prenatal use of magnesium sulfate (MS) among pregnant individuals at risk of early preterm birth improves the chance of their infant surviving without CP. Some recommend prenatal use of MS only before 30 weeks' gestation, and others before 32 or 34 weeks' gestation. This trial assessed the effects of MS compared with placebo administered to pregnant individuals at risk of imminent PB between 30 and 34 weeks'gestation, conducted at 24 Australian and New Zealand hospitals between January, 2012 and April, 2018. Of the 1433 pregnant individuals enrolled and their 1679 infants, 1365 (81%) offspring (691 in the MS group and 674 in the placebo group) were included in the primary outcome analysis. Death or CP at 2 years' corrected age was not significantly different between the MS and placebo groups (3.3% vs 2.7%, respectively; risk difference 0.61% [95% CI 1.27% to 2.50%]; adjusted RR 1.19 [95% CI 0.65 to 2.18]. No serious adverse events occurred. Study concluded intravenous MS prior to preterm birth at 30 to 34 weeks' gestation did not improve child survival free of CP at 2 years.

Platelet transfusions in preterm infants: Current concepts and controversies: A systematic review and meta-analysis. (*Eur J Pediatr. 2023;182:3433-43*)

Thrombocytopenia mainly affects preterm infants and critically ill neonates. Platelet transfusions remain the principal approach for treatment. This systematic review and meta-analysis is aimed to evaluate the risks and benefits of platlet transfusion in preterm infants compared to not transfusing or using different platlet count thresholds for transfusion. Primary outcomes were mortality and major bleeding, and secondary outcomes include sepsis and necrotizing enterocolitis (NEC). They identified 18 reports of 13 eligible studies. Results suggest significant association between platlet transfusion and mortality (RR 2.4, 95% CI 1.8–3.4; P <0.001), as well as sepsis (RR 4.5, 95% CI 3.7-5.6; P<0.001) and found significant correlation between platlet transfusion and NEC (RR 5.2, 95% CI 3.3–8.3; P<0.001) after a leave-one-out sensitivity analysis. Platlet transfusion in preterm infants is associated with higher risk of death, sepsis and NEC and, possibly, higher incidence of intraventricular hemorrhage (IVH). But not able to reduce heterogeneity in the assessment of the relationship between platlet transfusion and IVH, no conclusion could be drawn.

Early human milk fortification in infants born extremely preterm: A Randomized Trial (*Pediatrics.2023;152:e2023061603*)

The first two postnatal weeks delineate period of great opportunity to prevent energy and protein deficits in critically ill infants born extremely preterm at 28 weeks of gestation or less. During this critical period for growth and development, provision of protein-enriched human milk (HM) diets could prevent nutritional deficits. This double-blinded, randomized controlled trial (RCT) was conducted to test the hypothesis that HM diets fortified with a HM–based product soon after birth increase fat-free mass (FFM) accretion in such infants extremely preterm. In this trial, starting on feeding day 2, Extremely preterm infants fed maternal or donor milk were randomized to receive either a diet fortified with a HM-based product (intervention group) or a standard, unfortified diet (control group). Total 150 infants were randomized between 2020 and 2022. Primary outcome was assessed in 105 infants (70%). FFM for-age *z* scores did not differ between groups. Length gain velocities were higher and declines in head circumference-for-age *z* score were less pronounced from birth to 36 weeks PMA in the intervention group. Study concluded, HM diets fortified soon after birth do not increase FFM accretion at 36 weeks' PMA, but they may increase length gain velocity and reduce declines in head circumference-for-age *z* scores.

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Perineal Groove

A baby girl was born to a 26-year-old G2A1 mother, post in vitro fertilization-embryo transfer conception, by normal delivery at 37 weeks of gestation. Mother received folic acid in first trimester, and was on labetalol for pre-eclampsia. Anomaly scan done during second trimester revealed no gross congenital anomalies. The baby weighed 2620 g at birth and was noted to have a groove from posterior vaginal fourchette to the anterior ridge of anal opening (**Fig. 1**). The clinical diagnosis was congenital perineal groove. There was no discharge or signs of inflammation around the lesion. Rest of the perineal examination was normal. The ultrasound abdomen revealed no abnormality. The baby was discharged after counselling.

Perineal groove is a rare midline defect of the perineum, an extremely rare form of anorectal malformation mostly seen in females. Exact incidence is not known, with not more only a few case reports on this subject so far in literature. It is characterized by an exposed wet sulcus with non-keratinized mucous membrane, which extends from the posterior vaginal fourchette to the anterior ridge of the anal orifice. This entity is likely to be either missed or unnecessarily investigated by a clinician. It is often an isolated finding, but it may be associated with other urological or genital defects like imperforate anus, perineal ectopic anus, hypospadias or rectal prolapse. The differential diagnosis is contact dermatitis, diaper rash, trauma, or even sexual abuse. The condition is generally self-resolving by 2 years of age; however, the non-epithelized mucous membrane may pose the risk of local infection and irritation, and sometimes urinary tract infection. Very rarely, this condition may need surgical correction. Awareness of this congenital perineal groove at birth is needed for appropriate parental counselling and follow-up.

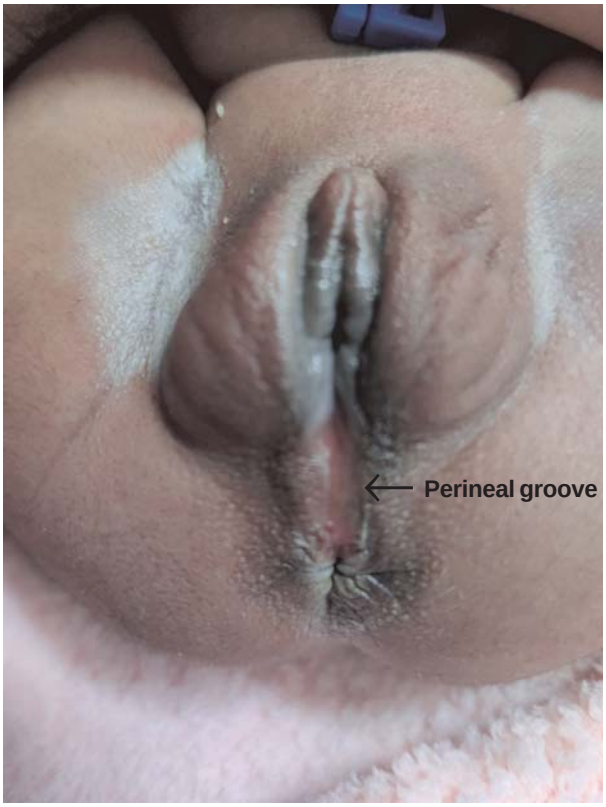

Fig. 1 Perineal groove from posterior vaginal fourchette to the anterior ridge of anal opening.

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