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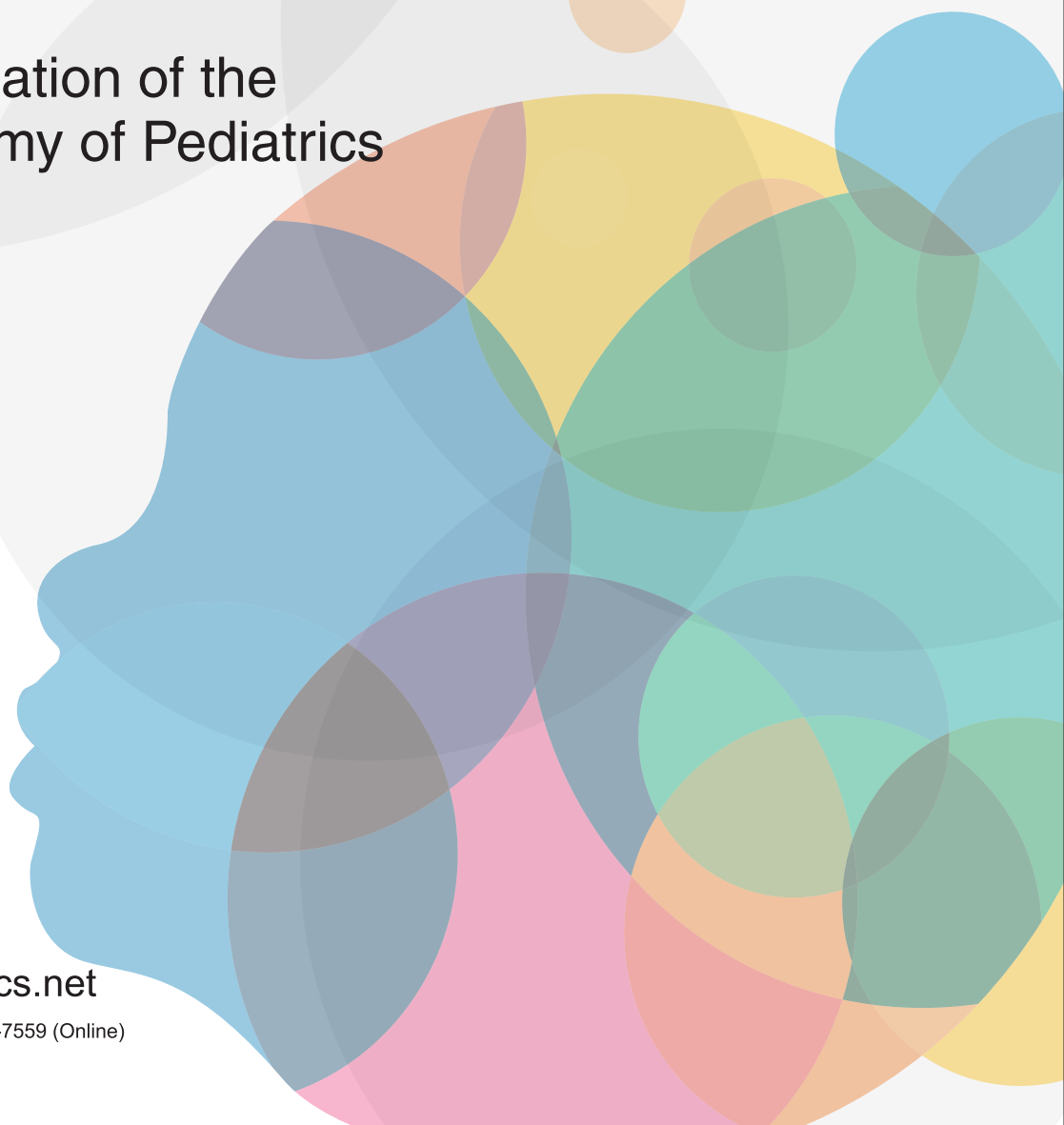

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PRESIDENT'S PAGE

dIAP: Knowledge Sharing Amidst the Pandemic

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This year has been a year of firsts for the Indian Academy of Pediatrics (IAP). It started two years ago, when you all elected me as the President elect of our mother organization IAP, unopposed – first time in the history of IAP in last four decades. This shows the faith and affection you all have for me, and honestly, that has left me greatly humbled. It motivated me to go the extra mile to achieve the best for our mother organization IAP. I had a vision which would change the way that our medical fraternity works, and benefit our many fellow pediatricians who are generally practicing in the remote locations and rural areas. The dIAP platform – a technology driven academy – was established for the first time. With dIAP we reached the unreached, taking whatever the IAP has to offer to every corner of our country and beyond.

None of us were prepared for what happened next. COVID-19 struck – an epidemic of global proportions! Before the financial year ended, India was forced into a lock-down situation. Academics became a secondary require-ment – survival was of utmost importance. We, the Doctors and the healthcare industry started working overtime, trying to prevent the spread and find a cure, to help people survive. This was the time for IAP to come to the rescue of members and community to continue its academics, social and community activities. No one knew what to do. Desperate times called for desperate measures. We had to start thinking of different ways and so called 'new norms'. Physical distancing, the necessity to use masks, and avoidance of close contact led many to search for 'work from home' options. Likewise, students in various disciplines are being taught by dedicated teachers using the online platform. Medical students, both undergraduates and postgraduates are allowed limited or no bedside learning time to avoid unnecessary exposure. Apart from the routine work done by postgraduates in wards, where they learn practical skills, formal teaching activity has mainly remained restricted. Grand rounds, combined teaching from faculty, and bedside case presentations have come to a halt. Seminars with PowerPoint presentations involving large gatherings in the departments have also been suspended.

Worldwide, it has been recognized that while it is important to provide patient care, it is also necessary to ensure adequate training and teaching of medical students who are future physicians. But the logical and practical concerns of patient safety remain, as these students may act as asymptomatic carriers of SARS-CoV-2 (Severe acute respiratory syndrome – Coronavirus 2). Technology has come to our rescue to continue education through the digital platform. Medical education has transformed through the use of online media for virtual team meetings, clinical skills learning, and even for conducting examinations. Many medical colleges have converted their usual classroom teaching to the e-learning platform using various applications available for online classes and webinars. As most of the teaching hospitals cater to a massive burden of patients and most of the teaching staff is involved in clinical work, it allows them lesser time to dedicate for teaching. Also, the senior faculty is actively involved in administrative issues like ensuring preparedness for managing the pandemic efficiently on a large scale.

Keeping these points in mind, the Indian Academy of Pediatrics has rightly introduced digital lectures, by the name of Digital-IAP (dIAP), to facilitate e-learning in all spheres of pediatrics. The dIAP team was already working quite hard. As the pandemic spread, they needed to pull up their socks and ensure that they could deliver well before the expected timeline. I am happy to say that IAP was amongst the first organizations to start the webinar concept on such a large scale. It was and still is hugely popular. People across the country have started viewing and absorbing the knowledge shared in these webinars. Knowledge was not only limited to COVID-19 and other academic topics, but rather a holistic approach was taken to ensure the best interests of our members requirements like teleconsultation solution, health and death insurance, medicolegal support, COVID-19 guidelines, connecting with government, charitable and social responsibilities, and so on. These sessions are being conducted daily, including topics from all sub-specialties and cover the curriculum of postgraduate teaching. dIAP is freely accessible to all, and daily reminders are sent to IAP

members via social media and registered email IDs. Apart from live streaming, an option to view the recorded version has been made available in the archives. Webcast attendees may actively participate in these sessions, ask queries, and share opinions using the chat box or direct communication in personal meetings.

IAP has conducted 422 online sessions from March 16, 2020 to August 31, 2020, with an overwhelming response in each of these sessions from all over India (***Fig.* 1**). Twenty-three (5%) sessions were conducted during the morning hours (9 AM to 12 PM), 278 (66%) sessions in the afternoon (1 PM to 4 PM), and 121 (29%) sessions in the evening (4 PM onwards). A total of 7,71,375 views with an average of 1886 views per session have been documented. The specialty-wise distribution is shown in ***Fig.* 2**. Twenty-three (5%) of these sessions were directly or indirectly related to COVID-19, and the postgraduate clinics on Thursdays constituted 20 (4.7%) of these sessions. The Pediatric Intensive Care Chapter of IAP has begun the PICU e-Gurukul program, in which weekly lectures are taken by stalwarts in the field of critical care. They have also started P2P PICU Febinar (Peer-to-Peer PICU Fellows' Webinar), providing a national platform for the pediatric intensive care fellows to present, teach and learn from each other. It is a program 'Of the Fellows, By the Fellows, For the Fellows.' The IAP respiratory chapter has started 'Respinars' for pulmonology teaching, in which the experts of the field take lectures.

Similarly, each zone/state wing of IAP has also formulated their teaching/academic sessions online. dIAP has also partnered with the NHS UK through the Alder Hey academy global pediatric lecture series (GPLS), thereby allowing an opportunity for Indian students and pediatricians to participate in distinguished lectures overseas. IAP has also come up with the unique concept of conducting online conferences through dIAP. The zonal meetings of IAP are being conducted by the name of 'PediWeek'. Each zone was given one week, and this activity was a huge hit and has been appreciated by one and all. It was a mix of scientific and cultural activities. All pediatricians and members of IAP had actively participated in these PediWeeks.

The dIAP sessions have helped in reaching students, private practitioners, and pediatricians at various hospitals, who have benefitted from these classes. The online learning archives could form a database for teaching in the future. There have been some sessions involving parents where they join hands with the pediatricians for the wellbeing of the children. dIAP has brought the teaching to your homes; it is eco-friendly, paperless, saves travel and a lot of time. Moreover, all the sessions are recorded, and one can watch them at their convenience.

However, it also has a few disadvantages inherent to the online platform (***Fig.* 3**). Literature on the impact of the pandemic on online medical education has flagged communication and student assessment problems, technology-related issues, and difficulties in time management in these sessions. Despite these challenges and technophobia, a majority have been able to achieve the expertise quickly to conduct digital classes. Another drawback is that it has decreased the personal touch and

Fig.1 *Trend of webinar numbers over the weeks.*

Fig. 2 *Sub-specialty distribution of online teaching sessions on the dIAP platform.*

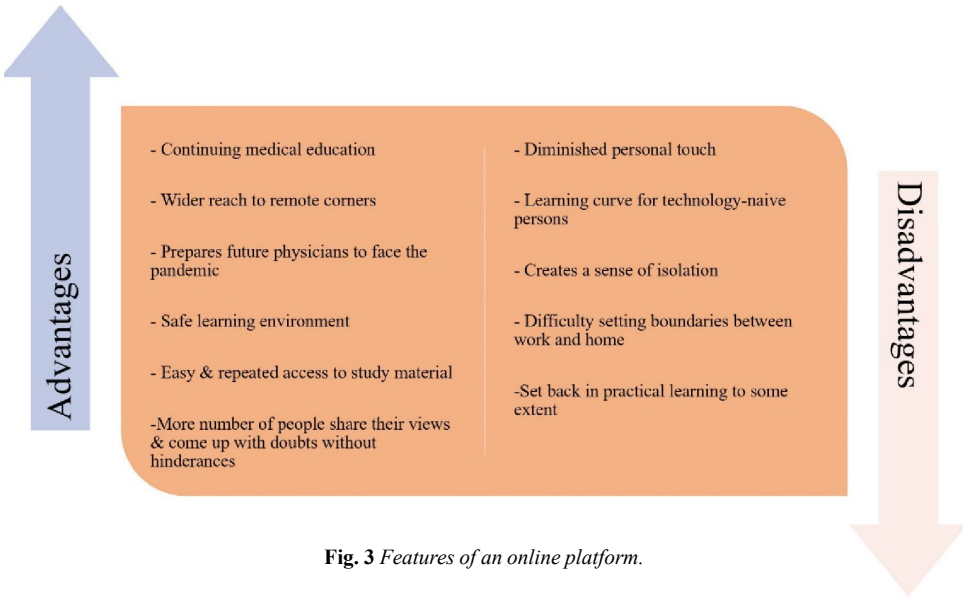

Fig. 3 *Features of an online platform.*

warmth, which was there during the physical meetings. To overcome the various problems, IAP has come up with specific solutions like facilitating 24-hour teaching modules with feedback for practical learning. The BLS (Basic life support) and ALS (Advanced Life Support) modules have been remodeled to suit e-learning. dIAP is also planning to include the live answers from the audience during the lectures through the e-notepad. With this software, the audience can easily select one of the options given by the speaker. This year of the pandemic will culminate with the highlight activity of IAP, *i.e*., the National PediWeek – dIAP will be conducting a virtual national conference which will take virtual teaching to a different level.

Charles Darwin said, "*it is not the most intellectual of the species that survives; it is not the strongest that survives, but the species that survives is the one that is able best to adapt and adjust to the changing environment in which it finds itself*." Online learning is the new way of life that we must adapt to in the days and weeks to come, which has been put into action by IAP.

I would like to personally thank Dr. Arun Bansal, Dr G V Basavaraj and Dr Namita Ravikumar who have spent their valuable time and effort to come up with the facts and figures pertaining to the different aspects in this document, making it an interesting and informative read. I also hope that we can achieve even greater heights by having a common goal – to enhance childcare in our country and ensure that IAP becomes a well-known organization, not just across the country, but rather across the entire world. Let us strive to make the best of these trying times and ensure the best for our mother organization.

Jai Hind! Jai IAP!

Sudden Unexpected Death in Epilepsy (SUDEP) - What Pediatricians Need to Know

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Sudden unexpected death in epilepsy (SUDEP) is a devastating complication in children with epilepsy. Children with generalized tonic-clonic convulsions, nocturnal seizures, and co-morbid developmental delay/intellectual disability are at higher risk of SUDEP. The pathogenic mechanisms are incompletely understood and involve cardiac, respiratory, autonomic and cerebral dysfunction. Prone positioning is also significantly associated with SUDEP and may be a target for SUDEP prevention. Good epilepsy control also attenuates the risk; hence, it is important to provide adequate antiepileptic drug therapy with stress on drug compliance as well as early surgical referral for seizure control, wherever necessary. It is recommended that parents of children with epilepsy be counseled about the risk factors for SUDEP and potential measures of SUDEP prevention. We herein provide a pediatric perspective of the problem and guidance about parental counselling for its prevention.

Keywords: *Counselling, Morbidity, Outcome, Prevention, Uncontrolled epilepsy*.

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Mortality in children with epilepsy is significantly higher than the general population [1]; although, most deaths in children with epilepsy are not related to seizures or epilepsy [2]. The higher risk is explained by several factors: respiratory illness with underlying neurological condition that presents with seizures, systemic comorbidities, indirect factors as well as deaths presumably or demonstrably due to seizures. Sudden unexpected death in epilepsy (SUDEP), which belongs to the last group, has gained prominence as a cause of death in epilepsy in recent years.

DEFINITION

SUDEP is defined as a "sudden unexpected witnessed or unwitnessed, non-traumatic, non-drowning death in a patient with epilepsy with or without evidence of a seizure and excluding documented status epilepticus in which post-mortem examination does not reveal a toxicological or anatomical cause of death [3]." This definition requires a postmortem examination to diagnose SUDEP, which is not available in the majority of instances. Hence, criteria have been described for definite, probable and possible SUDEP [4] (***Box* I**).

BURDEN

The incidence rates of SUDEP in children have been reported to be 0.36-0.43 per 1000 person-years [5-7]. Although SUDEP rates have been reported to be lower in children compared to adults, the American Academy of Neurology (AAN) practice guidelines on SUDEP established the incidence rate of SUDEP in children with epilepsy to be 0.22/1000 patient–years (95% CI 0.16-0.31) after a systematic review of 12 class I studies [8]. Due to imprecision in incidence data results, random-effect meta-analysis was further performed. SUDEP was found to affect 1 in 4,500 children with epilepsy in one year, making the risk of SUDEP rare.

Risk Predictors

There are very few studies assessing risk factors in childhood SUDEP and most of the data is derived from larger studies in adults.

- The presence and frequency of generalized tonic-clonic seizures (GTCS) is an important risk predictor for SUDEP [8].
- The relative risk of SUDEP is 7.7 times higher in patients with onset of epilepsy between 0-15 years compared to onset after the age of 45 years [9].
- All-cause mortality, including SUDEP, is also higher in children with developmental delay [10].
- Children with uncontrolled seizures have a higher risk [11].
- SUDEP has also been shown to increase with the duration and severity of seizures, with 15-fold risk

Box I Classification and Definition of Subtypes of Sudden Unexpected Death in Epilepsy (SUDEP)

Definite SUDEP

- Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus in which postmortem examination does not reveal a cause of death.

Probable SUDEP

- Same as definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

Possible SUDEP

- SUDEP cannot be ruled out but a competing cause of death is present. If a death is witnessed, a cutoff of death within one hour from acute collapse is suggested.

with more than 50 GTCS per year, nocturnal seizures and the occurrence of GTCS [12], as well as prolonged tonic state leading to post-ictal immobility [13].

- Postictal generalized EEG suppression beyond 50 seconds also may have a predictive role in SUDEP and is associated with sleep, shorter duration of clonic phase, symmetric tonic extension posturing and terminal burst-suppression after a seizure [14].
- Symptomatic epilepsy has a higher risk of SUDEP compared to idiopathic generalized epilepsy. Patients with Dravet syndrome are also at a higher risk of death [15].

SUDEP shares certain features with the syndrome of sudden infant death (SIDS), suggesting possible common mechanisms. SIDS is sudden and unexpected death that occurs in infants below the age of one year. Both SIDS and SUDEP are diagnoses of exclusion, and autopsy findings are usually not revelatory. Deficiency in arousal response to rise in carbon dioxide in both syndromes may contribute to death, suggesting that these two entities may lie on a continuum [16].

PATHOPHYSIOLOGY

The pathophysiology of SUDEP is not well elucidated and is believed to arise from an interaction between predisposing factors and triggers. Predisposing factors include effects of long-standing seizure disorder such as altered autonomic function, etiology of epilepsy (*e.g.* symptomatic, familial), factors related to drug therapy such as abrupt withdrawal or polypharmacy *etc*. A triggering seizure leads to preterminal events including cardiac, respiratory, autonomic and cerebral dysfunction. The various mechanisms (***Fig.* 1**) include the following:

Cardiac dysfunction: Sudden cardiac arrest is a proposed mechanism with certain ion channel abnormalities being implicated in both epilepsy and cardiac arrhythmia. The most widely implicated is the sodium channel abnormality, which may also explain the higher rates of SUDEP in Dravet syndrome [17]. Another link is the association between long QT syndrome and familial epilepsies, both of which are channelopathies.

Respiratory dysfunction: Severe peri-ictal hypoxia occurs in one-fourth of patients with SUDEP [17]. Autopsy changes of pulmonary edema have also been observed in SUDEP cases, but this is likely an effect than a cause of SUDEP.

Autonomic dysfunction: Various autonomic abnor-malities have been described in patients with refractory epilepsy and include lower parasympathetic and higher sympathetic tone, increased vasomotor tone and impaired heart rate variability [18]. Changes in ictal heart rate also suggest autonomic dysfunction, with tachycardia occur-ring in up to 60% of seizures and bradycardia in 6% of focal seizures [17,19]. As per the Mortality in epilepsy monitoring units study (MORTEMUS), an initiative that assessed cases of SUDEP and near-SUDEP in patients admitted for video-EEG monitoring, post-ictal centrally mediated cardiac and respiratory depression associated with post-ictal generalized EEG suppression was a strong mechanism leading to SUDEP [20]. The switch from parasympathetic to sympathetic state, combined with sympathetic over-drive that accompanies the state of drug withdrawal that accompany seizures may be a possible precipitant.

Channelopathies: Channelopathies are disorders characterised by dysfunction of ion channels. Traditionally channelopathies have been considered genetic defects *eg*., long QT syndrome and Dravet syndrome. In inherited channelopathies, the same ion channel abnormalities are expressed in the heart as well as the brain. Hence, these epilepsies are associated with an arrythmia-prone cardiac condition.

Recently, there is an emerging concept of acquired channelopathy *i.e.*, channel dysfunction in patients with chronic epilepsy. Animal studies have shown that epilepsy alters the expression of sodium, potassium, calcium and cationic channels in the heart. In these

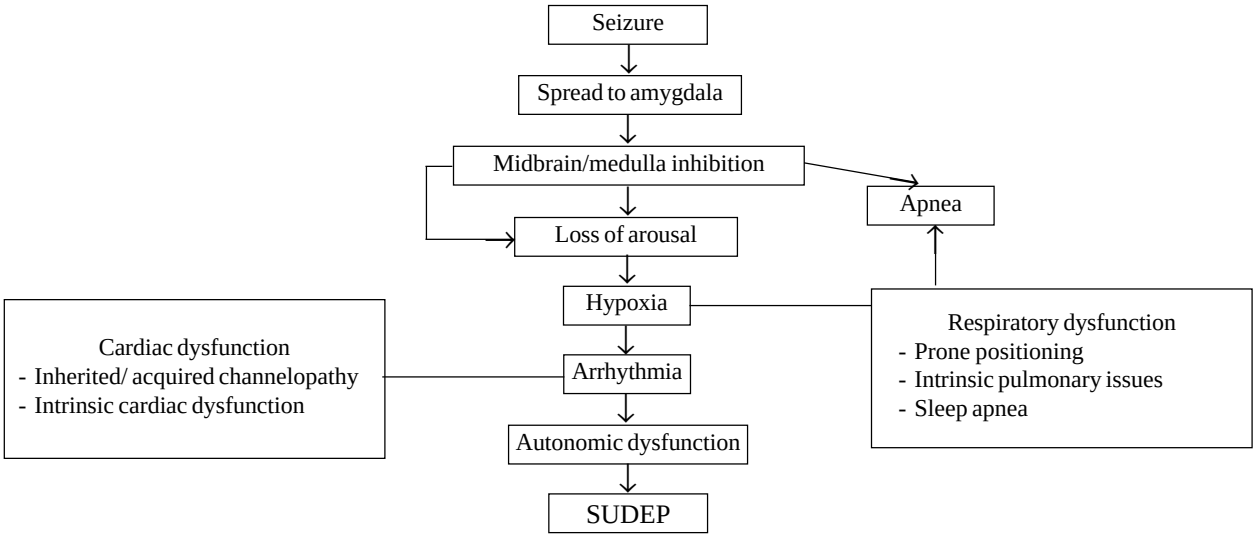

Fig. 1 *Various pathophysiological mechanisms leading to sudden unexpected death in epilepsy (SUDEP).*

acquired cardiac channelopathies, epilepsy increases the pro-arrhythmic state increasing predisposition to sudden death [21].

Cerebral dysfunction: SUDEP occurs more often in sleep and almost all cases are nocturnal and associated with the prone position. Various neurotransmitter abnormalities have been reported in association with SUDEP including low serotonin state [22] and excessive opioid [23] and adenosine activity. Brainstem serotonin modulates respiratory drive and has also been implicated in sudden infant death syndrome [24]. It may contribute to SUDEP by a similar mechanism.

INTERVENTIONS FOR PREVENTION

As uncontrolled epilepsy is a known risk factor, effective epilepsy treatment to reduce frequency and duration of seizures as well as GTCS should be targeted. Nocturnal supervision was found to be protective in one case-control study [25] and may be combined with seizure detection devices, but clinching evidence in SUDEP prevention is lacking. It is of potential benefit in children with uncontrolled or nocturnal seizures. In India, nocturnal supervision of children is generally culturally acceptable as co-sleeping of children with their parents is common. A blanket 'back to sleep' advice to avoid prone positioning may be recommended, with the caveat that it is the post-ictal turning prone which is usually responsible. Hence parents should be counseled to turn the child to a lateral position and avoid prone position after the seizure. The use of lattice or safety pillows may reduce the contribution of prone position to post-ictal cardiorespiratory distress.

In terms of preventive drug therapy, it has been observed in mouse models of SUDEP that selective serotonin reuptake inhibitors (SSRI) such as fluoxetine may decrease apnea risk [26]. Serotonergic neurons in the brainstem are believed to be responsive to rise in CO_2 and fall in pH levels in the blood and thereby stimulate respiration and arousal. In a retrospective study on adults with focal seizures [27], it was noted that patients on SSRIs (for co-morbid mental health problems) had a reduced likelihood of post-ictal oxygen desaturation as compared to patients who were not on SSRIs. Recently, two randomized controlled trials have been completed to evaluate the role of fluoxetine to prevent post-seizure apneas and desaturation; however, the results have not been published yet. Massive release of endogenous opioids and adenosine is induced by seizures and helps in seizure termination [28]. However, this surge can also lead to post-ictal apnea. Naloxone is currently under a randomized trial for this purpose. Adenosine antagonists may also be beneficial for this purpose.

These therapies; however, are still in the emerging phase and currently being tried in adults. More evidence is needed before the data can be extrapolated to children.

Parental Counseling

Counseling of caregivers and sensitization towards SUDEP is imperative. Caretakers should be educated regarding the importance of adherence to treatment, nocturnal supervision, especially to avoid prone position after seizures, as well as basic life support training imparted to willing caregivers. However, whether all patients with epilepsy should be counseled about the risk

of SUDEP or only high-risk patients remains a matter of debate, and scientific data till date does not permit the establishment of evidence-based guidelines for the same. However, disclosure of SUDEP risk to all epilepsy patients has been endorsed by multiple neurological societies, including a joint task force of the American Epilepsy Society and the Epilepsy Foundation and the American Academy of Neurology (AAN) [29], and in India by the joint consensus document on parental counseling by Association of Child Neurology (AOCN) and Indian Epilepsy Society (IES) [30]. In a study on parental views regarding the counseling of SUDEP risk, parents generally expressed a preference for receiving routine SUDEP counseling at the time of the diagnosis of epilepsy [31]. In another study from Malaysia (32% of participants were of Indian origin), 70.9% of parents felt that receiving SUDEP information was positive [32]. Most parents did not report any impact on their own functioning. However, increasing numbers over time reported an impact on the child's functioning. In a study from UK, 74% of pediatric neurologists conveyed SUDEP information to a select group of patients only. In contrast, 94% of parents of children with epilepsy expected the physician to provide SUDEP information [33].

In India, many neurologists and pediatricians feel that imparting the knowledge of SUDEP may increase parental anxiety and stress levels, which may be unwarranted as the complication is so rare. However, it is also known that many parents are afraid their child would die when they witness the child having a seizure for the first time. The information that the risk of death is very low may be reassuring. Also, the knowledge of this condition may improve drug compliance, as seen in studies from outside India. In an Indian study of SUDEP counseling of adults with epilepsy and their caregivers, it was shown to increase drug adherence without any increase in anxiety or stress levels in either the patients or their caregivers [34]. More experience is needed in this field to understand parental perceptions and reactions.

CONCLUSION

SUDEP is an under-recognized but important threat in patients with epilepsy. It is important to assess SUDEP risk in all epilepsy patients, particularly in those with generalized tonic-clonic convulsions, nocturnal seizures, as well as co-morbid developmental delay. Appropriate antiepileptic drug therapy with stress on compliance, early surgical referral for surgically remediable epilepsies, avoiding post-seizure prone positioning, and caretaker counseling and support will go a long way in the prevention of this condition.

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EDITORIAL COMMENTARY

Refining Clinical Triage and Management of Dengue Infection in Children: A Timely Approach

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The World Health Organization (WHO) declared dengue infection to be one of the top ten threats to global health in 2019. In defiance of medical progress, dengue has achieved the notoriety of being an infectious disease that has relentlessly increased in magnitude and geographic reach over the past several decades. The dramatic increase in the magnitude and frequency of dengue has been attributed to unprecedented human population growth, unplanned urbanization and expansion of travel and globalization. Modelling estimates indicated that there are 390 million dengue virus infections annually, with approximately 100 million cases manifesting clinically, with 70% of the actual burden being in Asia [1]. The vast majority of those infected are children. The global suffering caused by this vector-borne virus, while eclipsed in magnitude by the current SARS-CoV-2 pandemic, has not abated in parts of the world where dengue is endemic. Unexpected surges of dengue case counts have been reported this year in many places, and this phenomenon is likely to pose serious challenges to already overburdened healthcare systems across the world [2]. As dengue and COVID-19 share several clinical and laboratory features, cases of misdiagnosis, serological cross-reactivity and co-infection have been described, further complicating management [3]. It is therefore especially critical, now more than ever, that the classification systems for dengue ensure validity and reproducibility for both clinical management and research studies.

The traditional WHO classification for dengue, implemented from 1974 onwards based on experience with pediatric dengue in Thailand, was revised in 1997, and classified dengue disease as dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. This classification, despite being evidence-based, was critiqued for underestimating the clinical burden of the infection, and for poorly distinguishing the milder and more severe forms of dengue [4]. The revised 2009 classification that eventually replaced the previous system describes the following categories: dengue without warning signs, dengue with warning signs, and severe dengue [5]. This classification was mainly aimed at optimizing the recognition of warning signs early in the disease course, thereby enhancing clinical decision making and disease management. Seven clinical signs were identified as warning signs for severe dengue, based largely on global expert consensus and supplemented by findings from the DENCO study, a large multicenter study in Southeast Asia and Latin American countries conducted in 2006-2007 [6]. Severe dengue was defined as infection with at least one of the following: severe plasma leakage leading to shock or fluid accumulation, with respiratory distress, severe bleeding, or severe organ impairment. However, this classification fails to identify the precise parameters that define these signs, leading to a great deal of heterogeneity in the use of this system, a problem well-described in a recent systematic review [7]. The sensitivity of this classification to identify severe dengue has ranged between 59-98%, and specificity between 41-99% [8]. It has been argued that the severe dengue entity as defined by the 2009 classification represents a mix of end-stage manifestations involving various clinical pathways, potentially including comorbidities and other iatrogenic factors [9]. Most importantly, the 2009 classification fails to identify standard, quantifiable clinical endpoints which are needed to ensure reproducibility and comparability of research findings, thereby limiting its application in research studies, such as studies aiming to study the safety, efficacy and effectiveness of a dengue vaccine or therapeutic agent.

An expert working group assembled in 2015 used the Delphi method of interactive consensus-driven guideline formulation to derive dengue disease severity endpoints for use in clinical trials of dengue therapeutics and vaccine research [10]. Consensus was reached on most parameters including, moderate and severe plasma leakage, bleeding, and organ involvement (liver, heart and neurologic disease) [10]. By applying these new definitions on the 2006 DENCO dataset to identify measurable clinical endpoints, experts concluded that

severe vascular leakage is an entity distinct from other severe manifestations such as bleeding or organ dysfunction, and may be used as a reliable endpoint for intervention research [11]. While definitions for mild and severe dengue disease were established, a clear definition of 'moderate' disease severity was identified as a need for conducting cross-validated research. It is clear that further prospective studies to validate standardized clinical endpoints for dengue disease of differing severity categories are important for filling these gaps.

Sreenivasan, *et al*. [12] are to be commended for embarking on the exceedingly difficult task of determining how the warning signs described in the 2009 WHO classification of dengue can predict time for disease progression from moderate to severe dengue among children. They conclude that vascular leakage as manifested by clinical fluid accumulation, and hemoconcentration measured by hematocrit ≥40%, are important manifestations that are predictive of a shortened time towards progressing to severe dengue [12]. Their findings imply the need for heightened surveillance and supple-ment other studies of clinical endpoints in dengue. The hallmark of severe dengue, particularly in the younger age group, is vascular permeability leading to plasma leakage, and subsequent circulatory shock and its consequences, which can be life threatening. The authors highlight the importance of other clinical manifestations such as persistent vomiting and mucosal bleeding in predicting time to severe disease progression. Early recognition and close monitoring of these clinical manifestations, along with timely institution of appropriate management can spell the difference between therapeutic success and failure among children with dengue infection. In the current pandemic era, while resources are diverted to address the devastating effects of COVID-19, the toll of ongoing infections such as dengue must not be forgotten. The overlapping challenges of dengue and COVID-19 prompt an urgent call to action for continued disease surveillance, ongoing attention to clinical and environmental management, and increased focus on research needs.

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EDITORIAL COMMENTARY

Identifying India's Dual Nutrition Burden: Role of Body Mass Index Quick Screening Tool

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A dual nutrition burden of undernutrition with rise in childhood obesity was recognized in India in the latter decade of the twentieth century [1].Yes, the pendulum has swung from the era of undernutrition from 1960s-80s to the era of plenty, leading to over-nutrition from late 90s till the present. The healthcare systems are now focusing on the burden of obesity in childhood because of its long term consequences of non-communicable diseases in adulthood [2]. However, surveillance for undernutrition is imperative as part of the life cycle approach to ensure optimum health at birth and later in life. The Prime Minister's Overarching Scheme for Holistic Nourishment (POSHAN) Abhiyaan, a multi-ministerial convergence mission, was initiated in 2018 by the Government of India to ensure adequate nutrition of pregnant women and lactating mothers and holistic development of children, with a vision to attain malnutrition-free India by 2022 [3] .

Body mass index (BMI) is currently the best simple available anthropometric estimate of fatness for public health purposes, proposed first by Cole, *et al.* [4] in children in 1979, which adjusts weight for both height and age. The validity of anthropometric data as a proxy for body fat identifies children at risk and correlates better with measures of body fat mass [4]. The International Obesity Taskforce (IOTF) pooled data from six international BMI references to define the centile cut offs at 18 years of age to match the adult cut offs of 25 kg/m^2 and 30 kg/m^2 for overweight and obesity. However, studies conducted in India showed the IOTF reference classified participants as having a lower weight and concluded that IOTF criteria were not suitable for Indian and South Asian children [5]. Thus, lower BMI cut-offs of 23 kg/m^2 and 25 kg/m^2 have been suggested by the World Health Organization (WHO) and IOTF for Asian Indian adults for overweight and obesity, respectively but these are not applicable for children and adolescents [6]. Over the years, there has been a lack of consensus on the various cut-points or definitions used to classify obesity and overweight in children and adolescents. This makes it difficult to interpret and compare the global or national prevalence rates. For children and adolescents, overweight and obesity are usually defined using age and gender specific nomograms of BMI. The Indian Academy of Pediatrics recommends the revised growth charts for height, weight and BMI for assessment of growth of Indian children aged 5-18 year. Overweight and obesity have been defined using adult equivalent of 23 kg/m^2 and 27 kg/m^2 cut-offs presented in BMI charts in children from 5-18 years [7]. Higher prevalence of obesity and overweight was reported with IAP 2015 reference than IOTF and WHO 2007 standards in the age group of 8-18 years, with good agreement [8].

With the need to identify over nutrition early, it is important to calculate and plot BMI at least once a year in all children and adolescents, and identify weight patterns relative to linear growth. The use of charts helps track BMI to give guidance. Monitoring of BMI is; however, often overlooked in routine clinical practice unless the issue is recognized by parents, which may be rather late at times. Many parents would need an interpretation of their child's BMI and assessment of their child's health risks. Defining one or more cut-off points on the BMI chart determines the advice to be communicated to the parents at a stage when interventions might be easier.

The 'ELIZ health path for adolescents and adults (EHPA)' novel growth assessment chart was designed to plot the height on the X axis and weight on the Y axis and then read the BMI from the right margin in accordance with the International Obesity Task Force (IOTF) recommendations for the various age groups [9]. The lower and the higher cut-off indicators on this chart were found appropriate for preliminary screening of a large number of children and adolescents in the community setting [9,10].

In this issue Khadilkar, *et al.* [11] report on the development of a graphic tool for the BMI cut offs, without need for calculating BMI, for screening from 8 years onwards for underweight, overweight and obesity,

which complements the existing IAP 2015 charts. They validated the tool using de-identified data on children from school health surveys and found that the BMI tool had a sensitivity of 100% for both boys and girls with a specificity of 88.9% and 82.4% for boys and girls, respectively for underweight. The sensitivity and specificity was 95.7% and 85.7% for boys, and 95.7% and 89.7% for girls, respectively for detection of overweight and obesity. Thus, the tool demonstrated high sensitivity and specificity for screening children for underweight, overweight and obesity against IAP BMI charts. They also observed that the tool may wrongly categorize children at extreme ends of height for age. However, larger studies with a bigger sample size are required for validation and generalization of the tool. The tool is gender-specific and is based on height and weight, which eliminates the need for calculation of BMI, and may help pediatricians to rapidly screen for any changes in BMI in a busy clinical practice.

Efforts to decrease the existing nutritional scenario of dual burden of undernutrition alongside emerging over nutrition should be a top priority. The present narrative shows that overweight and obesity rates in children and adolescents are increasing among the higher socio-economic groups and in the lower income groups where underweight still remains a major concern. No country can aim to attain economic and social development goals without addressing the issue of malnutrition. This suggests the need for a balanced and sensitive approach addressing economic and nutrition transitions to effectively tackle this double burden paradox in India. Since the comorbidities of undernutrition, low birth weight, and overweight/obesity with associated non-communicable diseases co-exist in India, it is important to integrate nutritional concerns in developmental policies.

The key to long-term solutions lies in prevention with a proactive approach.BMI performs moderately well as a proxy for nutritional indicators and is the best available tool for monitoring progress in the campaign for identifying malnutrition in India. A robust quality assured anonymized data collection and analysis system can provide national and local data that would inform the planning and evaluation of intervention programs. BMI can be an effective screening test for undernutrition; however, the statistical cut-off points are inherently arbitrary and must be followed up by a more detailed evaluation to assess the risks and plan intervention.

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RESEARCH PAPER

WHO 2009 Warning Signs as Predictors of Time Taken for Progression to Severe Dengue in Children

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Objective: To identify WHO 2009 warning signs that can predict time taken for progression to severe dengue in a pediatric population.

Design: Prospective analytical study over 1 year and 2 months.

Setting: Tertiary care center.

Participants: 350 children aged 1 mo-12 y with serologically confirmed dengue without co-morbidities/co-infections; consecutive sampling.

Procedure: At admission, clinical and laboratory details were noted. Disease progression, time of onset of each warning sign, hematocrit, and platelet counts were recorded daily till discharge/death. If progressing to severe dengue, its time of onset was noted. Time to event analysis with Log Rank test, Kaplan Meier plots and Cox Proportional Hazards Model was done.

Outcome Measures: Primary outcome was time interval from onset of first warning sign to onset of severe dengue (defined as per WHO 2009 guidelines). Predictors were WHO 2009 warning signs: abdominal pain, lethargy, persistent vomiting, mucosal bleed, clinical fluid accumulation, hepatomegaly >2 cm, hematocrit ≥0.40 and platelet count <100x10^9/L.

Results: Among 350 children followed up completely till discharge/death, 90 developed severe dengue (event) while 260 did not (censored). Median age of study population was 7.75 y. Clinical fluid accumulation [(*P*=0.002, Hazard Ratio (HR) 2.19, 95% CI 1.33-3.60)] and hematocrit ≥0.40 [(*P*=0.009, HR (95%CI) 1.715, (1.13-2.60)] were significant in univariate analysis. Final multivariate model includes clinical fluid accumulation [(*P*=0.02, HR (95%CI) 1.89, (1.116-3.202)], hematocrit ≥0.40 (*P*=0.07), mucosal bleed (*P*=0.56) and persistent vomiting (*P*=0.32).

Conclusion: WHO warning signs that predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed. Study results have implications in policy making and practice guidelines to triage children attending a health care facility with or without warning signs.

Keywords: *Hematocrit, Management, Outcome, Prognosis.*

Dengue is a globally prevalent arboviral infection with high morbidity and mortality in India [1]. Kerala reported 19,912 dengue cases with 37 deaths in 2017 [2]. Dengue is dynamic with febrile phase, critical phase (appearance of warning signs at/around defervescence mark onset of capillary leak) and convalescent phase [3]. Seven warning signs *viz*. abdominal pain, lethargy, mucosal bleed, persistent vomiting, clinical fluid accumulation, hepatomegaly >2 cm and rising hematocrit with a concurrent fall in platelet count below 100×10^9/L are evidence-based signs selected by the World Health Organization (WHO) [3,4]. Potentially lethal severe dengue can manifest as shock, severe bleed or severe organ impairment in the critical phase or in the febrile phase without preceding warning signs [3]. Close monitoring and timely initiation of intravenous fluids in the presence of any warning signs remain the only effective treatment modality in dengue [3]. Severe dengue manifests as mostly shock in children and as severe bleeding and organ impairment in adults [5].

A prognostic prediction model using seven WHO warning signs to determine severe dengue in children has been published earlier [6]. Dynamicity of illness can be captured by taking into consideration the time to time variations in clinical and laboratory variables [7]. The present study aimed to identify warning signs which can predict time taken for progression to severe dengue in children admitted to a tertiary care center.

Editorial Commentary: Pages 895-96.

METHODS

This prospective study was done in a tertiary care setting over one year and two months (2015-16). All serologically confirmed dengue patients (either NS1Ag positivity, if admitted within first 5 days of fever, or IgM positivity, if after 5 days of fever) between 1 mo-12 y without co-morbidities or co-infections were enrolled by consecutive sampling. At admission, baseline history, clinical examination and laboratory investigations (total

count, hematocrit, platelet counts, liver and renal function tests) were recorded. Close monitoring was done to note the time of onset of warning signs and severe dengue if any and need for administration of intravenous fluids till discharge or death. Daily examination for clinical fluid accumulation, hepatomegaly, hematocrit and platelet count were done in all patients. In case of rising hematocrit, intravenous fluids were started, titrated (as per WHO 2012 guidelines) and hematocrit repeated. In patients with clinical worsening, 4 hourly hematocrit, 12 hourly platelet count, and 2 hourly clinical examinations were done, as per hospital protocol. Ethical clearance was obtained from Institutional Review Board.

Primary outcome was time duration from onset of first warning signs to onset of severe dengue defined as attainment of either severe plasma leak leading to shock and/or fluid accumulation with respiratory distress, severe bleed or severe organ impairment [3]. Seven WHO, 2009 warning signs (dichotomized as yes/no) were: abdo-minal pain (severe enough to warrant medical attention), lethargy (without altered sensorium), persistent vomiting (≥2 episodes of vomiting that amounts to fatigue or requires intravenous fluids), mucosal bleed (any bleed from gastrointestinal/genitourinary mucosa, nose, conjunctiva), clinical fluid accumulation (either pleural effusion not severe enough to cause respiratory distress as evidenced by reduced intensity of breath sounds on auscultation of axillary areas or ascites as evidenced by shifting dullness), hepatomegaly >2 cm, hematocrit ≥0.40 (cut-off decided by constructing a receiver operating characteristic curve) and a fall in platelet count $<100\times10^9$/L [6].

Sample size for number of events in each group in survival analysis was calculated where in δ is natural logarithm of the expected ratio of hazards at a given time [8]. For a two-tailed test (α 0.05 and β 0.2), by keeping δ arbitrarily as 1.6, number of events (severe dengue) needed in each group was calculated as 71; by keeping δ arbitrarily as 2, events needed in each group was 33.

Statistical analyses: Descriptive statistics and time to event data analysis were performed with SPSS version 20. Univariate analysis was done for each warning signs with time taken for progression to severe dengue as outcome; Kaplan Meier graphs were drawn. Predictor significance for inclusion in the multivariate model was predetermined (α 20%). Cox proportional hazards model was checked by looking for parallel lines with and without each predictor in scatter plots with log time along *X*-axis and -log [-log (Survival function)] along *Y*-axis [9].

RESULTS

Among 386 serologically confirmed dengue patients, 9 had co-morbidities, 8 had co-infections, 7 did not have any warning signs and 2 had onset of severe dengue before onset of the first warning signs. They were excluded and among remaining 350, 90 (25.7%) progressed to severe dengue (event); 4 patients with severe dengue died. Remained 260 children (74.3%) did not progress to severe dengue and were considered 'right censored' in time to event analysis.

Median (IQR) age of study population was 7.75 (4.75, 10.25) year. There were 21 infants and 188 (53.7%) were males. Proportion of children who progressed to severe dengue as evidenced by compensated shock, decompensated shock, respiratory distress, severe bleed and severe organ impairment as per WHO definitions were 23.1%, 16%, 4.6%, 1.4% and 4.6%, respectively. Median (IQR) day of admission to our center was on day 5 (4, 6). 154 subjects were NS1Ag positive, 163 were IgM positive and 33 were both positive; 22.1%, 29.4% and 24.2% progressed to SD respectively. Median (IQR) length of follow-up was 5 (4, 6) days **(*Table* I)**.

Log rank test was applied to the data and Kaplan Meier curves were drawn to compare between groups with and without each warning sign **(*Table* II**, ***Fig*. 2*a*, 2*b*)**. Final model includes all warning signs with $P<0.2$ in univariate analysis (clinical fluid accumulation, mucosal bleed, persistent vomiting and hematocrit ≥0.40) (***Table* III**).

Receipt of intravenous fluids could confound time taken for progression to severe dengue, but statistical significance was not obtained in univariate analysis with time to event as outcome.

DISCUSSION

The study shows that clinical fluid accumulation, hematocrit ≥0.40, mucosal bleed and persistent vomiting predict time taken for progression to severe dengue. Earlier, authors developed a prognostic prediction model to determine severe dengue in children that included clinical fluid accumulation hematocrit ≥0.40 with platelet count $<100\times10^9$/L and persistent vomiting [6].

In the present study, clinical fluid accumulation appeared late with a median time of onset of 144 h from onset of fever. Moreover, median time of onset of severe dengue is only 2h from onset of clinical fluid accumulation. In most situations, authors were the first to identify clinical fluid accumulation; being a tertiary setting, exact time of onset of clinical fluid accumulation could not be delineated. In our study, hematocrit appeared late probably because the investigation was not sent before admission to our center. Even then, median time of onset of severe dengue was 5h after onset of

Table I Time of Onset of Warning Sign and Time of Onset of Severe Dengue (*N*=350)

Characteristic	*Abdominal pain*	*Persistent vomiting*	*Lethargy*	*Hepatomegaly >2cm*	*Clinical fluid accumulation*	*Mucosal bleed*	*Platelet count <100×10⁹/L*	*Hematocrit ≥0.40*
Total with WS*	217 (62)	99 (28.2)	327 (93.4)	162 (46.2)	64 (18.2)	72 (20.5)	284 (81.1)	123 (35.1)
Time of onset of WS (h)	72 (6,120)	24 (6,120)	6 (6,72)	144 (120,168)	144 (144,168)	132 (96,162)	120 (120,144)	144 (120,168)
Total with WS before event*	211 (60.2)	98 (28)	326 (93.1)	143 (40.8)	46 (13.1)	56 (16)	270 (77.1)	113 (32.2)
Total events*	58 (16.5)	35 (10)	86 (24.5)	36 (10.2)	26 (7.4)	21 (6)	69 (19.7)	42 (12)
Time to onset of event after WS (h)	48 (6,120)	120 (24,144)	120 (48,144)	2 (2,3)	2 (1,4)	24 (4,48)	18 (2,24)	5 (2,24)

*Values in median (IQR) except *n(%); WS-warning sign.*

Table II Children With Each Warning Sign Who Progressed to Severe Dengue (Event) and Event Free Time

Warning sign	*Total*	*Events n= 90*	*Survival Time (95% CI), min*	*P value*	*Crude OR (95% CI)*
Yes	211	58 (153)	359.7 (328.98-390.43)	0.87	1.04
No	139	32 (107)	324.1 (291.19-357.02)		(0.67-1.59)
Lethargy					
Yes	326	86 (240)	362.5 (337.46-387.60)	0.69	1.26
No	24	4 (20)	167.2 (141.90-192.59)		(0.39-3.99)
Persistent vomiting					
Yes	98	35 (63)	276.4 (242.73-310.04)	0.13	1.38
No	252	55 (197)	384.1 (356.53-411.64)		(0.90-2.10)
Clinical fluid accumulation					
Yes	46	26 (20)	178.3 (146.04-210.48)	0.002	2.19
No	304	64 (240)	379.1 (353.64-404.59)		(1.33-3.59)
Hepatomegaly					
Yes	143	36 (107)	363.8 (339.18-388.35)	0.81	1.01
No	207	54 (153)	370.7 (338.81-402.67)		(0.69-1.59)
Mucosal bleed					
Yes	56	21 (35)	204.8 (177.67-231.89)	0.14	1.45
No	294	69 (225)	370.3 (342.62-398.01)		(0.89-2.36)
Hematocrit ≥0.40					
Yes	113	42 (71)	265.5 (232.60-298.35)	0.009	1.71
No	237	48 (189)	392.3 (364.75-419.91)		(1.13-2.59)
Platlet count <100x10^9/L					
Yes	270	69 (201)	314.6 (291.83-337.30)	0.97	1.01
No	80	21 (59)	382.0 (333.96-430.14)		(0.61-1.66)

hematocrit ≥0.40. This time gap is clinically valuable for initiating close monitoring, intensive care and early referral if needed. This makes hematocrit ≥0.40 a clinically relevant warning signs. Kaplan Meier curves drawn for clinical fluid accumulation and hematocrit ≥0.40 as predictors intersect at some points. Hence confounders do exist for which stratum specific analysis might have been helpful. Administration of intravenous fluids was thought of as a potential confounder but statistical significance was not obtained in univariate analysis. Possibility of unknown confounders should be thought of in this context.

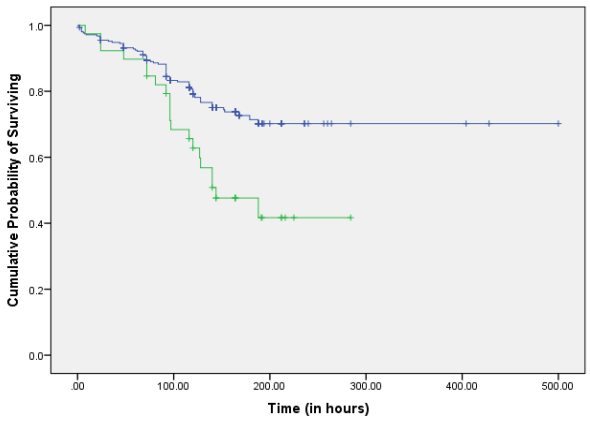

Fig. 1 *Kaplan Meier Curve showing survival function over time in the absence (upper line) and presence (lower line) of CFA as predictor.*

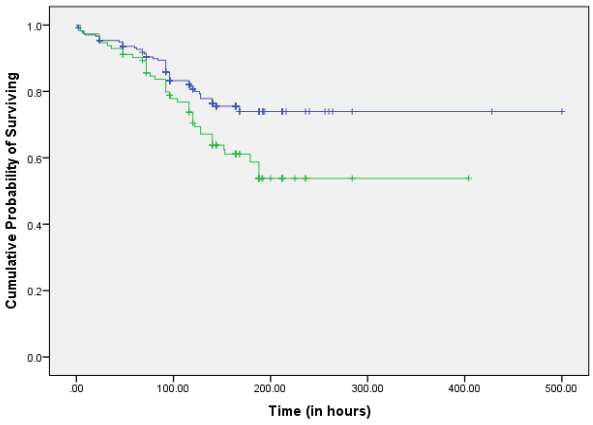

Fig. 2 *Kaplan Meier curve showing survival function over time in the absence (upper line) and presence (lower line) of HCT >0.40 as predictor.*

Mucosal bleed and persistent vomiting are two objective symptoms, time of onset of which the caretaker may easily notice. An added advantage of persistent vomiting is its early appearance in the disease course. A sufficient time gap between time of onset of persistent vomiting and time of onset of severe dengue was also demonstrated in our study. Due to these clinical reasons, mucosal bleed and persistent vomiting were included in the final model.

In our tertiary care setting, some patients had onset of warning signs even before admission to our hospital. To minimize this recall bias, details from referral letters were collected and telephonic conversations with referring doctor were done wherever needed. Though technically, 260 patients were right censored, all were completely followed up till recovery as evidenced by fever free period of 48 hours, disappearance of clinical warning signs, rising trend of platelet counts and a normal hematocrit. Secondary infection is a strong risk factor of progression to severe dengue and hence may influence time to event. Detailed investigations to delineate infection as primary or secondary were not done in our study. Our study period included two dengue seasons, but only 90 patients progressed to severe dengue which was below the estimated sample size.

Table III Cox Proportional Hazards Model With Selected Warning Signs

Warning signs	*Model including CFA, HCT ≥0.40, PV and MB*		*Model including CFA, HCT≥0.40 and MB*	
	HR (95% CI)	*P value*	*HR (95% CI)*	*P value*
CFA	1.89 (1.11-3.20)	0.02	1.85 (1.09-3.12)	0.02
Hct ≥0.40	1.49 (0.96-2.29)	0.07	1.54 (1.00-2.35)	0.05
MB	1.17 (0.69-1.97)	0.56	1.25 (0.76-2.07)	0.38
PV	1.25 (0.80-1.95)	0.32	-	-

CFA: Clinical fluid accumulation; Hct: Hematocrit; PV: Persistent vomiting; MB: Mucosal bleed; HR: Hazard ratio.

A previous survival analysis assessed survival of adult dengue patients in relation to the severity of liver dysfunction [10]. Survival analysis of a pediatric population has identified that acute renal failure adversely affects survival rates [11]. In these studies, event was mortality whereas in our study, event severe dengue. Lam, *et al*. [7] have found that prediction models with serial daily platelet counts demonstrated better ability to discriminate patients who developed shock than models based on enrolment information only [7]. They concluded that development of dynamic prediction models that incorporate signs, symptoms and daily laboratory measure- ments could improve dengue shock prediction. In our study, all seven WHO warning signs have been included for the purpose of prediction.

Our results may be generalized to children attending a health care facility with dengue. As India is hyperendemic for dengue, the study results have implications in policy making and practice guidelines, especially to triage children attending a health care facility with or without warning signs. To conclude, WHO warning signs that can predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed.

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Ethics clearance: Institutional Review Board, Government

WHAT IS ALREADY KNOWN?

- Among seven warning signs suggested by WHO in 2009, clinical fluid accumulation, rising hematocrit concurrent with rapid fall in platelet count <100x10^9/L and persistent vomiting predict severe dengue in children.

WHAT THIS STUDY ADDS?

- WHO warning signs that predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed.

Medical College, Thiruvananthapuram; No. 06/62/2015/MCT, dated December 09, 2015.
Contribution: PS: conceived the idea, designed the methodology, collected and analysed data and prepared the manuscript; GS: guided conduct of the study, critically reviewed the manuscript; SKA: elaborated the concept, interpreted the results, critically reviewed the manuscript and approved final version to be published. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Body Mass Index Quick Screening Tool for Indian Academy of Pediatrics 2015 Growth Charts

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Objective: To develop gender-specific graphic tool in which BMI cut offs can be read from height and weight, without need for calculating BMI and to validate the tool against Indian Academy of Pediatrics (IAP) 2015 BMI charts. **Methods**: Validation of tool was performed using de-identified data on children from school health surveys. **Results**: For detection of overweight and obesity, the BMI tool had sensitivity of 95.7% and specificity of 85.7% for boys, and 95.7% and 89.7% for girls, respectively. For underweight, sensitivity of 100% for boys and girls, and specificity of 88.9% for boys and 82.4% for girls was observed. **Conclusion**: We present a graphic BMI tool for screening for underweight, overweight and obesity, which complements the existing IAP charts.

Keywords: *Diagnosis, Growth chart, Obesity, Overweight, Underweight.*

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In recent times, while undernutrition is common in India [1], childhood obesity is an important health problem in urban areas, and seen commonly in older children and adolescents than younger children [2]. Early recognition of obesity is important to prevent adverse health consequences in adulthood such as hypertension and type 2 diabetes [3]. Further, undernutrition during adolescence can potentially retard adolescent growth spurt [4]. Indian Academy of Pediatrics (IAP) Guidelines provide body mass index (BMI) charts for Indian children to screen for under or over-nutrition [5]. BMI needs to be computed and then plotted on a growth chart. However, in a busy pediatric out-patient clinic, calculating BMI is time consuming and is often omitted [6]. BMI may not be plotted and hence overweight and underweight may be missed. Thus, there is a need to create a screening tool based on height and weight that eliminates need for BMI calculation and helps pediatricians rapidly screen for overweight, obesity and underweight. The objective of present study was to develop a gender-specific graphic tool in which BMI cut offs can be read from height on *X*-axis and weight on *Y*-axis, without the need to calculate BMI.

METHODS

The health-related risks of obesity such as metabolic syndrome are more common after 10 years of age or at the onset of puberty and likewise recommendations for screening for metabolic syndrome [7-9]. We therefore designed the BMI tool for use from 8 years. The mean value of height, weight and cut-offs for underweight, overweight and obesity were used from the IAP charts [5] to design the tool. Ethics approval for the study was obtained from the institutional ethics committee. The height range for boys and girls for the age group of 8-18 years was plotted on the *X*-axis. Based on the BMI cut off value for that particular age the corresponding weight to a particular height was calculated and plotted on the secondary *Y*-axis (Microsoft Excel 2015). Thus, height was plotted on the *X*-axis, weight on the *Y*-axis and three lines *viz*, for underweight, overweight and obesity were constructed on secondary *Y*-axis. The meeting point of the two lines gives the BMI. Depending on where the BMI point lies, child may be classified as being, obese, overweight, normal weight or underweight. If plotted reading falls below lowest line the child is underweight, if it is between underweight and overweight lines, the child has a BMI within reference range, if the reading falls between overweight and obese lines the child is overweight, and if above obese line, the child is considered obese. Separate tools were created for both genders.

Editorial Commentary: Pages 897-98.

Sample size was calculated using external prognostic modeling [10] and was recommended to be more than 200. The tool was validated on de-identified data from a health survey [11]. Data were distributed over BMI categories as per the IAP charts into underweight, within reference

range, overweight and obese, and used to test sensitivity and specificity of BMI tool. Data on height and weight from validation data set were plotted on BMI tool and simultaneously on the IAP BMI charts. The number of children classified as underweight, within reference range, overweight and obese by the tool and IAP charts was noted. Sensitivity and specificity of the tool against IAP charts was computed (SPSS 25).

RESULTS

Data on 221 (112 boys) children age 8-18 years were used. The gender-wise BMI screening tools are illustrated in ***Fig*. 1** and **2**.

For detection of overweight and obesity in comparison with IAP charts, sensitivity was 95.7% for both boys and girls, whereas specificity was 85.7% for girls and 89.7% for boys. For detection of underweight, sensitivity was 100% for both genders and specificity was 88.9% for boys and 82.4% for girls.

DISCUSSION

We have presented a graphic tool based on IAP growth charts in which BMI can be read by plotting height and weight without the need to calculate BMI. The tool demonstrated high sensitivity and specificity for screening children for underweight, overweight and obesity, when tested against IAP BMI charts.

The limitations of the tool are that it is likely to categorize children wrongly at extreme ends of height for age, thus, too tall and very short children may be wrongly classified. The tool cannot be used in children younger than 8 years, and larger studies with a bigger sample size are required for validation and generalization of the tool.

In a study where questionnaires were sent to Ministries of Health of 202 countries, authors found that growth charts were mainly used for children from 0-5 years, and covered birth to adolescence in only 29% [12]. More than half of the countries, including 18 Asian countries, used weight for age charts instead of BMI charts [17]. In a questionnaire-based study to assess usage of growth charts, over two-third of doctors reported a positive attitude towards monitoring of growth; how-ever, perception of high workload was associated with lower usage of growth charts [8]. There are fewer preventive visits to hospitals as children get older [13]. These reports thus underline the importance of devising simple graphic tools to assess nutritional status for use in busy clinical settings.

A similar unisex chart was proposed by Elizabeth, *et al*. [14] in 2001 based on the International Obesity Task Force cut-offs [15], which may not be appropriate for Indian children at present. Unisex charts may not be appropriate as girls stop growing earlier than boys. The tool designed in the current study may be used in conjunction with IAP charts, and the cut-offs for BMI used are more appropriate for Asian Indian children, who have a higher body fat for a given BMI. However, it is important to remember that this is a quick screening tool and children who are found to be abnormal on the tool or at borderline of categories should be rechecked on the IAP BMI charts after calculating the BMI with standard formula.

To conclude, we present a graphic BMI tool for screening for underweight, overweight and obesity to complement existing IAP charts. The tool is gender specific and is based on height and weight, which

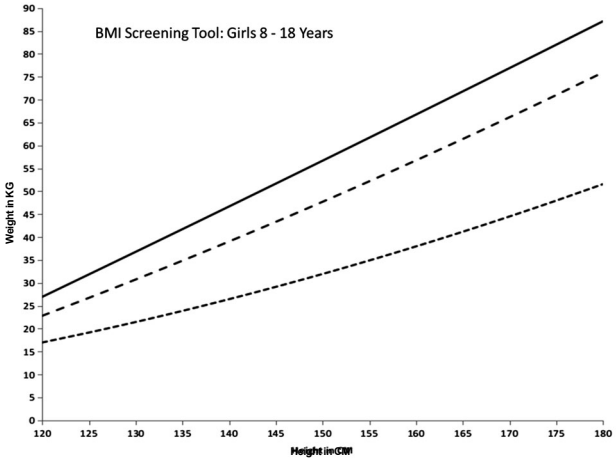

Fig. 1 *Body mass index screening tool for girls aged 8-18 years.*

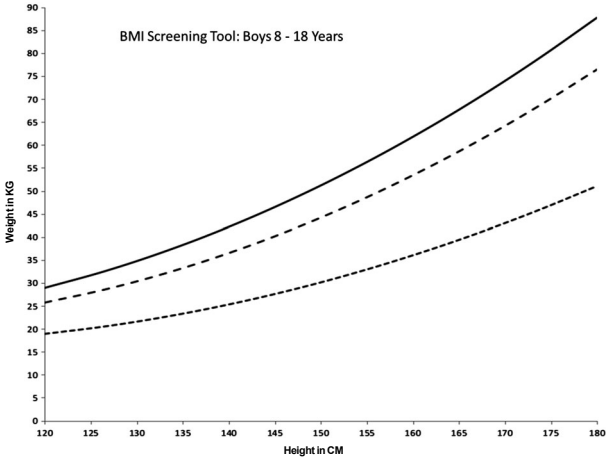

Fig. 2 *Body mass index screening tool for boys aged 8-18 years.*

WHAT THIS STUDY ADDS?

A body mass index (BMI) look-up tool using height and weight has been presented for screening for overweight, obesity and underweight in children aged between 8 and18 years.

eliminates the need for calculation of BMI, and may help pediatricians to rapidly screen for perturbations in BMI in a busy clinical setting.

Ethics clearance: Institutional ethic committee of Jehangir Clinical Development Centre; dated June 21, 2016.
Contributors: VK: concept and design of study, statistical analysis and manuscript draft; NL, SC, AK: data collection, statistical analysis and manuscript draft.
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RESEARCH PAPER

Progression of Thyrotropinemia in Overweight and Obese Children From Puducherry, India

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Objective: To assess the progression of thyrotropinemia to overt hypothyroidism in overweight and obese children. **Methods**: 150 overweight and obese children aged 5-15 years were enrolled. Free T4 and thyroid stimulating hormone (TSH) were done at enrollment and for those with TSH >5 mIU/L, TSH levels were repeated after 1 year. **Results**: The mean (SD) body mass index (BMI) and TSH were 23.8 (3.19) kg/m^2 and 2.70 (2.44) mIU/L, respectively. 17 children had thyrotropinemia (TSH between 10-15mIU/L); 10 (84.6%) of these children attained normal TSH levels at one year follow-up, and none progressed to overt hypothyroidism (TSH >15 mIU/L). **Conclusion**: Levels of 5-15 mIU/L are common in asymptomatic overweight and obese children. Majority of these children revert back to normal TSH levels on follow-up.

Keywords: *Body mass index, Metabolic syndrome, Sub-clinical hypothyroidism, Thyroid stimulating hormone.*

Comprehensive National Nutrition Survey (CNNS) 2016-18 reported that 4% of all school age children and 5% of adolescents were overweight based on body mass index (BMI) [1]. Subclinical hypothyroidism (SCH) is very common in overweight and obese children and has an estimated prevalence of about 9% compared to 6.1% in non-obese children in India [2-4]. Risk factors for SCH are female sex, Hashimoto thyroiditis, reduced iodide intake, radiation exposure, *etc* [2].

Diagnosing SCH in obese children remains controversial as increased TSH levels (thyrotropinemia) are frequently present in obese children [4,5]. Although, the exact mechanism of TSH elevation in obesity is unclear, some studies have attributed thyrotropinemia to increased deiodinase levels converting T4 to T3 as a compensatory mechanism to increase basal metabolic rate, and reduced expression of TSH and T4 receptors in adipose tissue of obese children [6]. Two large population-based studies from India reporting normograms for TSH in normal Indian children are available [3], but there is no consensus in cut-off levels of TSH for obese children [7,8].

Thyroxine replacement for marginal elevations of TSH in childhood obesity has questionable benefits [9]. Obesity may be associated with TSH surge but it does not signify hypothyroidism in all cases. It is unclear if SCH (thyrotropinemia) progresses into overt hypothyroidism in obese children [2].Though there are various studies evaluating the intriguing relationship between fT4 and BMI in childhood obesity, the findings are inconsistent [6-8]. Therefore, we studied the progression of thyrotropinemia (SCH) to overt hypothyroidism in obese and overweight children.

METHODS

This longitudinal study was conducted from July, 2018 to July, 2019 at a tertiary care pediatric hospital in Puducherry, India. Children between 5-15 years of age attending the pediatric out patient department with body mass index (BMI) more than 23 kg/m^2 adult equivalent according to standards for Indian children [10]. Children with BMI between 23 to 27 kg/m^{2}and >27 kg/m^2 were categorized as overweight and obese, respectively. Children on anti-thyroid medication, family history of thyroid disorders, and sick children with acute illness requiring admission were excluded from the study. Approval from Institute's research and ethics committee were obtained before commencement of the study. Informed written consent was obtained from the parents and assent from older children.

All children were checked for presence of goiter and symptoms of hypothyroidism like constipation, dry skin, cold intolerance, hair loss, hoarse voice and growth retardation.Weight, height, waist circumference and hip circumference measurements were recorded. Enrolled

children were screened for hypothyroidism with free T4 (fT4) and TSH values following overnight fasting of 12 hour. fT4 and TSH levels were estimated by chemiluminescence method using immunoassay analyzer. Based on a school based Indian study, the reference values of mean fT4 were 1.13-1.34 ng/dL for boys and 1.11-1.22 ng/dL for girls, and TSH 2.57-3.6 mIU/l for boys and 1.83-3.58 mIU/L for girls [4]. Children with TSH >15 mIU/L irrespective of symptoms and TSH between 10 -15 mIU/L with symptoms of hypothyroidism were treated with thyroxine [11]. Lifestyle modifications like healthy eating patterns, increased physical activity and decreased sedentary behavior were advised to all participants. Children with SCH (TSH 5-15 mIU/L) were followed up for a period of one year and serum TSH levels were repeated.

Statistical analysis: Data entry was done in MS Excel 2010. Data was analyzed using SPSS version 16.0. Pearson correlation coefficient was used for correlation studies.Wilcoxon signed rank test was applied for comparing baseline and follow-up variables. Values of $P<0.05$ were considered statistically significant.

RESULTS

Among 150 overweight and obese children (49.3% males; mean age, 10.2 year) included in our study, 132 (88%) children were found to have a TSH value of 0-5 mIU/L (euthyroid); 17 (11.3%) had a TSH value corresponding to SCH levels with 15 (10%) having TSH between 5-10 mIU/L). One child (0.66%) had TSH >15 mIU/L diagnosed as overt hypothyroidism and started on thyroxine. The mean fT4 in subgroups with TSH 5-10 and 10-15 mIU/L were 1.40 and 1.78 ng/dL, respectively. The mean (SD) BMI and TSH of the study group were 23.78 (3.19) and 2.70 (2.44) mIU/L, respectively. There was no association of TSH level with overweight or obese children ($P=0.56$). The correlation coefficient of BMI with fT4 and TSH were $r=0.08$ and $r=0.016$ (both $P>0.05$), respectively.

On follow-up of 17 children with SCH,10 (84.6%) had become euthyroid and 7 (15.4%) remained at subclinical hypothyroid levels. None progressed to overt hypothyroidism.The mean (SD) baseline and following TSH values were 6.33 (2.15) and 4.92 (2.14) ($P=0.47$). Comparison of mean baseline BMI with follow-up BMI is given in ***Table* I**. No correlation was found between weight loss and TSH change ($r=0.138$; $P=0.598$).

Table I Baseline and Follow-up Body Mass Index (BMI) in Overweight and Obese Children Aged 5-15 Year With Initial Thyroid Stimulating Hormone Level 5-15 mU/L (*N*=17)

	BMI, kg/m²		*P value*
Baseline TSH, mIU/L	*Baseline mean (SD)*	*Follow up mean (SD)*	
TSH 5-10	22.48 (2.2)	22.49 (2.1)	0.56
TSH 10-15	25.62 (3.4)	25.59 (3.1)	0.42

DISCUSSION

Our study revealed majority (84.6 %) of obese kids with SCH (TSH 5-15 mIU/L) reverted back to euthyroid state within one year. In another study from India, among 40 children (aged 2-16 years) presenting with subclinical hypothyroidism, majority (52.5%) became euthyroid after the follow-up period of 3 months to 1 year, which was similar to our findings [14]. TSH levels decreased in more than 80% of obese children following life style interventions for obesity without thyroxine therapy [15]. Weight reduction and TSH normalization were attained only with diet and life style modifications [15]. In our study, though TSH levels normalized in most of the children, majority had no weight reduction on follow-up. This was mainly attributed to lack of compliance to life style modifications and lack of regular follow-up.

In this study, we found poor correlation between BMI and TSH/T4 levels, whereas Ghergherehchi, *et al*. [12] demonstrated that levels of TSH and fT4 were significantly higher in children with obesity compared with the control [12]. In a study published from South Korea, BMI was positively correlated with serum concentrations of TSH and negatively correlated with serum concentrations of fT4 after adjusting for age [13]. In this study, we could not demonstrate the relationship between baseline BMI and baseline TSH, which is discordant with many similar studies, which have confirmed the increasing TSH levels with BMI. Similarly, fT4 levels were not associated with BMI in our study though some studies revealed a positive or negative correlation with BMI [12,13].

Relatively smaller sample size and lack of autoimmune thyroid profile data in the study population are some of the limitations of this study. Further multi-centric studies with long term follow-up are needed to detail the cause of hypothyroidism among obese children, and course of thyrotropinemia in adolescence and young adulthood.

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Contributors: ST,AT: conceived the study; ST, RB: collected data and managed the cases; ST,RB: reviewed the literature and drafted the initial version of the manuscript; AT contributed to literature review and critically revised the manuscript. All authors contributed to drafting of the manuscript and approved the final version of the manuscript.

Ethics approval: Institute Ethics committee IGMC&RI, Puducherry; No. 06/IEC/IGMC&RI/F-7/2018 dated June 6, 2018.

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WHAT THIS STUDY ADDS?

- Subclinical hypothyroid levels of TSH (5-15 mIU/L) were common in overweight and obese children, and reverted back to normal after a one-year follow-up.

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RESEARCH PAPER

Weight of Schoolbags Among Indian Schoolchildren in Pune and Hyderabad

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Objective: This study was done to determine proportion of children carrying heavy school bags and to compare new guidelines issued by Government of India on school bag weight limit, based on class of the child with previous guidelines based on child's weight. **Methods**: A cross-sectional study was done among students of schools from two cities of India – Pune and Hyderabad. Weight of school bag of 1321 children was measured and classified as 'heavy' or 'normal' based on existing as well as new guidelines. Agreement between two guidelines was also calculated. **Results**: In our study, 722 (77.2%) out of 935 students from class 1-10 were found to be carrying 'heavy' school bags. Kappa coefficient for agreement between two guidelines was 0.55 (0.47,0.60) indicating moderately strong agreement. **Conclusions:** Large proportion of school children are carrying school bags with weight beyond permissible limits. There is a need for all stake holders to take steps to reduce weight of school bags.

Keywords: *Bags, Child, Education, India, School*.

In present times, school children have to carry heavy schoolbags due to number of books, notebooks and variety of other materials they are required to bring in their school. Heavy school bags can lead to number of musculoskeletal problems like backache, shoulder pain, pain in hand and wrist, and spinal deformities among children [1-6]. Heavy school bags have also been found to be associated with poor educational outcomes and absenteeism. There are laid down guidelines that school bag should not be more than 10% of child's weight [2,7,8] and there shall not be any school bag for a child studying in nursery and kindergarten classes [9]. However, various studies carried out in India as well as in other countries have brought out that school children are carrying school bags with weight beyond permissible limits [1-6,10-12]. Recently, Ministry of Human Resource Development, Government of India issued new guide-lines for school bag weight [13]. According to these guidelines, maximum permissible weight of school bags has been specified according to the class in which a child is studying. We carried out this study on school bag weights of school children in India to estimate proportion of children carrying schoolbags heavier than recommen-ded weight as per previous as well as newer guidelines. We also investigated level of agreement between these two guidelines in our study

METHODS

This cross-sectional study was done in selected schools in Pune and Hyderabad city of India. School children studying in all grades of selected schools *i.e*. from Nursery to 10th standard were included in this study. Minimum sample size required to estimate proportion of school children carrying heavy school bags in our study, assuming that proportion to be 76% [10], with 95% confidence level and 2.5% error of margin was 1121. Assuming non-response rate of 15%, we planned to include 1325 students in this study. Simple random sampling was used to select the students for this study

Administrative permissions were taken from respective school authorities to carry out this study. Institutional Ethics Committee approval was also obtained. Parents' consent and children assent was taken for participation in this study. Students particulars including date of birth were obtained from school records. A digital weighing machine was used to measure weight of students with bag and without bag. Difference in these two weights was used to calculate weight of school bag. Shoes of students were removed before measuring weight. We used two criteria to classify school bag as 'heavy': (*i*) Criterion 1 –According to child's weight - If school bag weight was more than 10% of child's weight [9]; and (*ii*) Criterion 2-According to class - If school bag weight was more than 1.5 kg for class 1 & 2, more than 3 kg for class 3-5, more than 4 kg for class 6-7, more than 4.5 kg for class 8-9, and more than 5 kg for class 10th [13].

Statistical analysis: Student t test was used to compare

continuous variables between two groups. Kappa co-efficient was used to measure agreement between two guidelines regarding overweight of school bags. R software ver 3.2.0 was used for data analysis.

RESULTS

A total of 1321 students (708 male) participated in this study, mean (SD) schoolbag weight was 3.81 (2.45) Kg. Distribution of students as per different classes is shown in ***Table* I**. Class 8 students had highest mean school bag weight [8.05 (2.87) kg]. However, class 6 students were found to be carrying highest school bag weight in terms of their body weight [21.65 (8.93)%]. Mean school bag weight as per different classes is shown in***Table* I** and ***Figs*. 1** and **2**. There was no significant difference in mean (SD) school bag weight of boys and girls in our study [3.92 (2.67) kgs *vs* 3.68 (2.17) kg, *P*=0.07], or mean (SD) school bag weight as percentage of body weight [13.9 (6.55) *vs* 13.9 (5.95); *P*=0.9].

According to guidelines, children studying in nursery and kindergarten should not be carrying any schoolbag. However, in our study we found that children studying in these pre-primary classes were also carrying school bags with weights as mentioned in***Table* I**. Hence, we assumed that 100% of these pre-primary school children were carrying 'heavy' school bags. We excluded these children from further analysis.

We used two criteria to classify school bag weight as 'high' for school children studying in grades 1-10. We found that more than 77% school children were carrying school bag with more than recommended weight. Distribution of these students as per their grade is shown in ***Table* II**.

Table I Weight of Schoolbag in the Enrolled Children (*N*=1321)

Grade	*Number of children*	*Schoolbag weight (kg)*	*Schoolbag weight as body weight percentage (%)*
Nursery	101	1.08 (0.40)	7.6 (2.9)
LKG	145	1.94 (0.58)	11.9 (3.92)
UKG	140	2.18 (0.54)	12.3 (3.78)
1	82	3.15 (0.91)	14.9 (5.37)
2	145	3.33 (1.12)	14.9 (5.55)
3	147	3.40 (1.21)	14.4 (6.11)
4	132	3.65 (1.26)	13.8 (5.76)
5	186	4.15 (1.44)	13.8 (6.12)
6	38	6.89 (2.53)	21.6 (8.93)
7	41	7.78 (2.86)	20.4 (9.14)
8	53	8.05 (2.87)	18.9 (7.86)
9	50	7.46 (2.38)	16.9 (6.02)
10	61	7.56 (2.15)	12.0 (4.0)

LKG: Lower kindergarten; UKG: Upper kindergarten; values in mean (SD).

Although Criterion 1 and Criterion 2 classified almost equal number of school bags (724 and 722, respectively) as 'heavy'; only 647 bags were classified as heavy by both criteria (***Table* III**). Overall, agreement in these two criteria for classification of schoolbag weight as heavy or otherwise was 83.7% [Kappa co-efficient (95% CI): 0.55 (0.47, 0.60)] indicating moderately strong agreement in these two guidelines.

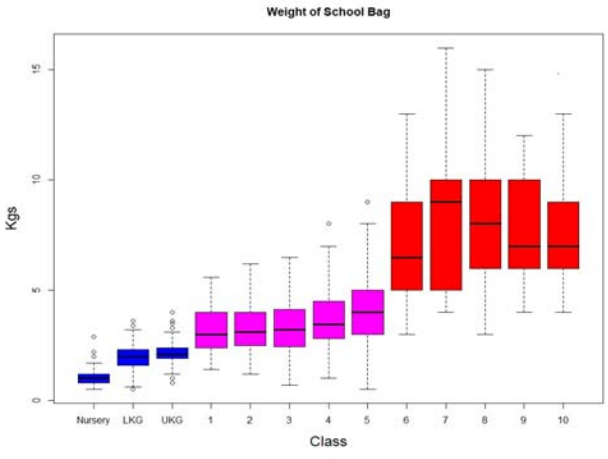

Fig. 1 *Boxplot showing weight of school bag (in kgs) for different grades.*

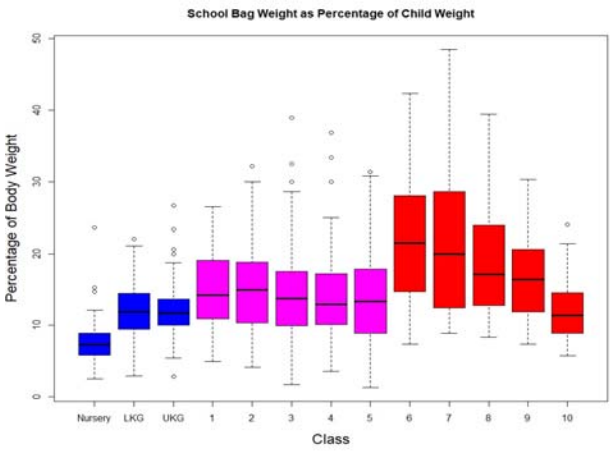

Fig. 2 *Boxplot showing weight of school bag (as percentage of body weight) in students of different grades.*

Table II Distribution of Children Carrying Heavy School Bags in Pune and Hyderabad (*N*=935)

Grade	*No.*			*Number (%) carrying heavy school bags**	
	M	*F*	*Total*	*Criterion I n=724*	*Criterion II n=722*
1	35	47	82	67 (81.7)	79 (96.3)
2	80	65	145	111 (76.6)	138 (95.2)
3	79	68	147	108 (73.5)	78 (53.1)
4	77	55	132	102 (77.3)	82 (62.1)
5	103	83	186	129 (69.4)	131 (70.4)
6	22	16	38	35 (92.1)	31 (81.6)
7	21	20	41	38 (92.7)	36 (87.8)
8	26	27	53	49 (92.5)	50 (94.3)
9	28	22	50	46 (92.0)	47 (94.0)
10	29	32	61	39 (63.9)	50 (82.0)

**Criterion I -Bag weight >10% of Bodyweight* [9] and *Criterion II – Bag weight more than guidelines issued by Government of India* [13].

DISCUSSION

In this study, we observed that weight of school bags was much higher than recommended weight-limit. Though pre-primary students should not carry schoolbags, in our study all pre-primary students were carrying school bags with books and note-books. We found that very high proportion of students in grades 1-10 were carrying heavy school bags, which should be a cause for concern. We also observed that problem of heavy weight of school bags increased from class 6 onwards. Similar proportion of children were classified as carrying heavy school bags by both the guidelines for school bag weights and there was moderately strong agreement between these two guidelines.

This is the first study to evaluate new guidelines issued by Government of India regarding schoolbag weight with previous guidelines and we included students from all classes of school in our studyHowever, major limitation of this study is that we have included selected schools from two cities only; hence, generalizability of study findings is limited.

Table III Agreement Between the Two Criteria for Classifying Schoolbag Weight as 'Heavy' or 'Normal'

		Criterion 1	
		Heavy (n=724)	*Normal (n=211)*
Criterion 2	Heavy (*n*=722)	647	75
	Normal (*n*=213)	77	136

Criterion I -Bag weight >10% of Bodyweight [9] and *Criterion 2 – Bag weight more than guidelines issued by Government of India* [13].

Our findings are similar to study by Oka *et al*. [10] in two urban areas which also found 76% of schoolchildren carrying heavy bags, though another study [12] in rural Maharashtra found less than 50% of students with heavy school bags. These variations indicate that there may be difference in number of books and notebooks being carried by students in urban and rural area schools. Few studies [5,6] had reported that boys carry heavier school bags as compared to girls; however, we did not find any significant difference in weight of school bags of boys and girls. Our finding of significant increase in school bag weight in higher classes of school is similar to previous studies [3,11].

Our findings highlight the need to implement Government guidelines regarding school bag weight in true spirit. Education department can make curriculum more practical problems oriented and less theory intensive, which will help in reducing the burden of books children have to carry . Schools can also make timetable for classes in such a way that students need to bring books related to few subjects only on a given day. Also, books and note books which students may not require at home, can be kept in school itself. Use of papers and files instead of notebooks can also help in reducing weight of school bags. Judicious use of computers and tablets in schools can also reduce the burden of books for students. Parents also need to ensure that their child carried minimum required books and notebooks to school, as many times children tend to take all books and notebooks to school.

Contributors: RKJ: study design, data collection and analysis, preparation of manuscript; SM: Data collection, analysis and manuscript preparation; AYR: study conceptualization, data collection and critical revision of manuscript; LP: study design, data collection and manuscript preparation; MK: Study conceptualization and design, data collection, interpretation and critical revision of manuscript. All authors approved the final version of manuscript and agree to be accountable for authenticity and integrity of the work.

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WHAT THIS STUDY ADDS?

- New guidelines regarding schoolbag weight based on class of child have moderately strong agreement with previous guidelines based on child's weight.

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RESEARCH PAPER

Epidemiological and Clinical Characteristics of COVID-19 in Indian Children in the Initial Phase of the Pandemic

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Objective: To assess the epidemiological and clinical characteristics of pediatric inpatients with COVID-19, early in the pandemic. **Methods**: Clinical and laboratory profile and outcomes were studied for children (aged 1 month - 18 years) presenting between 1 April, 2020 and 20 May, 2020 with positive nasopharyngeal swab for SARS-CoV-2 by RT-PCR. **Results:** 50 children (56% male) with median (IQR) age of 6 (2-12) years were included. Majority (56%) were from families belonging to Kuppuswamy upper lower socioeconomic class. 45 (90%) had positive household contact, and 33 (66%) had overcrowding at home. 29 (58%) children were asymptomatic while 20 (40%) had mild symptoms. Fever, cough, and sore throat were the most common symptoms. High C-reactive protein levels were seen in 15 (30%) children. There was no mortality. **Conclusion:** The disease burden appears high in lower socio-economic group with majority having a positive household contact. Milder disease pattern in the pediatric age group is reiterated.

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

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been in circulation for more than six months now [1]. Though there have been a growing number of studies focused on COVID-19, limited data is available on epidemiological features, clinical manifestations, and transmission patterns in children with COVID-19, more so from India. Early observations in a pandemic are pivotal in improving the understanding of the physiological patterns and varied clinical profiles, so as to improve early recognition and appropriate management. We, therefore, describe the clinical and epidemiological features of pediatric patients seen at a single tertiary-care institution.

METHODS

This was a cross-sectional study conducted in a dedicated pediatric COVID-19 center in Pune, Maharashtra between 1 April, 2020 and 20 May, 2020. Prior approval was taken from the institutional ethics committee. All children between one month and 18 years of age who tested positive by the RT- PCR technique for nasopharyngeal swab were included in the study – these also included asymptomatic children as per the management guidelines in force. Written informed consent was taken from the parents of all children and assent was taken from children who were greater than 9 years of age. Detailed information including demographic data, travel and contact history, living conditions and overcrowding, symptoms, and presence of co-morbid conditions were taken. The children were examined and categorized as per degree of severity based on standard criteria [2].

Baseline laboratory parameters (complete hemogram and C-reactive protein) were evaluated and repeated as required. Chest radiograph was done in all symptomatic children. On chest *X*-ray each lung was divided into three zones. Each zone was given a score of 1 if there was any opacity and 0 if there were none. Total score of 3 was considered as 50% involvement [3]. All children admitted were managed as per the hospital protocol. The children were monitored daily for changes in disease severity. Discharge from hospital was as per prescribed World Health Organization (WHO) guidelines which stated that asymptomatic children who tested negative for two nasopharyngeal swabs taken 24 hours apart after day 14 of illness were fit for discharge [4]. Overcrowding was defined based on persons per room criteria [5].

Statistical analyses: The data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 25.0. Spearman's Rho correlation coefficient was used to determine the correlation with disease severity. A *P* value <0.05 was considered significant.

RESULTS

A total of 178 children presented to us with suggestive features during the study duration, of which, 153 were negative and 25 were positive for SARS-CoV-2 by RT-PCR. Another 25 children with a positive RT-PCR were referred from other hospitals. Thus, a total of 50 children (56% males) with median (IQR) age of 6 (2-12) years were included. Majority (82%) of the cases hailed from containment zones in Pune. There was history of positive household contact in 45 (90%) children; with 42 having family members with mild illness and three with severe illness. Travel history to affected area was documented in only one child (***Table* I**).

More than half (58%) of the children were asymptomatic while 20 (40%) had mild symptoms. In symptomatic children, fever was the chief complaint in 17 (34%). None of the children had hypoxemia measured by pulse oximetry. Only two children had co-morbidities; one child had history of simple febrile seizures, and another had underlying type I diabetes mellitus and had presented with diabetic ketoacidosis. Immunization was complete in 32 (64%) of the children as per universal immunization program, and 49 (98%) children had a BCG scar.

The mean (SD) leucocyte count was 8864 (3727.2) $X10^9$/L (range, 3300-19300 $X10^9$/L). Leucopenia was seen in 3 (6%) children while leukocytosis was seen in 13 (26%) children. Lymphopenia, eosinopenia and thrombocytopenia were not seen in any child. Neutrophil-lymphocyte-ratio (NLR) (r=0.35, P=0.01) and lymphocyte-monocyte-ratio (LMR) (r=-0.31, P=0.03) showed a significant correlation with the severity of the illness, while platelet-lymphocyte ratio (PLR) (r=0.28, P=0.06) and CRP (r=0.05, P=0.73) did not show any correlation with severity of the disease.

Chest radiograph was done in 20 (95.2%) of 21 symptomatic children. It was found to be normal in 18 (85.7%), while two showed bilateral lower zone haziness (<50%). The disease category for all patients remained same all through the hospital stay and no mortality was seen.

DISCUSSION

Majority of children in our study were detected in the identified containment zones, most of them reporting exposure to a positive household contact. Majority of the children were either asymptomatic or had mild disease.

Most children were from lower socio-economic groups, a pattern also witnessed in other countries [6]. Though the disease was seen in all age groups, children less than five years of age accounted for nearly half the cases. This can be attributed to the inability of this age group to comprehend and follow social distancing norms and their frequent close contact with parents.

Pediatric observational studies published early in the spread across China reported similar clinical findings with fever being the most common symptom followed by cough and sore throat [7]. A recent meta-analysis has also shown that most of the patients have mild to moderate disease (96%) with only 1% of all the symptomatic pediatric cases being critically sick [8]. The reported mortality rate of COVID-19 in children is less than 1% [9]. Various hypotheses have been proposed for the lesser disease severity in children [10], though a definite answer is still awaited.

Table I Epidemiological and Clinical Characteristics of Children With SARS-CoV-2 Infection in Pune, 2020 (N=50)

Parameters	*No. (%)*
Male	28 (56)
Age	
1 mo to 1 y	9 (18)
>1 to 5 y	15 (30)
>5 to 10 y	12 (24)
>10 to 15 y	11 (22)
>15 to 18 y	3 (6)
Weight-for-age (3-97centile)	45 (90)
Overcrowding	33 (66)
Contact with patient of COVID- 19	45 (90)
*Socio-economic status**	
Upper lower	28 (56)
Lower middle	17 (54)
Upper middle	5 (10)
Severity of illness	
Asymptomatic	29 (58)
Mild	20 (40)
Moderate	1 (2)
Severe	0 (0)
Symptoms	
Fever	17 (34)
Cough	8 (16)
Sore throat	7 (14)
Myalgia	4 (8)
Diarrhea	2 (4)
Headache	2 (4)

**As per Kuppuswamy classification; One child each had rash and conjunctivitis.*

WHAT THIS STUDY ADDS?

- Majority of Indian children with SARS-CoV-2 infection had a mild course of disease during the initial stages of the pandemic.

Malnutrition has been deemed a risk factor in adult COVID-19 [11]. In children, malnutrition is known to foster infections; however, in this study, majority of the children were well-nourished as per weight-for-age criteria. The hematological profile of adults with COVID-19 has demonstrated leucopenia with associated neutrophilia, lymphopenia; eosinopenia and thrombocytopenia. Also, higher NLR, LMR and PLR have been associated with severe disease and used for prognostication [12]. Leucopenia, however, was seen in only 6% of our children and there was no evidence of lymphopenia, thrombocytopenia or eosinopenia. Increasing NLR in our study showed a moderate positive correlation coefficient while LMR showed a negative correlation. High CRP values have now become synonymous with severe COVID-19 infection among adults as seen in majority of the studies [13]. The value of CRP did not correlate with disease severity in our study. These discordant results may be due to the majority of our patients being asymptomatic or mildly symptomatic, or due to a different history of antigen exposure and immune response.

Repeat RT-PCR of nasopharyngeal swab was done on day 14 and 15 to check for infectivity status. All the children except one tested negative by RT-PCR on both the days. For the child who tested positive for one swab, a repeat swab was negative after three days, thus indicating that clearance of viral load may vary in different individuals. The degree of infectivity of these individuals after 14 days remains questionable as RT-PCR detects genetic fragments of the virus and cannot distinguish between dead or live virus [14]. In such scenarios, doing a viral culture may be the plausible method of detecting live virus and demonstrating continued infectivity. As performing a viral culture is difficult and requires advanced laboratory facilities, using GeneXpert platform with (cycle threshold) *Ct* values ≥ 24 may also be beneficial for predicting lack of infectivity [15].

The findings of our study are limited by the size of the cohort and may require further validation by a study with a larger sample size. Being a study in the initial phase of the pandemic with lockdown in place, it may not cover the entire spectrum of clinical presentations, severity and magnitude of SARS-CoV-2 in children from different geographical areas. We could also not collect data for calculation of body mass index (BMI) and Z-scores.

Table II Laboratory Investigations of Children With SARS-CoV-2 Infection in Pune, 2020 (*N*=50)

Parameter	*Value*
Absolute neutrophil count (x 10^9/L)	2480 (1995.5-3339)
Absolute lymphocyte count (x 10^9/L)	4071 (2912-5964)
Absolute monocyte count (x 10^9/L)	576 (402.5-744)
Absolute eosinophil count (x 10^9/L)	156 (68.5-437.5)
Leucopenia*	3 (6)
High C-reactive protein*	15 (30)

*All values in median (IQR) except *no.(%); leucopenia-leucocyte count <4000×10^9/L; High C-reactive protein- value >6 mg/dL.*

In conclusion, our study shows that there is a higher disease burden in lower-socioeconomic groups with majority of children having a positive household contact. A milder disease pattern is seen in majority of children with COVID-19.

Ethical approval: Institutional Ethics Committee of Bharati Vidyapeeth Medical College and Hospital; No. BVUDMC/IEC/1B, dated 10 April, 2020.
Contributors: VSR,BS,AP,MC: management of the patients; VSR,BS: collected the data, reviewed the literature and drafted the first version of the manuscript; BS,JSO,NM,SL: conceptualized the study, reviewed the literature, revised the manuscript and critically reviewed the manuscript. All authors contributed to manuscript preparation and approved the final version of the manuscript.
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RESEARCH PAPER

Maternal Occupational Tobacco Exposure and Newborn Umbilical Cord Serum Leptin Concentration

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Objective: To assess the effect of maternal occupational tobacco handling (*bidi* rolling) on cord serum leptin levels. **Methods:** We enrolled 64 neonates born to women who were *bidi*-rollers, and 64 small for gestational age (SGA) neonates and 57 term appropriate for gestational age (AGA) neonates born to mothers with no tobacco exposure. Cord blood leptin levels between the groups were compared. Adjusted mean difference in leptin was calculated using regression model. **Results:** Cord leptin showed moderate correlation with birthweight (r=0.16; P=0.027) across the groups. Mean (SD) cord serum leptin levels (ng/mL) of study group was 19.79 (13.32), in comparison to 21.4 (13.4) of SGA (P=0.497), and 27.70 (13.96) of term AGA (P=0.002). Maternal occupational tobacco exposure contributed to significant decrease in cord leptin (adjusted mean difference (95%CI): -4.5 ng/mL (-8.82, -0.19); P=0.041). **Conclusion:** Maternal occupational tobacco exposure causes significant reduction in fetal leptin levels.

Keywords: *Barker hypothesis, Bidi-rolling, Cotinine, Nicotine, Small for gestational age*.

Fetal growth is determined by the integrity of the utero-placental unit and fetal adipokine axis. The Barker theory on the role of leptin in initiating the fetal-programming cascade in small for gestational age (SGA) neonates has been of interest for decades [1]. Leptin secreted by the placenta and fetal adipose tissue is important in maintaining energy homeostasis [2]. Leptin has positive correlation with birth weight independent of other maternal factors [3,4]. Smoking during pregnancy causes placental insufficiency and fetal neuro-endocrine dysfunction resulting in SGA neonates [5]. Studies show normal [6-10] to decreased [3,4] cord serum leptin in term and preterm infants born to mothers who smoke, independent of birthweight.

Bidi-rolling is another form of tobacco exposure. Coastal Karnataka is home to *bidi* industry and women constitute the major labor pool involved in rolling and packaging [11]. In a cohort study, we established that occupational tobacco exposure through *bidi* rolling resulted in increased relative risk for SGA and a lower adjusted birthweight [12]. We hypothesized that similar to maternal smoking, tobacco handling during pregnancy may have an effect on the newborn umbilical cord serum leptin levels independent of birthweight.

METHODS

The study was conducted over two years (October, 2017-September, 2019) after institutional ethics committee clearance. The group of interest were 64 neonates born to *bidi* rollers by occupation (Group I). Controls were 64 SGA (Group II) and 57 term appropriate for gestational age (AGA) newborns (Group III) with no maternal occupational tobacco exposure or history of smoking. Group II and Group III newborns were included subsequent to enrolment of each Group I newborn. Infants born to mothers exposed to any other form of tobacco exposure like snuff, chewing, passive and active smoking were excluded in all. Multiple gestations, maternal pre-existing systemic illnesses, early preterm (<32 weeks), very low birthweight, and newborns with major congenital anomalies were also excluded.

Mothers were interviewed for *bidi* rolling practices. Co-variates included pre-pregnancy body mass index (BMI), weight gain, anemia, gestational hypertension (GH), prematurity and neonatal anthropometry. Standard definitions and measurements were used [13]. AGA was defined as birthweight between the 10th and 90th centile and SGA as less than 10th centile in the Lubchenco charts [14].

Cord serum leptin assay was done for all participants; maternal and cord serum cotinine assays were performed only in the study group. Both assays were done by commercial ELISA kits and expressed as ng/mL. A serum

cotinine value ≥2 ng/mL was considered indicative of nicotine absorption [15]. Sera were separated and stored at –80°C until analysis. The tests were repeated twice to minimize errors.

Primary outcome was to assess the effect of maternal tobacco handling on cord serum leptin independent of birthweight and being SGA. Secondary outcome was to look into specific maternal tobacco handling practices that influenced the leptin level.

Sample size calculated was 57 in each group using online software OpenEpiv3 for 90% confidence level, 20% allowable error, 1:2 ratio of study to control groups and mean difference in cord serum leptin of 1.04 ng/mL [4]. Informed written consents were obtained from the participating women.

Statistical analyses: These were performed using SPSS v20.0. For categorical data, frequencies (*n*) and percentages (%) were calculated and Chi square or Fisher exact was applied for significance. For continuous data, either mean (SD) or median (IQR) was calculated based on normality distribution. Intergroup comparisons were performed using independent sample *t* test or ANOVA. Correlation was done by Pearson correlation or Spearman correlation test. Multiple linear regression model was used to determine adjusted mean difference (aMD) of cord leptin for maternal tobacco exposure. A *P* value less than 0.05 was considered significant.

RESULTS

Of the 64 mothers with occupational tobacco exposure, 16 (25%) were SGA. Other maternal and newborn characteristics that influenced the birth weight and/or the cord serum leptin levels are given in ***Table* I**. Cord serum leptin showed moderate correlation with birthweight (r=0.16; P=0.027) across the groups, with no difference between females (n=92) 23.25 (12.78) ng/mL and males (n=93) 22.10 (14.90) ng/mL (P=0.58).

As compared to group III (term AGA with no maternal tobacco exposure), cord serum leptin levels were significantly lower in group I (maternal tobacco exposure) [Mean difference (95% CI)= –7.91 (–12.92,–2.90); P=0.002] and group II (SGA with no maternal tobacco exposure) [MD (95% CI) = –6.30 (–11.33, –1.28); P=0.014]; even term AGA newborns of group I had significantly lower levels than term AGA newborns of group III [MD (95% CI) = –8.5 (–13.89, –3.11); P=0.002]. No significant difference was found between the levels in group I and group II (P=0.49).

Mothers in the study group started *bidi* rolling at median (IQR) age of 20 (18,23) years. Their median (IQR) tobacco exposure was 6.75 (4,10.75) years. They rolled a median (IQR) of 500 (500,600) *bidis* a day and majority (84.4%) stopped rolling by median (IQR) 22 (20.5,29.5) weeks of gestation. Evidence of nicotine absorption was found in 24 (37.5%) of maternal and 22 (34.4%) of cord blood. Median (IQR) maternal cotinine was 3.35 (0,15.15) ng/mL; and median (IQR) cord serum cotinine 4.0 (0, 17.25) ng/mL (range 0-30.45). Cord leptin had significant negative correlation with longer years of occupational tobacco handling (r = –0.34; P=0.001) and longer tobacco exposure (gestational week) during pregnancy (r = –0.33; P=0.007). There was no correlation between cord leptin, maternal cotinine and cord cotinine.

Maternal occupational tobacco exposure contributed to significant decrease in cord leptin by 4.50 ng/mL [95%CI: –8.82, –0.19; P=0.041] when adjusted for maternal gestational hypertension, prematurity and birthweight. *Bidi* rolling practices associated with decrease in cord leptin value included longer years of occupational exposure [aMD (95%CI): –1.31 (–2.22, –0.41); P=0.005] and longer weeks of exposure into pregnancy [aMD (95%CI): –0.72 (–1.35, –0.09); P=0.025] when adjusted for number of *bidis* rolled in a day, quantity of tobacco stored at home and engagement of other family members in the same occupation.

DISCUSSION

In our study, the cord serum leptin levels of the newborns born to mothers who were *bidi* rollers were significantly

Table I Comparison of Maternal and Neonatal Variables Among the Study Groups

Variable	*Group I (n=64)*	*Group II (n=64)*	*Group III (n=57)*
Maternal			
Age, y	28.3 (4.03)	27.3 (4.5)	26.9 (4.01)
BMI, kg/m^2	21.7 (3.6)	21.8 (2.8)	22.7 (1.9)
Weight gain, kg$^{\$}$	9.96 (2.71)	8.23 (1.80)	9.5 (2.30)
Hemoglobin, g/dL	11.6 (1.2)	11.6 (1.2)	11.9 (0.9)
Newborn			
Gestational age, wk	38.2 (1.3)	37.9 (1.2)	38.4 (0.9)
Birthweight, g*	2829.4 (374.3)	2355.9 (182.9)	3213.9 (300.2)
Length, cm*	48.6 (1.88)	47.2 (1.44)	49.3 (1.99)
HC,cm*	33.7 (1.13)	32.5 (1.06)	33.8 (0.8)
Leptin, ng/mL$^{\wedge\#}$	19.79 (13.31)	21.4 (13.40)	27.7 (13.96)

All values in mean (SD); Group I: Maternal Tobacco Exposure, Group II: Small for gestational age without tobacco exposure, Group III: Term Appropriate for gestational age without tobacco exposure; HC-head circumference; BMI-body mass index; $^{\$}$Pregnancy weight gain; $^{\#}P=0.005$. $^{*}P<0.001$;^cord serum leptin.

WHAT THIS STUDY ADDS?

- *Bidi* rolling during pregnancy reduces the cord blood leptin levels independent of birthweight and being born small for gestational age.

lower when compared to those born to the reference group. Mantzoros, *et al*. [4] documented that the decrease in mean cord leptin in pregnant smokers was more pronounced in preterm neonates. A significant negative correlation between cord leptin and number of cigarettes smoked has also been reported [4,8]; though, Kayemba-Kay, *et al.* [3] showed a positive correlation. Fang, *et al.* [7] noted that the median cord leptin concentration in smokers was less than that of the non-smokers.

Nicotine influences cord leptin through decreased secretion due to uteroplacental insufficiency, decreased birthweight and catecholamine-mediated decreased fetal adiposity [4]. In the present study, longer the years of tobacco exposure and longer the mother continued with her occupation into pregnancy, lower was the cord leptin. The lower age in most women in this study substantiates that they begin this occupation in late adolescence, unwittingly helping their mothers [11]. The cord blood leptin level of the tobacco exposed newborns was comparable to the unexposed SGA babies. This indicated that these newborns with *in utero* tobacco exposure had an adiposity similar to that of an SGA newborn in spite of being born AGA. It also suggested a common pathophysiology compromising the circulation of the growing fetus in both. Maternal malnutrition may be an additional factor common to both the groups [2].

This was a single centre study with a small sample size. Nicotine absorption was demonstrable only in about one-third, probably related to altered metabolism kinetics during pregnancy [12,15]. There is wide variation in reported cord leptin values with several maternal, labour and newborn factors influencing the same [7,16]. We included two control population of newborns and statistically adjusted various covariates that could influence cord leptin levels. Future considerations include a longitudinal study with other fetal hormones in newborns with maternal occupational tobacco exposure.

In conclusion, maternal occupational exposure to tobacco *via bidi* rolling decreases cord serum leptin independent of birthweight and being SGA. Maternal *bidi* rolling is a demographic risk factor for altered neuroendocrine function of the fetus.

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RESEARCH PAPER

Role of Flexible Bronchoscopy in Ventilator-Dependent Neonates

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Objective: To assess the usefulness and safety of flexible bronchoscopy in ventilated neonates with extubation failure. **Method:** This was a prospective observational study. Flexible bronchoscopy was done in eligible patients with failure of extubation form invasive ventilation. The main outcome measure was to find the presence of any anatomic or dynamic abnormalities of the airways of these patients and the organism profile of bronchoalveolar lavage (BAL) fluid. **Results:** Forty-eight babies (68.8% preterm) were enrolled in the study. The most common finding on bronchoscopy was airway edema seen in 13 (27%) patients. BAL culture was positive in 29 (74%) patients. Overall treatment was modified in 35 (73%) patients based on bronchoscopy findings/BAL culture. Majority of infants (83.3%) tolerated the procedure very well. **Conclusion:** Flexible bronchoscopy provides useful information in the management of newborn babies with extubation failure.

Keywords: *Bronchoalveolar lavage, Extubation failure, Management, Preterm.*

Prolonged ventilation may lead to multiple adverse effects, including subglottic stenosis, tracheobronchomalacia, nosocomial infection, bronchopulmonary dysplasia (BPD) and neurocognitive impairment [1-3]. Up to 30% of mechanically ventilated infants require a prolonged period of invasive mechanical ventilation and experience repeated extubation failures. Kurachek, *et al*. [5], in their study on pediatric patients, reported that upper airway obstruction like subglottic stenosis, laryngo-malacia, tracheomalacia are the leading causes of extubation failure [EF]. These observations demand prompt and precise diagnosis of these conditions. Similarly, ventilator-associated pneumonia (VAP) also increases the duration of mechanical ventilation.

Flexible bronchoscopy is a well-established tool for the evaluation of airway anomalies and infections in neonatal ICU, with excellent safety profile [6]. Moreover, therapeutic interventions with flexible bronchoscopy like mucus plug removal, can efficiently relieve airway problems and can decrease the duration of ventilation [7,8]. There is a paucity of literature regarding the role of flexible bronchoscopy in prolonged mechanical ventilation/failure of extubation in neonates. We studied the utility and safety of this modality in neonates on prolonged ventilation/extubation failure.

METHODS

We provide data on neonatal flexible bronchoscopy from May, 2014 to April, 2018 at a tertiary-care public hospital of India. The study participants were neonates with a gestational age of more than 32 weeks and failure of extubation (defined by a need for re-intubation within 48 hours of extubation). Eligibility for and benefit of bronchoscopy were determined by the attending neonatologists. Written informed consent was taken from parents/legal guardians before undertaking the procedure. The study was approved by the institutional ethical committee.

Flexible bronchoscopy was done in the neonatal intensive care unit (NICU) or bronchoscopy suite, which is in close proximity to neonatal ICU. The bronchoscopy team comprised of a bronchoscopist, bronchoscopy technologist, neonatologist, pediatric resident doctor and a nurse. Stable ventilated neonates were extubated for the duration of the procedure in order to check for any upper airway anatomic and dynamic abnormality. Pre-oxygenation to ensure oxygen saturation remained above 90% was carried out. The majority of bronchoscopies were performed trans-nasally, the trans-oral route was used in four patients (cleft palate in two patients, choanal stenosis in one patient and epistaxis in one patient). In 10 patients, bronchoscopy was done *via* an endotracheal tube with a tube size of 3.5 mm, because of high ventilator settings. Extubation was also attempted at some point in time in this sub-group. Upper airway could not be assessed in this subgroup. This subgroup consisted of six-term babies and four late preterm babies. The authors

used Olympus BF-XP160F (Olympus Corporation, Japan) scope with an outer diameter of 2.8 mm and a channel size of 1.2 mm. Electrocardiogram and pulse were recorded continuously during the procedure and non-invasive blood pressure was monitored every 3-5 minutes. Supplemental oxygen was given *via* nasal cannula. Desaturation ≤90% was managed by an increase in oxygen flow rate and the use of an oxygen mask. 2% lidocaine gel was used locally to anesthetize nasal mucosa. 1 mL aliquots of 2% lidocaine in 1:1 dilution with normal saline were instilled by the 'spray-as-you-go' technique. Additional doses were given, if required, to minimize patient discomfort. Bronchoalveolar lavage (BAL) was performed with the use of normal saline warmed to body temperature with a volume of 3 mL/kg administered in three divided doses. The bronchoscope was advanced until wedged in a desired subsegmental bronchus; this technique ensured the collection of a sample from the terminal airways with negligible contamination from the upper airways. It was sent for gram staining, lipid-laden macrophages, bacterial culture, and fungal culture. Bronchoscopy findings were noted if present. Tracheobronchial abnormalities recorded included subglottic stenosis, tracheomalacia (tracheomalacia or bronchomalacia was diagnosed when there was a 50% reduction in the luminal diameter during expiration), tracheal stenosis, complete tracheal rings, tracheoesophageal fistulas, vascular rings, bronchomalacia, hemangiomas, or mucus plugging. Therapeutic procedures carried out were also noted. BAL culture was done by using the BacT/Alert automatic culture system. Culture results including organism profile and culture sensitivity were recorded.

A standardized data extraction form was used to obtain the demographic and clinical data including patient age, sex, weight, co-morbidities, procedure indication, total midazolam dose, pulse rate, baseline and lowest blood pressure, oxygen saturation, adverse events if any during and/or within one hour of the procedure.

Statistical analysis: It was performed using SPSS 20.0. The normality of the data was checked by using the Shapiro- Wilk test. Categorical variables are presented as percentages and continuous data as mean (SD)/median (IQR).

RESULTS

During the study period, 998 newborn babies received mechanical ventilation for different indications; 48 of these (68.8% preterm) underwent flexible bronchoscopy with or without BAL. The mean (SD) gestational age and birthweight of the study population was 36.4 (2.2) weeks and 2.5 (0.67) kg, and the median (IQR) chronological age at which procedure was done was 15 (9.25,20.75) days. Three patients were classified as chronic lung disease at the time of inclusion in the study. Ventilator-associated pneumonia (VAP) was diagnosed in 24 (50%) ventilator-dependent patients prior to bronchoscopy. Persistent lobar atelectasis was seen in 12 ventilator-dependent patients and bronchoscopy was done with diagnostic and therapeutic intent (removal of possible mucus plug). Respiratory distress syndrome (RDS) was the most common reason for mechanical ventilation [20], followed by post-surgery [7] and meconium aspiration syndrome [6].

***Table* I** shows bronchoscopy findings and organism profile of bronchoalveolar lavage culture. Bronchoscopy evaluations revealed airway abnormalities in 38 (79%) patients – more than one abnormality was found in 24 (50%). The most common finding was airway edema seen in 13 (27%) patients. Laryngomalacia/ tracheomalacia or bronchomalacia was seen in 25 (52%) of patients. Bronchoalveolar lavage was done in 39 patients, with adequate BAL sample collected in all. BAL culture was positive in 29 (74%) patients; the most common organism isolated was *Acinetobacter baumannii*.

Overall treatment was modified in 35 (73%) patients based on bronchoscopy findings/BAL culture, including tracheostomy in five patients (3, subglottic stenosis; 1, subglottic hemangioma; 1, severe tracheomalacia). Laser excision of subglottic stenosis through rigid bronchoscopy was done in two patients, successful

Table I Bronchoscopy and Bronchoalveolar Lavage Findings in Ventilator-Dependent Neonates (*N*=48)

*Findings**	*No. (%)*
Airway edema	13 (27)
Tracheomalacia	10 (20.8)
Laryngomalacia	8 (16.6)
Mucus plug	8 (16.6)
Bronchomalacia	7 (14.5)
Subglottic stenosis	5 (10.4)
BAL fluid culture	
A. baumannii	11 (22.9)
K. pneumoniae	10 (20.8)
P. aeruginosa	4 (8.3)
S. aureus	2 (4.1)
E. coli	1 (2.0)
C. albicans	1 (2.0)

**Subglottic hemangioma, H-type fistula, right bronchial agenesis, vascular ring, and choanal stenosis in one neonate each; BAL bronchoalveolar fluid.*

WHAT THIS STUDY ADDS?

- Flexible bronchoscopy is a useful intervention in select neonates with extubation failure.

mucus plug removal for atelectasis in five patients with mucus plug (post-bronchoscopy *X*-ray (*n*=3) showed persistent collapse of affected lobe), placement of oral airway for choanal stenosis in one patient, surgical procedure for H type fistula in one patient, and modification of antibiotics based on BAL culture in 21 patients. Overall 31 (64%) patients were successfully extubated within a week of the bronchoscopy procedure, and 39 (81.5%) patients could be extubated within 14 days of the procedure.

Procedural complications like transient hypoxia (*n*=4), bradycardia (*n*=2), transient apnea (*n*=1) and epistaxis (*n*=1) were seen in 8 (16.7%) patients.

DISCUSSION

We found flexible bronchoscopy to be a useful diagnostic and therapeutic tool in babies on prolonged mechanical ventilation. Bronchoscopy evaluations revealed airway abnormalities in a significant number of our patients. More than half of the subjects (25/48) had laryngomalacia, tracheomalacia, or bronchomalacia, which was likely due to bronchopulmonary dysplasia and/or chronic mechanical ventilation, which are known to cause tracheobronchomalacia [9]. Flexible broncho-scopy helped us to modify treatment in 73% of ventilator-dependent neonates based on the bronchoscopic/BAL culture findings.

A 7-year retrospective study on 599 neonates who underwent flexible bronchoscopy reported its importance as a diagnostic and therapeutic tool in the management of neonatal lung disease, Vijayasekaran, *et al*. [10] reported neonatal bronchoscopy safe in experienced hands and invaluable tools in the management of a neonate with various respiratory disorders. Others have also provided similar conclusions [6]. The most important factor responsible for ventilator dependence is ventilator-associated pneumonia [11]. Chest *X*-ray has poor sensitivity to diagnose VAP because the presence of pulmonary infiltrates on chest *X*-ray is one of the main criteria for diagnosing VAP, which may also be caused by other conditions like pulmonary edema, atelectasis or pulmonary hemorrhage [11]. Similarly, culture of the tracheal aspirate has a high chance of contamination with colonizing microorganisms [12]. BAL microbiology is a very good marker for the diagnosis of lung infection [13]. In a study by Wang, *et al.* [14] on risk factors of extubation failure in ELBW infants, atelectasis was also found as one of the causes of extubation failure. Extubation failure due to airway complications involving glottic, subglottic, or tracheobronchial pathology is well reported in the literature [15].

The study has some limitations. This is a review of records with no control group, and no standardization regarding the definition of prolonged mechanical ventilation; the decision for bronchoscopy was based on the clinical experience of the attending neonatologist. Secondly, the sample size is small and this was a single-center study.

To conclude, flexible bronchoscopy can be incorporated as a diagnostic and therapeutic modality in newborn babies with extubation failure, and we can get useful information about the cause of extubation failure.

Ethics clearance: Departmental Review Board, SIMS; No. SIMS/152/12/279; dated June 2, 2016.
Contributors: JIB, BAC: conceived the idea of the study and writing the manuscript; SZ: was involved in management and data collection; QIA: supervised implementation of the study; AAA: contributed to writing of the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Validation of the Testicular Workup for Ischemia and Suspected Torsion (TWIST) Score in the Diagnosis of Testicular Torsion in Children With Acute Scrotum

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Objective: To validate the Testicular Workup for Ischemia and Suspected Torsion (TWIST) score for the evaluation of children presenting with acute scrotum. **Methods**: This prospective study calculated TWIST score in patients of acute scrotum admitted to a pediatric surgery unit. The scoring system consisted of testicular swelling (2 points), hard testicle (2), absent cremasteric reflex (1), nausea/vomiting (1) and high-riding testis (1). All the patients were examined by a pediatric surgeon. **Results**: Among 96 children with acute scrotum, 68 (70.8%) patients had testicular torsion. In the testicular torsion group, the mean (SD) TWIST score was 5.7 (1.2) and in no torsion group, it was 1.46 (0.67). In the testicular torsion group, the number of patients with low, intermediate, and high risk was 0, 13, and 55, respectively and in without testicular torsion these were 21, 7, and 0, respectively. **Conclusions**: TWIST score has high predictive value for testicular torsion, and can be used for clinical diagnosis of testicular torsion.

Keywords: *Color doppler, Management, Orchidectomy, Spermatic cord torsion.*

Testicular torsion is the most common pediatric urological emergency, affecting 3.8 per 100,000 males younger than 18 years annually [1]. Around 10-5% of these are children with acute scrotal disease [2], and results in a 42% orchiectomy rate for boys undergoing testicular torsion surgery. Testicular salvage requires timely detection and treatment, and torsion should be excluded in all patients with acute scrotum. Doppler ultrasound (DUS) has been considered as the primary imaging method for the assessment of testicular torsion with high sensitivity and specificity [3]. However, for those with testicular torsion, the use of DUS can prolong the time in testicular ischemia and delay surgery. The availability of radiological imaging and the expertise of its operators and evaluators are also limited in many settings. Barbosa, *et al*. [4] developed a Testicular Workup for Ischemia and Suspected Torsion (TWIST) score based on clinical parameters [4]. Typically, there is a 4-8 hour window before permanent ischemic damage to testes occurs. Treatment delays may be associated with reduced fertility or may require orchiectomy. The purpose of this study is to study the utility of the TWIST scoring system for testicular torsion in boys presenting to the emergency room (ER) with an acute scrotum.

METHODS

This observational study was carried over a period of two years (May, 2017 to April, 2019) in a tertiary referral centre. Institutional review board and ethical committee approval were obtained. Participants included were males aged 0 days to 18 years, presenting to ER with chief complaint of testicular pain and/or swelling. Patients were excluded if their pain was due to trauma, if symptoms were present for greater than one week, there was a history of testicular disease or surgery, and if a diagnosis of testicular torsion had already been confirmed or excluded.

The TWIST score is based on the sum (ranging from 0 to 7) of the following findings: testicular swelling (2 points), hard testicle (2 points), absent cremasteric reflex (1 point), nausea or vomiting (1 point), and high riding testicle (1 point) [4]. The risk stratifying scores for those at low risk for testicular torsion is 0 to 2 points, intermediate risk was 3 to 4 points, and high risk for testicular torsion is 5 to 7 points [4]. The primary conclusion was a diagnosis of testicular torsion by TWIST score, confirmed by surgical exploration as the final diagnosis. Testicular loss was defined as either surgical orchiectomy or determination of significant atrophy at 6 months post-operative ultrasound. A more than 50% difference in volume compared with the contralateral testis or absence of blood flow on Doppler was considered to represent testicular loss [5].

The TWIST score was performed by a single pediatric

surgeon in all patients, and surgery was carried out by the same surgeon. The same sonologist did the DUS evaluation in all patients. Indication of surgery was impaired blood flow in DUS, and inability to rule out testicular torsion in the presence of intermediate TWIST score. All patients for whom surgery was indicated were immediately transferred to the operating room for scrotal exploration. All patients who underwent surgical exploration had confirmed diagnoses of testicular torsion.

RESULTS

A cohort of 96 males with acute scrotum was studied. The mean age of the patients in the study group was 10.1 (3.8) years (range 1 month-16 year). The TWIST score component and other clinical features are shown in ***Table* I**.

In the testicular torsion group, the mean TWIST score was 5.7 (1.2) (range 3-7), and in no torsion group, it was 1.46 (0.67) (range 0-4). In testicular torsion group, the number of patients with low, intermediate, and high risk was 0, 13, and 55, respectively, while the number of patients without testicular torsion was 21, 7, and 0 in low, intermediate, and high-risk groups, respectively (***Table* II**). Doppler ultrasound was obtained in all study subjects, which diagnosed testicular torsion in 65 patients. Three patients had equivocal ultrasound, showing no definite torsion with a lack of vascular flow, and neither increased blood flow to the epididymis. These patients were surgically proven to have testicular torsion on exploration. Thus, 68 (70.8%) patients were found to have testicular torsion. The 6-month follow-up DUS showed 46 equal sized and normal blood flow testes on both sides, with a salvage rate of 67.6% (***Fig.* 1**).

Table I Clinical Features of Children With Acute Scrotum (*N*=96)

Characteristic	*Torsion (n=68)*	*Non torsion (n=28)*
Testicular pain	65 (95.6)	26 (92.9)
Nausea and vomiting	65 (95.6)	26 (92.9)
Abdominal pain	21 (30.9)	9 (32.2)
Tenderness	29 (42.7)	7 (25.0)
Testicular swelling	27 (39.7)	7 (25.0)
High riding testes	55 (80.9)	0
Absent cremasteric reflex	65 (95.6)	0
Hard testicle	41 (60.3)	6 (21.4)
Erythema	16 (23.5)	1 (3.6)

*All values in no. (%); *P<0.01, #P<0.01, ‡P=0.02.*

Table II Testicular Workup for Ischemia and Suspected Torsion (TWIST) Score in Children With Acute Scrotum (*N*=96)

Risk group	*Twist score*	*Testicular torsion (n=68)*	*No testicular torsion (n=28)*
Low	0-2	0	21 (75)
Intermediate	3-4	13 (19.2)	7 (25)
High	5-7	55 (80.8)	0

All values in no. (%).

DISCUSSION

This current study validates the TWIST score, which risk stratifies patients presenting with an acute scrotum for testicular torsion. There were no patients with torsion in the low-risk category (0-2 twist score), and 100% of patients in the high-risk category (5-7 twist score) had torsion. In this analysis, the TWIST score was found to be an excellent diagnostic tool in the diagnosis of testicular torsion, which is comparable to other studies [4,6,7]. In this study, all low-risk and high-risk patients (73.9 %) could have avoided the use of an ultrasound scan.

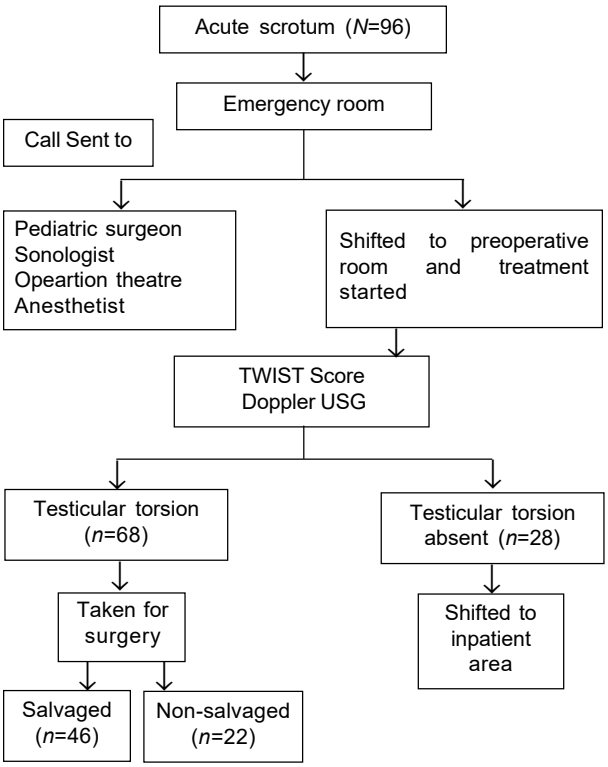

Fig. 1 *Flowchart of patients with acute scrotum enrolled in the study.*

WHAT THIS STUDY ADDS?

- TWIST score categorizes the patient with acute scrotum, and may be useful in situations where ultrasound facility is not available.

The original TWIST study included no patients with torsion (0/51) in the low-risk category and all 22 patients with torsion in the high-risk category [4]. Barbosa, *et al.* [4] found that only 20% of patients are in the intermediate-risk group and recommended that DUS is required only in this group. The testicular torsion scoring systems are now being tested in non-urologic medical providers [8] and reducing time delays, costs and reliance on DUS [9]. The TWIST score is intended to categorize patients requiring an ultrasound. This score is not designed to substitute doppler sonography [4]. Sheth, *et al*. [6] assessed TWIST score in non-pediatric surgery-trained emergency room caregivers diagnosing testicular torsion and found it equally effective. The absence of cremasteric reflex and high riding rotated testes are sufficiently reliable for the diagnosis of testicular torsion, as also reported by other authors [10,11].

In this analysis, the main limitations were the small number of cases observed. The TWIST score was evaluated by a single examiner. At least two examiners should have perform the physical examination, thus providing information on inter-observer variation.

In conclusion, this study has demonstrated that the TWIST score is reliable to identify testicular torsion in patients with acute scrotum. Since this study was conducted in one hospital, studies in multiple settings will support the internal validity of this method.

Ethics clearance: Institutional Ethics Committee; No. 17/ASH/Study 03/2017, dated January 01, 2017.
Contributors: PP: developed the concept and designed the study, collected and analyzed the data, drafted the manuscript.
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Hyperinflammatory Syndrome in Children Associated With COVID-19: Need for Awareness

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The pandemic of COVID-19 initially appeared to cause only a mild illness in children. However, it is now apparent that a small percentage of children can develop a hyperinflammatory syndrome labeled as Pediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS). Features of this newly recognized condition may include persistent fever, evidence of inflammation, and single or multi-organ dysfunction in the absence of other known infections. Some of these children may share features of Kawasaki disease, toxic shock syndrome or cytokine storm syndrome. They can deteriorate rapidly and may need intensive care support as well. The PCR test is more often negative; although, most of the children have antibodies to SARS-CoV-2. Although the pathogenesis is not clearly known, immune-mediated injury has been implicated. We herein provide current information on this condition, in order to raise awareness amongst pediatricians.

Keywords: *Kawasaki disease, Macrophage activation syndrome, Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19, Pediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS).*

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Children younger than 18 years have been reported to constitute only a small proportion of cases of coronavirus disease (COVID-19). Whilst initial reports described an asymptomatic or milder illness in children [1,2], several countries have now noticed a new hyper-inflammatory syndrome affecting a small percentage of children [3]. This condition appears to share features with pediatric inflammatory diseases such as Kawasaki disease (KD) and Toxic shock syndrome (TSS) [4].

The first case of classic KD with concurrent COVID-19 in a child was reported from United States [5]. Subsequently, health authorities in the United Kingdom (UK) issued an alert describing a serious illness requiring intensive care in children. A number of other regions significantly affected by COVID-19 such as New York, Italy and France also reported increasing numbers of children with a similar inflammatory syndrome [3]; the first such case was reported from India only recently [6]. The Royal College of Pediatrics and Child Health (RCPCH) published a guidance to raise awareness amongst clinicians for this newly recognized condition called Pediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) [4]. A similar clinical entity was defined as the Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 by the World Health Organization (WHO) [7] and Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 [8] by Centers for Disease Control and prevention (CDC) (***Box* I**). Although little is known about the epidemiology, cases of PIMS-TS seem to appear few weeks after the COVID-19 peak in the population. As of 13 May, 2020, there were more than 300 cases of suspected PIMS-TS in Europe and North America [3]. With India lagging behind the peak curve, the authors hypothesize that we may also see a spurt in this illness in the coming days.

CLINICAL FEATURES

One of the initial reports [9] described a cluster of eight children with hyperinflammatory shock. Mean age at presentation was 8.8 years with a predilection for boys of Afro-Caribbean descent and seven of these were above the 75th centile for weight. Mean duration of fever at presentation was 4.3 days. Mucocutaneous changes (rash, conjunctivitis, peripheral edema) with significant gastrointestinal symptoms were noted in all of them. All 8 patients developed severe refractory shock with a mean ferritin level of 1086.6 ng/mL. One child required extra-

Box I Proposed Case Definitions for the Hyperinflammatory Syndrome Associated With COVID-19 [4,7,8]

World Health Organization

Children and adolescents 0-19 years of age with fever >3 days

AND two of the following:

(*a*) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)

(*b*) Hypotension or shock

(*c*) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT proBNP)

(*d*) Evidence of coagulopathy (by PT, PTT, elevated D-dimer)

(*e*) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)

AND

Elevated markers of inflammation such as ESR, CRP or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Royal College of Pediatrics and Child Health

A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction.

This may include children fulfilling full or partial criteria for Kawasaki disease.

Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.

SARS-CoV-2 PCR testing may be positive or negative.

Centers for Disease Control

An individual aged <21 years presenting with fever, laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)

(*i*) Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.

(*ii*) Laboratory evidence (but not limited to) of one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin.

AND

No alternative plausible diagnoses

AND

Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; Or COVID-19 exposure within 4 weeks prior to the onset of symptoms.

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase.

corporeal membrane oxygenation (ECMO) for refractory shock but eventually died after 6 days of hospitalization. None of the children had respiratory symptoms and only two tested positive for SARS-CoV-2 PCR, while all of them tested positive for the antibody [9]. Ten children presenting with features of classic or incomplete KD were reported from Italy [10] with mean age and duration of fever of 7.5 years and 6 days, respectively. Apart from gastrointestinal and mucocutaneous symptoms, meningeal signs were also reported in this subset. Half of them developed KD shock syndrome (KDSS) with peak ferritin levels of 1176 ng/mL. In comparison to children

with KD in pre-pandemic times the current phenotype included older children with more severe disease, significant cardiac involvement and macrophage activation syndrome (MAS) [10]. Again, only two tested positive for SARS-CoV-2 PCR, but eight tested positive for the antibody. In both the groups, inflammatory markers (C-reactive protein, procalcitonin, ferritin, triglycerides, and D-dimer) were significantly elevated. An abnormal echocardiogram with myocardial dysfunction and coronary artery abnormalities were observed in 60% children, and two also had coronary aneurysms [10].

More recently, a French study [11] described a new syndrome complex of acute heart failure and hyperinflammation in children. Initial presentation predominantly included fever (100%) and gastro-intestinal symptoms (80%) such as abdominal pain, vomiting and diarrhea. Although mucocutaneous changes suggestive of KD were noted, none of them met the criteria for classic KD. Echocardiography was significant for left ventricular dysfunction with a low ejection fraction. Inflammatory markers (CRP, D-dimer) were raised in all. Coronary artery dilatation was seen in 17%, but as opposed to classic KD, none of them developed coronary aneurysms. Complete recovery was seen in 71% of children, suggesting that myocardial edema rather than necrosis was likely responsible for heart failure. This is in contrast to the adult population, where myocardial necrosis has been incriminated in the pathogenesis [11].

The importance of suspecting PIMS-TS in febrile adolescent children with gastrointestinal symptoms during this pandemic cannot be overemphasized. This unusual presentation was also reinforced in a case series of eight children from UK, initially suspected to have appendicitis [12]. Although they had very high CRP levels, abdominal imaging demonstrated non-specific features (*e.g.* lymphadenopathy or ileitis) rather than appendicitis. Subsequently, half of these children required intensive care admission for hemodynamic instability. Apart from peripheral or periorbital edema, none of them had features to suggest classic KD and five tested positive for SARS-CoV-2 [12].

In a larger case series of 58 children (median age 9 years) from UK [13], all presented with fever and combinations of abdominal pain (53%), diarrhea (52%) or rash (52%). Three clinical patterns were identified in this cohort- fever with raised inflammatory markers (39.6%) without features of KD, TSS or organ failure; shock (50%) with evidence of left ventricular dysfunction (62%); and those fulfilling criteria for KD. Coronary artery aneurysms were noted across all three groups (8/58). Compared to other inflammatory disorders, those with PIMS-TS were older and had lower hemoglobin levels and lymphocyte counts, and higher white blood cell count, neutrophil count and CRP levels (***Table* I**) [13].

It appears that these children may develop single or multi-organ dysfunction with persistent fever and features of inflammation (neutrophilia, elevated CRP and lymphopenia). This may progress on to shock. In patients who turn out to be SARS-CoV-2 PCR negative, other microbial causes need to be actively considered and excluded [4]. In addition to KD and TSS, secondary hemophagocytic lymphohistiocytosis (HLH) in association with common tropical infections should also be considered in similar clinical settings. Based on available data, we speculate that there could be three distinct phenotypes of hyperinflammation in children (***Table* II**).

PATHOGENESIS

Approximately two-thirds of patients with PIMS-TS are COVID-19 PCR negative, a proportion of these being serologically positive, suggesting an immune-mediated

Table I Comparison of PIMS-TS With Classic KD, KDSS and TSS [13]

Features	*PIMS-TS (n=58)*	*KD (n=1132)*	*KDSS (n=45)*	*TSS (n=46)*
Age at onset, y	9.0 (5.7-14)	2.7 (1.4-4.7)	3.8 (0.2-18)	7.38 (2.4-15.4)
CRP, mg/L	229 (156-338)	67 (40-150)	193 (83-237)	201 (122-317)
Hemoglobin, g/L	92 (83-103)	111 (105-119)	107 (98-115)	114 (98-130)
Lymphocytes, $\times 10^9$/L	0.8 (0.5-1.5)	2.8 (1.5-4.4)	1.6 (1-2.5)	0.63 (0.41-1.13)
Ferritin, µg/L	610 (359-1280)	200 (143-243)	301 (228-337)	–
NT-Pro-BNP, pg/mL	788 (174-10548)	41 (12-102)	396 (57-1520)	–
Troponin, ng/L	45 (8-294)	10 (10-20)	10 (10-30)	–
D-dimer, ng/mL	3578 (2085-8235)	1650 (970-2660)	2580 (1460-2990)	

Data are median (IQR); PIMS-TS: pediatric inflammatory multisystem syndrome-temporally related to SARS-CoV-2, KD: Kawasaki disease, KDSS: Kawasaki disease shock syndrome, TSS: Toxic shock syndrome, CRP: C-reactive protein.

Table II Possible Phenotypes of SARS-CoV-2-Related Hyperinflammation in Children [4,18, 24]

Classic Kawasaki disease	*Pediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2*	*Macrophage activation syndrome*
Clinical features		
• Younger children (<5 y)*	• Older children and adolescents	• Adolescents
• Fever (usually >5 d) with any 4/5:	• Fever with:	• Unremitting fever
• Non purulent conjunctivitis	• Gastrointestinal symptoms	• Pulmonary involvement
• Cervical lymphadenopathy >1.5 cm	• Mucocutanoeus changes	• Organomegaly(Hepatosplenomegaly)
• Erythematous rash	• Confusion or headache	
• Mucositis- strawberry tongue	• Single or multisystem dysfunction.	
• Extremity changes- swelling/peeling	• Rapid deterioration with refractory shock.	
• High incidence of coronary artery aneurysms.		
• Refractory to therapy		
Laboratory markers		
• CRP ≥3.0 mg/dL and/or ESR ≥40 mm/h	• High CRP	• Cytopenia (at least 2 cell lines affected)
• Elevated ALT	• Lymphopenia	• Hypertriglyceridemia
• Albumin ≤3.0 g/dL	• Neutrophilia in most	• Hypofibrinogenemia
• WBC >15,000	• Abnormal fibrinogen	• High ferritin
• Anemia for age	• High D-Dimers	• High AST
• Platelets >450000 (>7 d of fever)	• High ferritin	• Haemophagocytosis on bone marrow aspirate
• Urine analysis- 10 WBCs per high power field	• Raised LDH	• Low or absent NK cell activity
	• Hypoalbuminemia	• Elevated soluble CD25 levels
	• Transaminitis	
	• Elevated troponin, NT-proBNP	
Echocardiogram		
• Coronary artery dilatation or aneurysms.	• Left ventricular dysfunction	• Left ventricular dysfunction
	• Myocarditis	• Coronary artery dilatation or aneurysm
	• Valvulitis	
	• Pericardial effusion	
	• Coronary artery dilatation	

**We believe that children under 1 year of age are at particular risk of coronary aneurysms in KD seen in COVID era (unpublished data from authors). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: Lactate dehydrogenase; BNP: B-type natriuretic peptide.*

pathogenesis over a direct virus invasion-mediated tissue injury. Infection with COVID-19 triggers the formation of antibodies to viral surface epitopes. Virus neutralization is a direct function of the stochiometric concentration and affinity of the antibodies. It is believed that low titer non-neutralizing antibodies may accentuate virus triggered immune responses instead, thereby increasing the risk of severe illness in affected individuals [14]. While blocking antibodies against the angiotensin converting enzyme (ACE) receptor binding regions (such as the RBD and HR2 region of S protein) are deemed protective, those directed against nucleocapsid and other epitopes on S protein are not [15,16]. Weak antibody coated virus gets internalized by Fc receptors, followed by endosomal release of the virion and subsequent Toll-like receptor and cytosolic RNA sensor triggered IFN α responses. These antibody dependent enhancement (ADE) responses have been implicated in COVID-19 induced immune injury. Although evidence base for this pathway is demonstrated for coronaviruses [16], the exact role in PIMS-TS is only speculative [17].

MANAGEMENT

Conventionally, treatment of KD involves use of

intravenous immunoglobulin (IVIG) and high dose aspirin as first line agents [18]. The use of IVIG for PIMS-TS may help in facilitating neutralization of virus and associated superantigens and downregulation of the inflammatory cytokines [19,20]. IVIG (2 g/kg) has been used in most published series on PIMS-TS as first line therapy. The effects; however, may be short-lived [9,10]. In those with features of classic KD, it would be appropriate to consider use of aspirin (30-50 mg/kg/day followed by 3-5 mg/kg/day) along with IVIG [18]. The role of aspirin in children with hyperinflammation without features of KD is not known, and we believe that it has a limited role in these children. Although the role of anticoagulation is not clearly defined, it should be considered on a case-by-case basis in children with hyperinflammatory syndrome. The choice of anti-coagulation and their dosing regimen would also depend on the presence of coronary aneurysms.

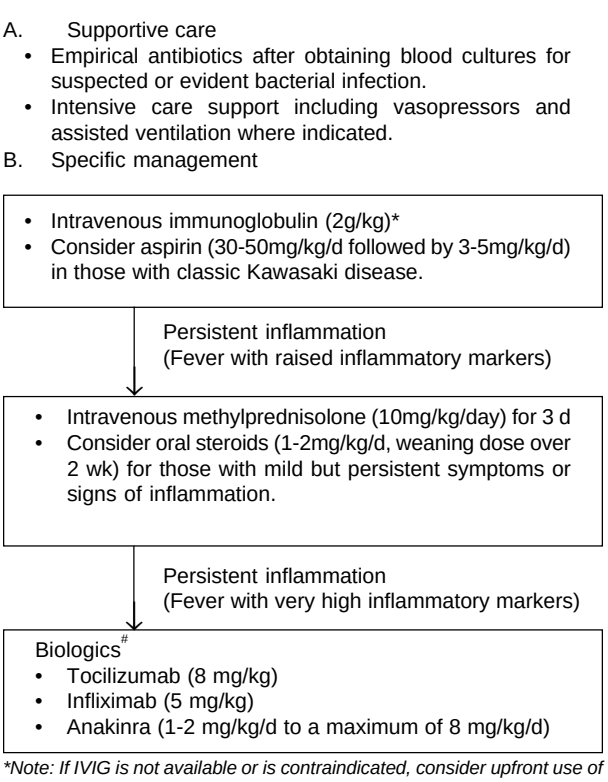
In select cases, especially those who do not respond to IVIG, adjunctive immunomodulatory therapy may be necessary to control inflammation. It is known that use of corticosteroids in KD is associated with earlier resolution of fever and lower incidence of coronary artery abnormalities [18,21]. Corticosteroids are also used as first line therapy in children with MAS. On this basis, it is plausible that these agents may be effective in PIMS-TS, especially in those with features of cytokine release syndrome (CRS). Recently published case series have shown that corticosteroids (initially pulse intravenous methylprednisolone 10 mg/kg/day for 3 days followed by oral prednisolone in a gradual tapering regimen) are useful adjuncts to IVIG in patients with PIMS-TS [9,10,21].

Whilst not much is known about the pathogenesis of PIMS-TS, it is clear that there is elevation of cytokines such as IL-1, IL-6, IL-18 and IFN-α in most children who develop MAS [22]. Although this does not necessarily establish causality, specific cytokine blockade has resulted in remission of MAS on many occasions [23]. Also, specific blockade of TNF-α with infliximab has been tried in children with KD resistant to IVIG [18]. Along with IL-6, several other cytokine blockade therapies are currently under evaluation in adults with COVID-19. As we understand more about targeted therapy in adults with COVID induced CRS, we might consider trials of these agents in PIMS-TS [24,25]. Extrapolating these data, it is possible that there may be a role for specific cytokine blockade in PIMS-TS as well. Apart from one case report describing the use of tocilizumab in a child with KD and SARS-CoV-2 [6], data on use of biologics for this indication are still lacking. Until such data are available, it would be reasonable to consider these therapies only under special circumstances (in children with high CRP levels and those refractory to IVIG/corticosteroids) either in controlled clinical trials or by clinicians experienced in use of biologics. Where considered appropriate, therapy with biologics such as tocilizumab (8 mg/kg) or infliximab (5 mg/kg) should be considered. Based on existing evidence, suggested management of children with SARS-CoV-2 related hyperinflammation has been summarized in ***figure* 1**.

Apart from immunomodulation, supportive care plays a key role in the management of these children. Deterioration can be rapid, and it is important for clinicians to monitor for signs of worsening inflammation [4].

FUTURE DIRECTIONS

The important answers lie in understanding the immune origins of this condition. There is a need for clinical trials using adaptive designs (Bayesian methodology) which would enable us to evaluate therapies including IL-6, IL-1 and anti-TNF blockade in children with this syndrome.



**Note: If IVIG is not available or is contraindicated, consider upfront use of corticosteroids; where possible, obtain blood samples for SARS-CoV-2 antibody testing or future research prior to administration of IVIG; Choice of anticoagulation and their dosing regimen would depend on presence of coronary artery aneurysms.*

#Only in centers with experience in use of biologics or in controlled clinical trials.

Fig. 1 *Suggested management of SARS-COV-2 related hyper-inflammation in children.*

Despite the emerging literature, there are still a lot of unknowns regarding SARS-CoV-2. It is important to gather data on the condition to understand the damage caused and risk for recurrence as well as long term implications including the risk for autoimmune disease later in life. Real time surveillance studies such as the WHO clinical data platform (*https://apps.who.int/iris/handle/10665/332236*) and the British Pediatric Surveillance Unit (BPSU) study (*https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory- syndrome-kawasaki-disease-toxic-shock-syndrome*) can gather information to help further our understanding of this disease. There is now an overwhelming need for registries for data collection and integration, especially in India [26,27]. Going forward, multicenter and perhaps multi-national collaborative studies may be required to fill existing gaps in our knowledge of the current pandemic and the new syndrome in children.

In the Indian context, we perceive a definite need for increased awareness of this unique clinical syndrome amongst parents and pediatricians alike in the midst of multitude of several common infections such as dengue, when a child presents with fever with variable accompanying symptoms and signs and raised inflammatory markers.

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SPECIAL ARTICLE

Cardiac Involvement in Children With COVID-19

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In contrast to adults, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) usually leads to a mild illness in children. However, a few children have been reported to have severe manifestations including pneumonia, acute kidney injury, multi-organ failure and cardiac injury. This review focuses on cardiac involvement during SARS-CoV-2 infection and the recently described likely immune mediated post-COVID-19 syndrome. Therapeutic strategies for cardiac dysfunction in both these settings are briefly discussed.

Keywords: *SARS-CoV-2, MIS-C, Myocarditis, Coronary dilation, Hypotension, Shock.*

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We are currently in the midst of a SARS-CoV-2 mediated novel coronavirus disease 2019 (COVID-19) pandemic. In contrast to adults, SARS-CoV-2 mostly leads to a mild illness in children typically manifested as fever, cough or gastrointestinal symptoms [1,2]. However, a few children have been reported to manifest severe disease which has been characterized by pneumonia, acute kidney injury, liver injury, metabolic acidosis, neurological injury, rhabdomyolysis, multi-organ system failure, and cardiac injury [1,3-5]. This review focuses on cardiac involvement during COVID-19 infection and the multisystem inflammatory syndrome in children (MIS-C) [6,7]. Therapeutic strategies for cardiac dysfunction in both these settings are briefly discussed.

CARDIAC INVOLVEMENT IN SARS-COV-2 INFECTION

Cardiac involvement, which can manifest as acute myocardial injury with elevated plasma troponin concentration, acute coronary events, heart failure and arrhythmias is both common and associated with a higher morbidity and mortality in adults with COVID-19 [8-10]. Hypothesized mechanisms of cardiac injury include direct viral invasion leading to cardiomyocyte death and inflammation and indirect mechanisms of injury - cardiac stress due to respiratory failure and hypoxemia and cardiac inflammation secondary to severe systemic hyper-inflammation, which is thought to be mediated by cytokines such as interleukin (IL)-6, IL-2, IL-7, TNF (tumor necrosis factor)-α and IFN (interferon)-γ [11]. Cardiac involvement during COVID-19 is not common in children who require pediatric intensive care unit (PICU) admission; use of inotropes was reported in 12 (25%) patients admitted to a North American PICU in a recent study [4]. The plasma concentration of cardiac bio-markers and echocardiographic findings in these patients were not reported, therefore it is unclear if inotropic requirement was due to primary cardiac dysfunction [4].

Cardiac involvement in patients with COVID-19 has included elevation in cardiac biomarkers such as troponin, CPK-MB, and pro-brain type natriuretic peptide (pro-BNP), echocardiographic abnormalities such as diminished left ventricular function with segmental or global wall motion abnormality and coronary artery dilation, and electrical abnormalities such as sinus tachycardia, atrial arrhythmias, non sustained ventricular tachycardia, first-degree atrioventricular block, premature atrial and ventricular contractions, and incomplete right bundle branch block [3,12-17] (***Table* 1**). In one of the largest pediatric series (n=2135) from China, 0.6% of children had symptomatic myocardial injury and heart failure [18,19].

It is difficult to draw any firm conclusions, given the small numbers and lack of any systematic prospective studies. However, currently available data indicates that cardiac involvement in children with COVID-19 is not common. In addition to clinical evaluation, electrocardiography and cardiac imaging, cardiac biomarkers such as plasma troponin, CK-MB and pro-BNP may be helpful in diagnosis. IVIG may have a role in treatment of children with cardiac involvement. The role of other drugs such as remdesivir and hydroxychloroquine is unclear at this time.

Table 1 Cardiac Involvement in Children With Coronavirus Disease 19

Author, No. of patients	*Age, sex, ethnicity*	*Clinical presentation*	*Cardiac biomarkers and ECG findings*	*Echo findings*	*Treatment*
Cui, *et al.* [3], 1	55 d, F Chinese	Respiratory symptoms	Mild ↑ troponin	-	-
Giacomet, *et al.* [12],1	2 mo	Fever and sinus tachycardia	↑ troponin and ↑ BNP	Hypokinesia of the inferior LV wall and the inferior interventricular septum. Mild ↑ LVEF	IVIG (2 g/kg)
Sun, *et al.* [13], 1	13 mo, M Chinese	Multiorgan dysfunction including cardiac dysfunction	-	-	Antiviral drugs, Glucocorticoids, IVIG, and Plasmapheresis
Xia, *et al.* [14], 5	1 d-14 y Chinese	Fever, cough, GI symptoms	↑CPK-MB (*n*=5), sinus tachycardia (*n*=1), atrial tachy cardia (*n*=1), PACs, PVCs and prolonged PR interval (*n*=1), and incomplete RBBB (*n*=1)	-	-
Su, *et al.* [15], 6	11 mo - 9.75 y, 3M/3F Chinese	Fever, cough	↑CPK-MB	-	Lopinavir/ Ritonavir, Interferon
Samuel, *et al.* [16], 6	12-20 y		↑troponin (*n*=2), monomorphic VT (*n*=5), sustained atrial tachycardia (*n*=1)	LV dysfunction (*n*=2), LV dilation (*n*=1), large circumferential pericardial effusion (*n*=1)	Beta-blocker (*n*=2), Amiodarone (*n*=1)
Oberweis, *et al.* [17], 1	8 y, M African	Fever, cough, malaise, weight loss	↑ troponin, ↑ BNP	LV dysfunction, trace mitral regurgitation and small pericardial effusion	IVIG (2g/kg)

LV: Left ventricle; BNP: Brain type natriuretic peptide; IVIG: Intravenous Immune Globulin; PAC: Premature Atrial Contraction; PVC: Premature Ventricular Contraction; CPK-MB: Creatine Phosphokinase-Muscle Brain subtype; LVEF: Left Ventricular Ejection Fraction.

CARDIAC INVOLVEMENT IN MIS-C

A few weeks following the peak of COVID-19 epidemic in the US and the European Union, a novel systemic illness which clinically overlaps with Kawasaki disease with or without shock syndrome, macrophage activation syndrome (MAS) and toxic shock syndrome (TSS) was reported in children. This entity was labeled as Multisystem inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC), USA and by the World Health Organization (WHO) [6,7]. A few cases have also been reported from India [20].

Cardiac involvement as evidenced by perturbation of cardiac chamber size and/or function, coronary artery abnormalities (ectasia, aneurysm) or elevated cardiac biomarkers such as troponin or pro-BNP is not only common in children with MIS-C but can also be severe (**Web *Table* I**). A vast majority of children with MIS-C had been previously healthy; a few have had minor comorbidities such as asthma and obesity. In addition to fever and weakness/malaise, gastrointestinal symptoms have been common at presentation. Many of these children have had marked hemodynamic instability requiring inotropic support and intensive care at admission. In addition, a small proportion has required extracorporeal membrane oxygenation support; though, mortality has been low [20-27]. In contrast to patients

with typical Kawasaki disease, atypical features including a higher incidence of cardiac involvement (60%), shock syndrome like features (50%), MAS (50%) and need for steroids following IVIG administration (80%) were noted in a previous study [22].

The precise mechanisms that underlie genesis of MIS-C and its cardiac manifestations are yet unknown. However, given the fact that a vast majority of children have presented 4-6 weeks after the peak of the local COVID-19 epidemic, many have been SARS-CoV-2 PCR negative but antibody positive, have had markedly elevated inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, ferritin, or interleukin 6, and have responded well to IVIG and immunomodulators; an immune origin is likely. Genetic factors may underlie the overall rarity of MIS-C and relative preponderance in African Americans.

Given the multiorgan dysfunction and potential for sudden and severe decompensation in patients with MIS-C, our practice has been to admit these patients to PICU where they are cared for by a team which involves specialists from pediatric rheumatology/immunology, pediatric critical care, pediatric cardiology, pediatric infectious diseases, and pediatric hematology. Inotropes should be initiated in children with MIS-C if clinically indicated and ECMO should be reserved for children with inotrope-refractory shock. In addition to clinical markers, mixed venous oxygen saturation and plasma lactate can be used to guide therapy. A vast majority of children with MIS-C have responded well to IVIG (1-2 g/kg), which as per the recently proposed American College of Rheumatology guidelines [28] should be the initial therapeutic agent. Though the data are scarce, patients with suboptimal clinical response (hemodynamic instability) or biochemical response (persistent elevation in inflammatory markers) to IVIG have benefitted from steroids (intravenous methylprednisolone 2 mg/kg/day) or immunomodulators such as anakinra (interleukin-1 antagonist) (2-8 mg/kg/day subcutaneous injection once or twice a day, maximum dose: 100 mg twice a day) and tocilizumab (interleukin-6 antagonist). The dosing of tocilizumab for systemic onset juvenile idiopathic arthritis is 12 mg/kg intravenous or 162 mg subcutaneous every other week for those weighing less than 30 kg and 8 mg/kg intravenous every other week or 162 mg subcutaneous every week for those weighing >30 kg. The optimal dose and dosing frequency for MIS-C is not known; intravenous doses of 400-800 mg and a subcutaneous dose of 162 mg has been used in adults with COVID-19 associated cytokine release syndrome [29], and 8 mg/kg in children [30]. Though adjunctive immune modifying therapies such as anakinra, tocilizumab and convalescent plasma have been used in patients with both acute COVID-19 and MIS-C, their role has not been systematically evaluated. Given the potential risk of thrombotic complications, we also initiate aspirin and low molecular weight heparin at admission, both of which we discontinue upon normalization of inflammatory markers. In addition to aspirin and low molecular weight heparin, we have typically discharged these patients on oral steroids which are gradually tapered as guided by their clinical status and cardiac and inflammatory biomarkers. Cardiac imaging with a focus on coronary arteries is obtained at regular intervals after discharge [28].

Cardiac involvement in children with COVID-19 is uncommon; however, a handful of patients have had severe involvement with markedly diminished ventricular function and hemodynamic instability. These patients have benefited from IVIG. The role of antivirals such as remdesivir, hydroxychloroquine, and adjunctive immunomodulatory therapies in patients with COVID-19 and cardiac involvement is unclear at this time. Cardiac involvement as evidenced by perturbation of cardiac chamber size and/or function, coronary artery abnormalities (ectasia, aneurysm) or elevated cardiac biomarkers such as troponin or pro-BNP is not only common in children with MIS-C but can also be severe. These children have responded to IVIG and or corticosteroids. A few have required additional immunomodulators such as anakinra and tocilizumab.

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Web Table I Cardiac Involvement in Children With MIS-C

Study	*Belhadjer, et al. [20]*	*Verdoni, et al. [21]*	*Riphagen, et al. [22]*	*Chiotos, et al. [23]*	*Feldstei, et al. [24]*	*Durfort, et al. [25]*	*Whittaker, et al. [26]*
Patients	35	10	8	6	186	99	58
Age*, y	2-16 (median 10)	2.9-16 (mean 7.5)	4-13 (mean 8.9)	5-14 (mean 8.5)	3.3-12.5 (median 8.3)	0-5 (31%), 6-12 (42%)	5.7-14 (median 9)
Male	51%	70%	62%	17%	62%	54%	66%
Chest pain	6 (17)	NA	0	0	-	11 (11)	-
Gastrointestinal symptoms	Nausea, diarrhea (83)	Diarrhea 6 (60)	Diarrhea 7 (88) Abdominal pain 6 (75) Vomiting 4 (50)	Diarrhea 4 (67) Abdominal pain/ Vomiting 5 (83)	171 (92)	79 (80) Abdominal pain 60 (61), nausea or vomiting 57 (58), diarrhea 49 (49)	Abdominal pain 31 (53), diarrhea 30 (52), vomiting 26 (45)
Cardiogenic shock	28 (80)	5 (50)	8 (100)	6 (100)	-	32 (32)	29 (50)
Arrhythmias	1 (3)	0	1 (12.5)	1 (17)	22 (12)	-	4 (7)
Cardiac high-sensitivity troponin concentration	347 (186-1267) ng/mL [median (range)]	Troponin I 1004 (1862) ng/L, mean (SD) Elevated in 5/9 (55)	Troponin > 50 ng/L 4 (50%), mean (SD), 252.5 (103.9) ng/L	Troponin>0.3ng/mL 2/6 (33%), mean (SD), 0.48 (0.22) ng/mL	Elevated troponin 64 (50) %	Elevated troponin 63 (71)	45 (8-294) ng/L (*n*=56)
BNP or NT-pro BNP	*NT-proBNP (*n*=5) 41484 (35811-52475) pg/mL; *BNP (*n*=28) 5743 (2648-11909) pg/mL, median (range)	1255 (929) ng/L; Elevated in 10 (100)	Elevated 5/8 (62.5) 19961.4 (5567.6) ng/L	BNP (> 100 pg/mL) 5 (100), 4671.4 (3,138.9) pg/mL	Elevated BNP (> 400 pg/mL) 112 (73)	Elevated BNP 74 (90)	*NT-proBNP 788 (174 -10548) pg/mL (*n*=29)
Systolic ventricular dysfunction	35 (100) LVEF <30% (28); LVEF 30-50% (72)	5 (50) LVEF 25-48%	6 (75)	4 (67) LVEF <30%	71 (38); LVEF <30%, 9 (5), LVEF 30-55% 61 (33)	51 (52), 32 (32) pericardial effusion	18/29 (62)
Coronary artery dilation (>2Z)	6 (17)	2 (20)	1 (12.5)	1 (12.5)	15 (8)[#]	9 (9)	8 (14.5)
ECMO	10 (28)	None	1 (12.5)	0	7 (4)	4 (4)	3 (5)
Inotropic support	28 (80)	2 (20)	8 (100)	5 (83)	89 (48)	61 (62)	27 (47)
IVIG	25 (71)	10 (80)	8 (100)	6 (100)	144 (77)	69 (70)	41 (71)
Corticosteroids	12 (34)	8 (80)	5 (62.5)	5 (83)	91 (49)	63 (64)	37 (64)
IL-1 receptor antagonist	3 (8)	0	0	1 (17)	24 (13)	-	3 (5)
Mortality	0	0	1 (12.5)	0	4 (2)	2 (2)	1 (2)

*All values in no. (%) except *range (mean/median)or detailed; BNP: Brain type natriuretic peptide; NT-proBNP: N-terminal pro-brain type natriuretic peptide; LVEF: Left ventricular ejection fraction; ECMO: Extracorporeal membrane oxygenation; IVIG: Intravenous immunoglobulin; corticosteroids: Intravenous corticosteroids; [#] z score>2.5.*

REVIEW ARTICLE

Medical Expulsive Therapy for Urinary Stone Disease in Children

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The rising incidence of urinary stone disease in children requires pediatric practitioners to keep abreast of management recommendations which are generally geared towards adults. Medical expulsive therapy (MET) is a non-surgical therapeutic option that can be trialed in patients who present with uncomplicated symptomatic ureteral stones. Seminal articles published and indexed in Medline on the topic of MET were extracted and reviewed. Studies suggest a potential benefit of alpha-blockade for the expulsion of distal ureteral stones that are >5 mm but ≤10 mm in adults and possibly >4 mm in children. Conversely, there does not seem to be any added benefit for MET in smaller stones (<5 mm) in which the spontaneous passage rate is high. **Conclusions**: The off-label use of these medications is one of the several barriers which contribute to the underutilization of MET in children. However, these may be a reasonable option in particular for older children and adolescents with the appropriate-sized stones.

Keywords: *Alpha-blockers, Calculi, Nephrolithiasis, Tamsulosin*.

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Urinary stone disease is a worldwide health problem with increasing incidence and prevalence in developed countries across Europe and Asia [1,2]. Clinical research in urinary stone disease has primarily focused on interventions aimed at reducing the morbidity and costs associated with initial presentation and symptomatic crises as well as long-term preventative strategies. Acute management strategies during a symptomatic event are often dictated by the degree of discomfort, associated infection, or the presence of an acute obstruction with resultant acute kidney injury. Additionally, the location and size of the stone and any associated anatomical abnormality of the urinary tract might impact clinical decision-making [3]. Interventions may involve the administering medications aimed at facilitating stone passage or surgical procedures which directly assist in stone removal. The strategy of administering medications to facilitate the passage of ureteric stones and ameliorate renal colic is generally referred to as medical expulsive therapy (MET). The purpose of this review is to both summarize and critically appraise the MET literature with particular emphasis on children.

BACKGROUND

The ureter contains a layer of smooth muscle which undergoes peristalsis and results in the propulsion of ureteral contents towards the bladder [4]. This can occur both autonomously *via* the release of neurotransmitters and can also be mediated *via* the autonomic nervous system [4].There are multiple different receptors types and second messengers located throughout the ureter which seem to play important roles in mediating this coordinated activity, the most relevant of which are a_1-adrenergic receptors, prostaglandin receptors and phosphodiesterases [4]. Activation of any of the above named receptor sites or increased phosphodiesterase activity typically leads to increased peristalsis [4]. The theoretical principle behind MET is to administer a medication which counteracts the contractile action of the ureters, resulting in smooth muscle relaxation and promoting the passage of stones from the ureter. Medications that have been studied in relation to ureteral stones include a-blockers (*e.g.*, tamsulosin), calcium channel blockers (nifedipine) and phosphodiesterase inhibitors (tadalafil) [5]; although, the latter two medications have not been studied in children [6,7].

In order to adequately assess the effectiveness of MET, one must first consider the natural history and likelihood of spontaneous passage of a stone without medical intervention. In general, stones that are smaller in size have been found to be more likely to pass spontaneously. One study in adults demonstrated that the rate of spontaneous expulsion was 87% for ureteral stones 1 mm in diameter, 76% for stones 2-4 mm, 60% for stones 5-7 mm, 48% for stones 7-9 mm and 25% for those larger than 9 mm [8]. In the pediatric population,

a retrospective study of 33 children revealed that 55% of children with calculi ≤3 mm passed their stones with hydration and narcotic therapy alone. All children with stones >4 mm required further intervention [9]. In addition, adult studies have demonstrated that the location of a stone within the ureter appears to affect the likelihood of spontaneously passage. Distal and ureterovesicular junction had the highest rate of spontaneous expulsion at 75% and 79%, respectively, followed by mid ureteral and proximal ureter stones with rates of 60% and 48% [8]. Other less well defined factors that may play a role include number of stones, and the degree of edema in the ureters [10].

A meta-analysis of nine randomized controlled trials (1981-2005) reported on 693 adults using a-blockers or calcium channel blockers as the primary therapy for MET and stone passage as the primary outcome [11]. The authors determined that subjects who received either tamsulosin or nifedipine had a 1.65 higher chance (95% CI, 1·45-1·88) of passing their stones. Based on this study and similar meta-analyses [12], both the European Association of Urology (EAU) and American Urologic Association (AUA) included recommendations that allowed for patients with stones <6 mm or stones <10 mm, respectively, the option of a trial of MET [6,7].

Adult studies: The Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial consisted of 1167 adults with a ureteral stone <10 mm. Subjects were randomized to receive either nifedipine 30 mg, tamsulosin 0.4 mg or placebo [13]. There was no difference between active treatment with MET and placebo or between tamsulosin and nifedipine. Further, no benefit was seen in patients with respect to stone size or location in the ureter [13]. Similar to the SUSPEND trial, Furyk, *et al*. [14] also reported no difference in overall rates of stone passage between patients in tamsulosin or placebo groups. Importantly, in the subgroup with stones >5 mm there was a 22.4% (95% CI 3.1 to 41.6, *P*=0.03) higher rate of stone passage in those who received tamsulosin as compared to the placebo group [14]. The Tamsulosin for Urolithiasis in the Emergency Department (STONE) study [15] did not find a significantly better stone passage rate in patients who received MET, as compared to placebo. In the largest randomized, double blind placebo controlled study to date, Ye, *et al*. [16] examined the difference in distal ureteral stone expulsion rates in 3296 patients receive either 0.4 mg tamsulosin or placebo for 28 days [16]. Results from the study demonstrated a statistically significant benefit for those patients who received tamsulosin (86% stone passage) versus those receiving placebo (79% stone passage) with a *P*-value <0.001 [16]. Patients treated with tamsulosin were also found to pass the stones sooner than those on placebo (148.3 *vs* 248.7 hours) [16]. Subgroup analysis demonstrated that there was no benefit for tamsulosin therapy for subjects with stones ≤5 mm and that the entire beneficial effect was driven by those subjects with stones >5 mm. These results perhaps explain the discrepant findings noted between the previous randomized controlled studies in which the majority of stones were small and underpowered to evaluate size effect.

In 2016, an updated meta-analysis of 55 randomized controlled trials (including 5990 patients) that evaluated the effect of alpha blockers on ureteral stone expulsion was performed by Hollingsworth, *et al*. [17]. The pooled risk ratio (RR) for stone expulsion was 1.49 (95% CI 1.39 to 1.61) for patients treated with alpha blockers as compared to those who were treated with placebo [17]. The effect of MET in relation to the location of the stone revealed that Tamsulosin increased the rate of stone passage in the upper and middle ureter (pooled RR of 1.48 with 95% CI 1.05 to 2.10) and confirmed the benefit in distal ureteral stones (pooled RR of 1.49 with 95% CI 1.38 to 1.63) as compared to controls [17].

In summary it appears that MET, and in particular alpha blockade, has beneficial effects on aiding expulsion of ureteral stones >5 mm in size in adults. This benefit appears to be most consistent for stones found in the distal ureter but may be beneficial for the management of stones >5 mm and <10 mm regardless of location.

Pediatric studies: There are multiple factors which contribute to the limited use of MET in pediatric patients. These include a lack of familiarity with MET by pediatric practitioners, a relatively larger stone size to the ureteral dimension ratio as compared to adults, physician and parental discomfort with off-label use of medications in children, and a fear of potential poor tolerance of alpha-blockers [18]. To highlight this point Ellison, *et al*. [19] performed a retrospective study using the Market Scan Commercial Claims and Encounters database to assess how often MET was being offered to pediatric patients [19]. Overall 1325 children between the ages of 1-18 years with either a renal or ureteral calculus were identified by ICD 9 code. Of these only 13.2% received MET [19]. Nonetheless, several studies have examined the efficacy of MET in the management of distal ureteral stones in the pediatric population with mixed results.

A prospective, randomized trial of 39 children with ureteral stones <10 mm in size compared the efficacy of ibuprofen alone as compared to doxazosin (0.03 mg/kg daily) on stone passage rates [20]. During a mean follow up period of 19 days, there was no significant difference between the groups in terms of expulsion rates and mean

time to expulsion [20]. Conversely, Erturhan, *et al*. demonstrated a benefit of doxazosin as compared to analgesia alone in a study of 45 children with distal ureteral calculi at three weeks follow-up [21]. In this study, only 28.6% patients in the control group had spontaneous expulsion of their stones as compared to 70.8% in the intervention group (P=0.005) [21]. It is noteworthy; however, that the spontaneous expulsion rate in the control group was substantially lower than what has been reported in other similar pediatric studies [10,20,22], thus potentially magnifying the effect of the MET.

Several studies have also examined the effect of tamsulosin in children. A placebo-controlled prospective trial in which 61 children with distal ureteral stones <12 mm were randomized to receive either analgesia plus tamsulosin or analgesia with placebo, found that after four weeks, patients who received tamsulosin were significantly more likely to have spontaneous stone passage (87.8%) as compared to the placebo group (64.2%) [10]. Additionally there was a significant difference in time to passage of the stone with those in the tamsulosin group passing stones on average 6 days earlier than the control group [10]. Aldaqadossi, *et al*. [22] demonstrated similar findings in 67 pediatric patients with distal ureteral stones <10 mm; 87% of 33 children receiving tamsulosin passed their stones with a mean time of 7.7 days while only 63% of the 34 controls passed their stones with a mean time of 18 days [22]. A multi-center retrospective study compared 99 children prescribed tamsulosin for ureteral stones <10 mm to 99 propensity matched controls who were treated with analgesia alone [23]. At six week follow up, 55% of patients receiving MET achieved stone expulsion as compared to 44% of controls (P=0.03) [23]. Logistic regression analysis adjusting for stone size and location showed an odds ratio of 3.31 (95% CI 1.49-7.34) for spontaneous stone passage in children receiving tamsulosin as compared to those receiving analgesia alone [23].

To date two pediatric meta-analyses have been performed. A meta-analysis [24] including four of the previously cited studies [10,20,21,23] and one abstract [25] included 465 subjects <18 years of age with ureteral stones demonstrated that MET significantly increased the odds of spontaneous stone passage (OR 2.21, 95% CI 1.40 -3.49) as compared to controls. Furthermore, when the analysis was restricted to the randomized controlled trials [10,20,21], MET significantly increased the odds of spontaneous stone passage (OR 4.06, 95% CI 1.84-8.95) as compared to controls [24]. The second meta-analysis [26] included 406 children who were treated exclusively with a-blockers from four of the previously cited prospective trials [10,20-22] and one cohort study [23]. This analysis also demonstrated a higher stone expulsion rate (OR 2.71, 95% CI 1.49-4.91) associated with MET usage but did not demonstrate shorter times to stone passage as compared to controls [26].

CONCLUSION

Pediatric urinary stone disease is an evolving condition whose incidence and prevalence have increased over the last several decades [27]. In response to this increased burden, MET has been well studied and guidelines for its use in adults are already available [7,28]. The most frequently studied medication has been tamsulosin, which potentially contributes to stone passage through the relaxation of ureteral smooth muscle thereby promoting the promoting the passage of stones. Notably, stones <4-5 mm have a high likelihood of spontaneous passage resulting in seemingly little added benefit of MET. Conversely, adult studies seem to suggest that MET likely may increases the likelihood of stone passage in patients with distal ureteral stones >5 mm and <10 mm in size. Although, studies in children are few in number and contain a limit number of patients, most studies indicate that tamsulosin might be of benefit in children with ureteral stones ≥ 4 mm but less than 10-12mm [9].

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Training-Module for Residents in Medical Educational Technologies (TRIM): Need and Operational Strategies

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Residents-as-teachers campaign started abroad during the last decade of the twentieth century. In India, though used informally for teaching of undergraduate students, residents have mostly been used for patientcare and their formal induction as teacher in Indian scenario is rare. Accordingly, not much effort has been made to train them formally in educational technologies.Teaching job requirements of residents are not the same as that of medical college faculty; as such, a program designed for medical college faculty will not prove equally effective for the residents. There is urgent need to train the residents in educational technologies for tapping their full potential as teachers and for this to happen, there must be a training module, tailor-made for the teaching-job requirements of the residents. This paper proposes such a program, after emphasizing the need of inducting residents in departmental formal teaching activities.

Keywords:*Faculty development, Educational technologies, Residents as teachers, Training module, Workshop.*

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Visiting memory lane back to the days of an undergraduate medical student, the first visuals appearing in flash-back of most medical graduate are those of clinical classes, held during the evening hours, conducted by residents, where one used to have in-depth discussion on clinical cases and used to finalize a work-up; where one could elicit sign and symptoms freely and in a non-threatening environment; where probably one was more comfortable in admitting mistakes and looking for ways to correct them. Those sessions by residents and demonstrators helped medical undergraduates immensely in honing their clinical reasoning and psychomotor skills.

Residents and demonstrators are involved in routine teaching activities in most of the departments. It has been estimated that residents spend approximately 25% of their time teaching medical students [1]. Another study found that residents spent 19% of their total time in teaching activities, with 90% of this effort devoted to teaching associated with patient care and 10% spent in classroom teaching [2]. Even medical graduates perceive that 18% of the knowledge they gained during clinical clerkships came from residents and 13% from interns, compared with 25% from attending physicians and 43% from the students' own initiative [3]. As evident, residents have always been involved in the departmental teaching activities. Of course, all these figures are from other countries and no such data could be found from India.

Is the picture same in India? Yes, to a large extent. Residents are being used in departmental teaching activities without being formally trained for the same in most of the non-clinical subjects. We don't have a data for clinical subjects either, but it seems that utilization is suboptimal. With the introduction of competency-based curriculum at undergraduate level there will be paradigm shift and residents will be increasingly used for formal teaching activities in India without any formal training. Should we not have tailor-made faculty development activities for residents, both senior residents as well as post-graduate students, in order to tap their full potential in the conduct of the teaching activities in the department? We are discussing some of these issues here.

RESIDENTS AS TEACHERS

Literature is full of the reasons and means of involving residents-as-teachers in various medical disciplines, as explained here.

Regulatory Obligations

The literal meaning of word doctor is – to teach (derived from Latin verb *docere*). Being christened with the title

'doctor', residents are licensed to teach. Various regulatory bodies also make it mandatory for residents to teach the undergraduate medical students as they are given teaching experience certificate for the same, which is counted for career progression. As per Medical Council of India (MCI) regulations, three-year experience as Junior Residents and one year experience as Senior Resident in a recognized medical college in concerned subject is necessary to be appointed as Assistant Professor [4]. Naturally residents, who are given teaching experience, must teach as per regulatory and statutory provisions.

Institutional Requirements

Regulatory bodies have also mandated certain number of senior and junior residents (tutors in pre- and para-clinical subjects) to be appointed in medical colleges in all clinical disciplines. These staffed residents will certainly be utilized for the teaching purposes of undergraduate students.

Moreover, with the implementation of competency based medical curriculum in India from the admission session 2019, it has become imperative to use the services of residents in the teaching – as more hands are needed for 'assessment for learning' purposes [5].

Refining Residents' Own Competencies

Teaching is the highest form of understanding. As is often quoted, 'to teach is to learn twice.' Being involved in teaching process in the department provides residents opportunities to improve their own perceived professional competencies. Over the time, residents have opined that teaching helps them in being good clinicians – as teaching stimulates critical thinking and reflection on knowledge, besides enhancing self-learning [6,7].

In another study, attending doctors expressed the opinion that students and residents both are benefitted due to teaching by residents and teaching by residents should be regarded as an integral part of residency program [8].Thus involving residents in the departmental teaching activities improve residents' professional and clinical competencies, as perceived by them.

BENEFITS OF USING RESIDENTS AS TEACHERS

Students often rate teaching by residents higher than faculty teaching; and often view residents as more approachable, thus encouraging them to acknowledge their mistakes easily and accept feedback readily [9-11]. Residents-as-teachers also provide a kind of support system for the students by acting as near-peer mentors.

When residents are used as teachers, it is not only beneficial for the professional development of the students and the residents but for the overall growth of the institutions also, thus paving the way for the ultimate improvement in patient care outcomes (***Fig.* 1**).

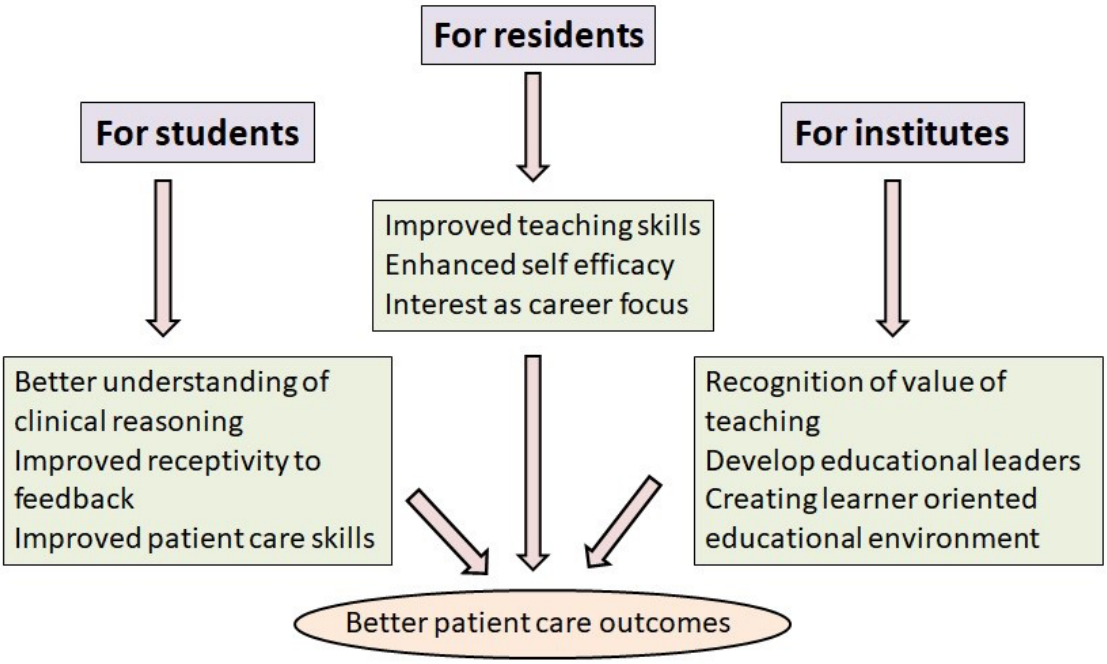

Fig. 1 *Beneficial effects of using residents as teacher.*

NEED AND IMPACT OF EDUCATIONAL TRAINING PROGRAM FOR RESIDENTS

For generations, residents teach the way they saw their teachers do that and imbibe skills through 'role modeling'. However, learning the art and science of teaching through role modeling alone is not the correct and optimal way of learning; one needs to have formal experiential learning through formal training. Only a formally trained resident in teaching technology will be motivated and dedicated enough to have overall professional development. There are many reports of formal residents-as-teachers program from many universities worldwide. However, considering the unique and contextual nature of educational content and environment, it may be worthwhile formulating our own program. Residents and demonstrators are usually involved in practical demonstrations, bedside teaching and sometimes in assessment activities like conduct of objective structured clinical/practical examinations (OSCE/ OSPE). They are also increasingly being used for skill development in the skill labs and other simulated environments.

Medical post-graduates are inherently trained to be competent in-patient care; they are not trained as 'medical teachers'. Unlike requirements of having an educational degree in the field of humanities and arts, there is no specialized degree in the field of medicine which they must acquire in order to be medical teachers. This precise reason has forced regulatory bodies to start faculty development programs in medical educational technologies for the benefit of the medical faculties. In India, Medical Council of India (MCI) has developed two such structured programs –Basic Course Workshop in Medical Educational Technologies and Advance Course in Medical Education [12]. If tailor-made faculty development programs are required to be structured for medical faculty, the logic weighs-in on the side of structuring and implementing such a training program in educational technologies for residents also.

Literature has evidence that the training improves the didactic, cognitive and clinical skills of the trainees [13]. Some qualitative and quantitative studies have provided evidence of utility of training for residents in educational technologies [6,14,15]. Morrison, *et al*. by using the Objective Structure Teaching Examination to determine the impact of a 13-hour teaching training program for residents found that compared to a control group, residents' having undergone training had an overall improvement in teaching scores by 28% [15]. However, Dunnington and DaRosa found minimal changes in resident teaching behavior by using OSTE, after introducing a residents-as-teachers intervention [16].

In another study, Snell by using triangulation of data method tried to evaluate the effectiveness of a training program for residents-as-teachers, which included five three-hour sessions. She proved that trained residents had improved resident teaching skills, showed better application of those skills and maintained those skills over the academic year [17]. This is perhaps the only kind of study using data from multi-sources to establish the effectiveness of training programs for residents in educational technologies.

It is also pertinent to note that many of these residents would be joining medical colleges as faculty. Others may end up teaching DNB residents. It would thus be a useful intervention to change the mindset towards teaching at an early stage of post-graduate career.

TRAINING PROGRAM - DOCUMENTED EFFORTS

Training modules for the formal training of residents in educational technologies and principles have been developed and implemented by various universities and colleges, ranging from 2 hour modules to workshops for 2-3 days to weekly / fortnightly one hour training for up to six months duration [15,16]. Longitudinal training programs in the form of electives for residents have also been designed, implemented and evaluated [18-20]. In most of these training programs and workshops, the most commonly used instruction methods were - lectures, small group interactive sessions and role-play. Large group interactive discussions and standardized students were the least commonly used methods [21].

A literature search could retrieve very few studies having used the concept of resident-as-teachers in India [22-24].Of these studies, only Senior Resident Training on Educational Principles (STEP) study has described a structured training module in the form of workshop delivered to senior residents for enhancing their teaching skills [22]. Maharashtra University of Health Sciences also started 'resident as teacher' program.[25] All such programs started at various institutes could not sustain for various reasons; one of them possibly being lack of conviction about utility of such an exercise. As literature shows content, structure, duration and delivery variability of different workshops/training programs designed for residents-as-teachers, with hardly any visibility of such training modules and programs in India and as the use of residents-as-teachers is in transient phase in congruence with the paradigm shifts in the medical education and undergraduate and post-graduate medical curriculum in India. It is imperative that a structured training program in medical education technologies for residents' training in India be designed.

PROPOSED TRAINING MODULE

Though the need and effectiveness of a structured program in educational technologies for residents is self-explanatory, less than 10% of residents and interns reported to have undergone any sort of training in teaching. This fact alone emphasizes the need to design and implement a structured program for residents-as-teachers, particularly tailor-made for our needs and requirements. Due to differences in teaching-job profile, the structured module used for training of the medical faculty can't be used for the residents also.

Accordingly, a 'Training-module for Residents' in India in Medical education technologies (TRIM)' in the form of workshop, based on some fundamental assumptions has been proposed here (***Box* 1**).

The goal of the proposed program is to orient the residents to the use of medical education teaching and assessment tools. The content of the proposed program has been designed by extracting data from three sources – previous experience of institutes in designing and implementing such programs; MCI requirements for residents in India; and curricular mandates requiring use of residents in students' teaching as per authors own experiences. Three main areas identified for training and orientation of residents are – teaching principles and tools, assessment and assessment tools, mentoring and teamwork.

The training module has been structured with the objectives of sensitizing and training residents in the concepts of – group dynamics and team-based learning, small group teaching, bedside teaching, simulation based teaching and assessment, assessment of learning and assessment for learning, and mentoring. These focused areas align well with the teaching job profile of the residents. However, efforts must be made to sustain this training through reinforcements during residency as well as during working period as faculty, as and when a resident joins as faculty in any institute. The description of the sessions and the instructional strategies proposed for delivery of those sessions has been briefed in ***Web Table* I**.

This workshop of 22 hours can be conducted over three days, with 30-35 residents. If three-day continuous workshop is not possible, the institute concerned can distribute sessions daily, as appropriate.Trained faculty members from all departments can be involved. A self-explanatory and most-appropriate instructional method for the conduct of each session has been recommended; however local factors like available infrastructure, availability of time, expertise of facilitators will ultimately decide the choice of any of these methods.

Local planners may consider adding sessions on – appropriate use of multimedia, integrated teaching, assessment in integrated teaching-learning, self-directed learning – if their local needs direct the same. Similarly, based upon expertise of the faculty other instructional strategies like – cine-meducation, team-based learning, team objective structured clinical examination – can be used [27-29]. One can also explore the possibility of using online platforms and educational strategies for the delivery of the content; even partially, if not fully. Combination of synchronous and face-to-face training followed by asynchronous or synchronous online training can be a viable option in institutes with heavy patient footfall, making time constraints for residents a real issue.

Box 1 Fundamental Assumptions for Designing Training Module for Residents

- Residents will be involved in teaching of cognitive, psychomotor and affective domains to undergraduates (UGs) including professionalism and ethics.
- Residents will be mainly involved in interactive small group teaching and bedside teaching.
- Residents will act as role models for UGs, thereby affecting soft skills including professionalism, ethics, communication of UGs.
- Residents will act as mentors for UGs.
- Residents will be used for assessment of UGs, of all domains, including assessment of knowledge.
- Residents will be particularly used for assessment in simulated conditions, and more for formative purposes.
- Residents will not be used for curriculum design or curriculum evaluation.

EXPECTED OUTCOMES

What is expected to be achieved with this module? It is not expected that with this training module the residents will be fully equipped with all the teaching and assessment tools available in the armamentarium. Only expectation is that the sensitized residents after the training will start applying these concepts in their teaching activities. They are expected to be handy resources as facilitators in the conduct of Objective structured clinical examination/Objective structured practical examination (OSCE/OSPE) in the department. After the training, they must be field-ready to act as instructors in the upcoming skill labs.

It is further expected that residents teaching skills will evolve and will improve from 'being novice' to at least 'advance beginners'. More importantly residents are expected to build the concept of 'transfer of training' at their young age as teachers and understand the utility of having a learner-oriented educational environment in the institute.

PROGRAM EVALUATION

A detailed plan of action for program evaluation of the proposed "Training-module for Residents' in India in Medical education technologies (TRIM)" is out of the scope of this paper. However, we are trying to issue generalized suggestions, so that the program is evaluated and monitored continuously for refinement as well as for ensuring accountability. The evaluation must include both process evaluation and outcome evaluation. While outcome evaluation will measure if the desired change has been achieved or not, the process evaluation will measure how the desired change was achieved – that is if the program was carried out as planned. Typically, a combination of logic and Kirkpatrick's model will be good enough for such a program evaluation.

CHALLENGES IN IMPLEMENTING TRAINING PROGRAM

First challenge will be to find trained faculty for the conduct of the training program of the residents as teacher. The faculty needs to be trained themselves. The Medical Council of India's new guidelines, making revised basic course workshop as mandatory requirement for promotion of faculty will result in many trained faculty members. Faculty inertia and resistance will be the next big challenge in the implementation of teachers training program for residents. The resistance is not baseless even. Faculty in medical colleges is already involved in multitasking – patient care, teaching postgraduates and undergraduates, curriculum development, administrative duties to name a few. Making arrangements and then conducting a workshop for residents will be labor intensive; though the very incentive that the trained residents will ultimately prove helping hands for these faculty members for undergraduate teaching will motivate faculty to plan and conduct such teachers training programs for residents.

Residents have multiple tasks to do – patient care, research, participation in continued medical education programs including training in research methodologies; so tapping their full potential as teachers is a challenge in itself. Consequently, many residents might be reluctant to attend teachers training program.However, owing to the huge personal and professional benefits of teaching undergraduate students, residents will get enough sensitization to attend such a training program.

The training program needs to be monitored also, at all levels, not only for continuous refinement and support but also for seamless implementation. Monitoring any program is a challenge in itself. Program evaluation and monitoring demands trained manpower, infrastructure, time and coordination among different stakeholders. Program evaluation plan, as proposed above, will be required to be designed, once such a program is adopted for implementation.

CONCLUSIONS

There is huge man-power and potential available with us in medical institute in India in the form of junior and senior residents. Though routinely used in patient care, they must be used as facilitators and instructors for departmental teaching and assessment activities. It is logical to assume that orientation and training of residents in the form of a workshop module will improve their acumen for teaching activities. An informed, sensitized, oriented and trained resident will prove to be a useful and productive resource for any institute.

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WebTable I Sessions and Instructional Strategies for the Delivery of the Proposed Workshop Module for Training Residents in Medical Education Technologies

Sessions	*Instructional strategies*	*Duration (h)*
Principles of group dynamics and team building	Crossing the river – group activity[26]	1
Goals, roles and competencies and domains of learning and system approach	Brainstorming, interactive lecture	2
Interactive small group teaching – Problem based learning, case-based learning, tutorials, flipped classroom	Interactive lecture followed by group activities and reporting	3
Bed-side teaching, one-minute preceptor	Interactive lecture, Brainstorming, Role-play	2
Simulation based teaching	Hands on training in skill lab	2
Assessment: Principles and concepts	Interactive lecture	1
Assessment in competency based medical education	Interactive lecture, brainstorming	1
Assessment for learning, feedback and its utility	Interactive lecture, brainstorming, demo	1
Assessment of knowledge – MCQs, essay (long and short) questions, viva-voce	Interactive session, brainstorming, group activity	1
Assessment of skills – OSCE / OSPE	Brainstorming followed by demo and group activity	2
Work-place based assessment including assessment of affective domain	Interactive lecture followed by mini-CEX demo	2
Simulation based assessment	Hands on training in skill lab	1
Mentoring: Concepts, utility and residents as role-models	Interactive lecture, Brainstorming followed by group activity and reporting	3

MCQs: Multiple choice questions; OSCE: Objective structured clinical examination, OSPE: Objective structured practical examination; mini-CEX: Mini clinical evaluation.

A Road Map for Simulation Based Medical Students Training in Pediatrics: Preparing the Next Generation of Doctors

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Current Medical training in India is generally didactic and pedagogical, and often does not systematically prepare newly graduated doctors to be competent, confident and compassionate. After much deliberation, the Medical Council of India (MCI) has recently introduced a new outcome-driven curriculum for undergraduate medical student training with specific milestones and an emphasis on simulation-based learning and guided reflection. Simulation-based education and debriefing (guided reflection) has transformed medical training in many countries by accelerating learning curves, improving team skills and behavior, and enhancing provider confidence and competence. In this article, we provide a broad framework and roadmap suggesting how simulation-based education might be incorporated and contextualized by undergraduate medical institutions, especially for pediatric training, using local resources to achieve the goals of the new MCI competency-based and simulation-enhanced undergraduate curriculum

Keywords: *Competency, Integration, Medical education, Undergraduate*.

Graduates, through didactic training and apprenticeships, focus on improving knowledge. However, graduates often have gaps in skills, behaviors and attitudes, so alternative forms of education are necessary to support competence, confidence, communication skills, and compassion in caring for children. Entering internship after the final year of medical school, students are required to perform many critical actions independently. Most of the students in the Indian subcontinent learn clinical care by practicing on real patients which may result in physiological and psychological harm to the patients and families, as well as excessive stress to the new graduate. Simulation is a powerful tool that can facilitate learning in a safe environment by deliberate practice and facilitated reflection. Using simulation to address individual and team skills, behaviors and attitudes was addressed previously in the journal [1] – we add to it in the light of the new MCI curriculum.

New MCI Curriculum

The Medical Council of India (MCI) has proposed an exciting new initiative to revamp medical training by creating a competency based undergraduate curriculum for the Indian medical graduate [2,3]. The new curriculum focuses on Attitude, Ethics and Communication (AETCOM); calls for preparing students to face India's health needs by training to be a "Clinician, Communicator, Team leader, Professional and Lifelong Learner"; emphasizes collaborative and inter-disciplinary teamwork, professionalism, respect and responsiveness to the needs of the patient; limits didactic lectures to less than a third of total schedule; integrates communication skills training; and uses simulation training and guided reflection

The new MCI competency-based pediatric medical graduate curriculum is based on seven core competencies (***Box* I**). MCI emphasises that the teaching should be aligned and integrated both horizontally (across disciplines in a given phase of the course) and vertically (across different phases of the course). This will allow graduates to provide comprehensive care for neonates, infants, children and adolescents based on a sound knowledge of growth, development, disease and their clinical, social, emotional, and psychological correlates in the context of national health priorities [4]. MCI has directed individual undergraduate medical institutes to form their own curriculum committees to implement these standards [5].

Can Simulation Bridge Current Gaps in Training?

The new MCI curriculum aspires to ensure that the medical graduate meets or exceeds global benchmarks in knowledge, attitudes, behaviors, skills and communication abilities, and is able to provide holistic care with compassion. How do we achieve this goal?

Box I The New Medical Council of India Competency-based Pediatric Curriculum of the Indian Medical Graduate Program [4]

Pediatric Competencies students must demonstrate

1. Ability to assess and promote optimal growth, development and nutrition of children and adolescents and identify deviations from normal.
2. Ability to recognize and provide emergency and routine ambulatory and First Level Referral Unit care for neonates, infants, children and adolescents and refer as may be appropriate.
3. Ability to perform procedures as indicated for children of all ages in the primary care setting.
4. Ability to recognize children with special needs and refer appropriately.
5. Ability to promote health and prevent diseases in children.
6. Ability to participate in National Programmes related to child health and in conformation with the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) Strategy.
7. Ability to communicate appropriately and effectively.

Didactic education will help the learner to gain knowledge, whereas simulation-based education (SBE) will help the learner to apply their knowledge by creating realistic experiences in a controlled, low risk and interactive environment. Debriefing, which is an integral component of the simulation experience, facilitates mindful reflection, active learning, abstraction, conceptualisation, and application of theory to real events. Integrating didactic teaching and SBE will provide shorter learning curves, higher retention and improved behavior in future patient care encounters, helping learners emerge as leaders, communicators, professionals and health advocates [1,6-8]. Studies have shown that pediatric trainees become more confident in recognising, assessing, managing sick children, and in communicating after simulation-based training [9-12].

Progress Towards SBE in India

It is encouraging to see a few institutions in India already taking an active interest in incorporating simulation for undergraduate training. At the All India Institute of Medical Science (AIIMS) Delhi, and many other institutions, skills are taught using a blended learning technique with both online and hands-on teaching sessions. The online segment consists of a brief description of the standard operating procedure (SOP) and a video of skills such as intravenous (IV) cannulation, hand washing, gowning and gloving, glucometer use, bag and mask ventilation, chest compressions, endotracheal intubation, laryngeal mask airway (LMA) insertion, basic suturing, and episiotomy suturing. The students need to answer a few multiple-choice questions based on the information given in the SOP and video and then they are allowed to come for hands-on sessions. Apart from the above, a simulation-based neonatal resuscitation program (NRP) is being run for the students during their 6th semester. Future steps include incorporating team training and human factors in simulation. Centres such as Father Muller Simulation and Skills Centre; DY Patil Medical Simulation Laboratory; Kasturba Medical College (KMC), Manipal; and GSL smart lab, Andhra Pradesh have already commenced incorporating simulation in pediatric undergraduate training.

OVERVIEW IN OTHER COUNTRIES

Use of simulation-based education in pediatrics is used in majority of institutions in USA [13]. SBE is based on 13 core 'Entrustable professional activities for entering residency' from the Association of American Medical Colleges [14]. Most centres in USA, Canada, United Kingdom and New Zealand introduce simulation to students in the first year of medical training and gradually increase the duration and complexity from year 2 onwards using both skill laboratories and in-hospital simulation.

Typically, students learn various procedural skills (such as cannulation, blood sampling, suturing, intubation, thoracentesis, aseptic precautions), history taking, basic life support, airway, focussed examination, leadership, handover, interprofessional and family communication in simulation centres, and management of emergencies with team training at hospital. Combinations of task trainers, manikins with varying amounts of technology (low, medium, high), virtual reality (VR) simulations, and standardized patients (SP) are used for training at simulation centres. Simulation is also used as an evaluation tool and to assess knowledge *e.g.,* Objective Structured Clinical Examination (OSCE) stations [15,16].

At the Children's Hospital of Philadelphia (CHOP), medical students undergo pediatric simulation training at a simulation centre at the University of Pennsylvania Perelman College of Medicine. In addition, during year 3 and 4 they undergo *in situ* simulation training at CHOP. Small batches of five third year students participate in simulation once-a-week to learn team training, neonatal apnea, asthma, croup, febrile seizure, hypoglycemic seizures for 5 weeks. Similarly, fourth-year students visit once-a-week to learn team training, identification of sick

child, high quality resuscitation, cardiac arrhythmias, anaphylaxis and septic shock using scripted scenarios and high technology manikins. Debriefing normally takes twice the time of conducting the scenario. Prior to commencing internship, medical students participate in a 5-day intense pediatric boot camp. The boot camp is structured to mimic real work in a Pediatric ward and emergency room involving allied professionals such as radiology, physiotherapy, occupational therapy, speech therapy, child life and lactation specialists. Emphasis on personal wellbeing in addition to skills such as PALS emergencies and handoff communication has made this boot camp a great success [11,17]. CHOP is also helping overseas centres conduct team training and debriefing through tele-simulation.

WHAT IS NEEDED FOR SIMULATION-BASED TRAINING?

To succeed in our mission to provide SBE, we need commitment by the faculty and administration, a clear roadmap, passion to succeed and, willingness to invest for our new generation of young doctors. Now that the need for SBE has been identified [2-5], next steps will be to develop faculty, secure funding, identify space for simulations, procure manikins and other equipment, train personnel, design curricula and script scenarios. Ongoing research and feedback to refine the curriculum will lead to high quality training (***Fig.* 1** and **2**).

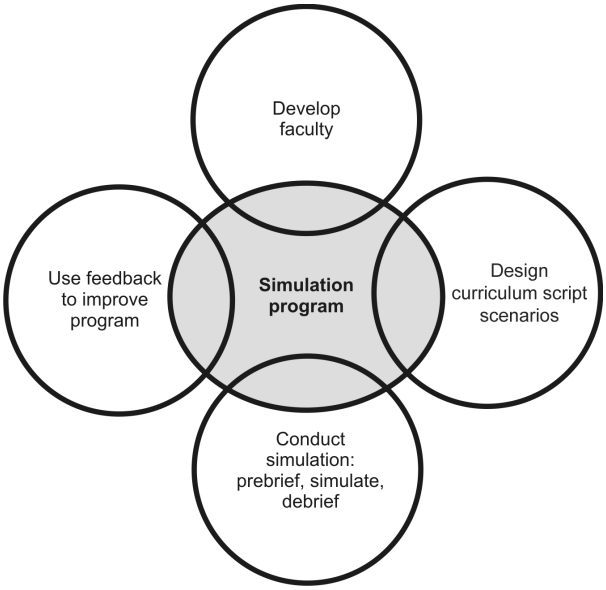


Fig. 1 *Designing a simulation program.*

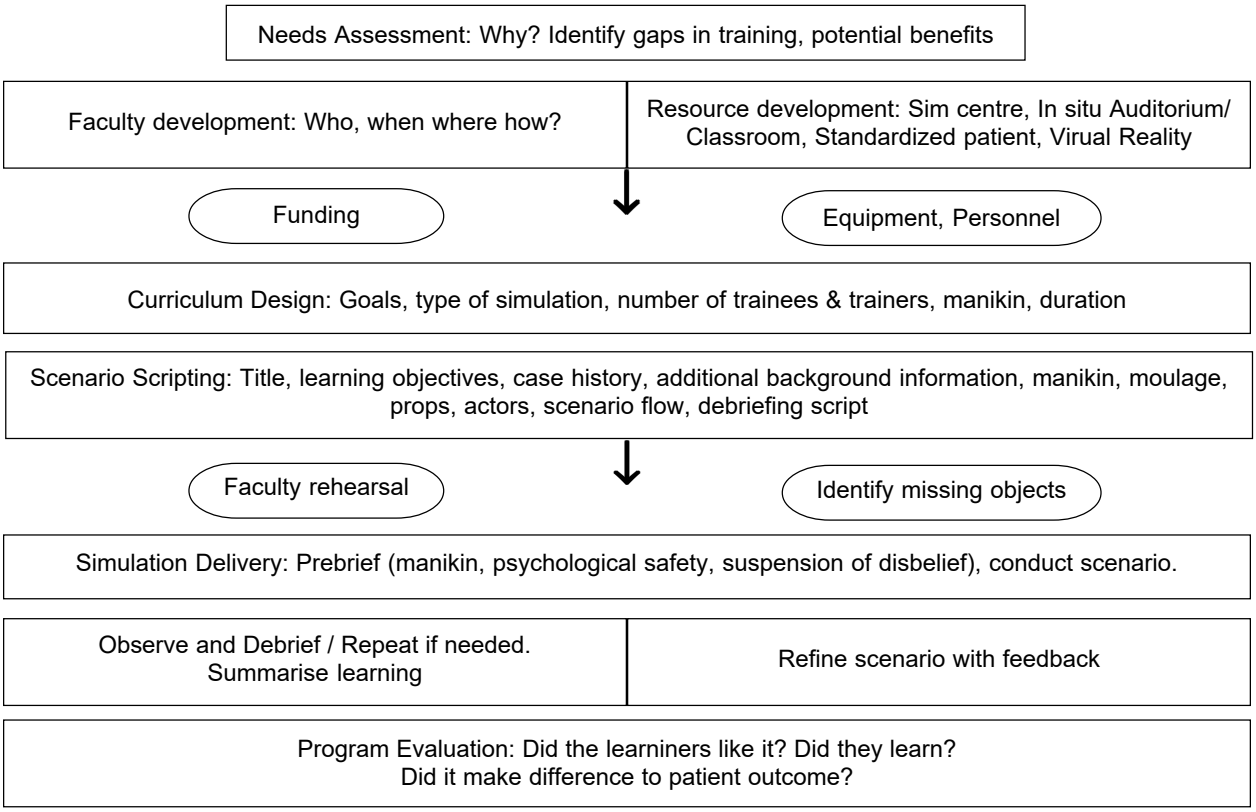


Fig. 2 *A road map for integrating simulation in medical education.*

Faculty development: This is the most vital part of a simulation program. There are 2 or 3-day simulation faculty development courses available, emphasizing curriculum development and debriefing followed by ongoing audit and mentorship.

Access to resources: Funding, identifying space, manikins, audio-visual aids, appropriate equipment to create a realistic patient-care environment, an enclosed observation room, debriefing room and personnel to manage the program are some of the resources required for a successful simulation program.

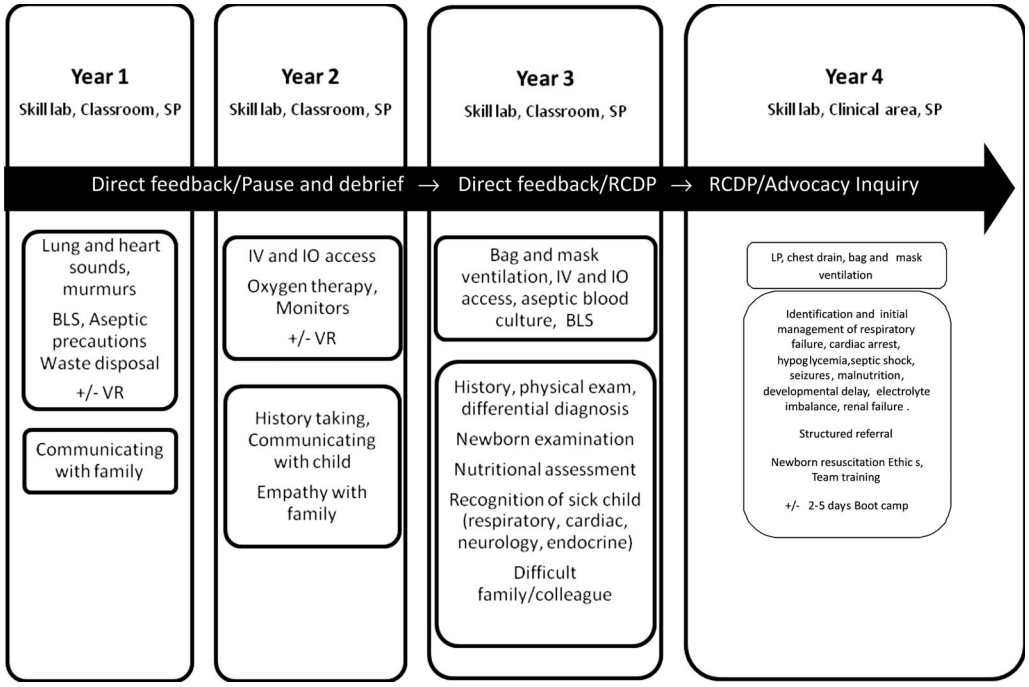
Curriculum design: SBE design involves appropriate needs analysis, clearly defined objectives, selection of the type of simulation, descriptions of learner and trainers, determination of place (simulation laboratory/in situ/other), identification of most appropriate simulation modality, decision about the duration of simulation, contextualized and validated evaluation tools, and any assessment needed. It is important to have specific and measurable objectives [17-19].

Scenario development: It involves scripting the scenario with a title, learning objectives, case history 'stem' to be told to the learners, manikin, props and moulages needed, additional background information for facilitators, scenario flow and debriefing script.

Delivering simulation: Prebriefing for psychological safety of the learners, introduction of the environment, parameters of simulation, capabilities of manikin, and suspension of disbelief about manikin is the key to facilitate learning during formative simulations. For immersive simulation, it is desirable that room should match the clinical area and instructors stay out of sight of the learners during the scenario. Appropriate audio-visual aids add realism to the scenario [18,19].

Debriefing: This is the heart of simulation and converts experience into learning. Learners are guided by a facilitator to reflect on their actions, reinforce correct responses, and plan for better performance. There are various types of debriefing techniques, including direct feedback, plus delta, pause and debrief, rapid cycle deliberate practice (RCDP) and advocacy inquiry [20-22]. Studies have shown that scripted debriefing might be more beneficial to novice faculty [23]. Attention is focused not only on 'what could be improved' but also 'what went well', and often asks learners to develop their own insights into 'why' processes went well or needed improvement.

Research, feedback and refinement: Research into the program to measure the impact of training and ongoing feedback to refine the curriculum and scripts are key for a successful simulation program, but must be carefully



SP: Standardized patient; BLS: Basic life support; VR: Virtual reality; IV: Intravenous; IO: Intra osseous; LP: Lumbar puncture; RCDP: Rapid cycle deliberate practice [21].

Fig. 3 *A guide to integrate simulation for pediatric medical students.*

Table I Suggested Solutions for Overcoming Barriers to Implement Medical Student Simulation

Faculty Training

- Create a central body to govern undergraduate medical simulation
- Collaborate with national and international simulation societies such as the All India Institute of Medical Science (AIIMS), International Pediatric Simulation Society (IPSS), International Network for Simulation-based Pediatric Innovation, Research and Education (INSPIRE)
- Implement tele-simulation with centres pioneered in simulation program.
- Provide incentives to faculty who become simulation facilitators - promotions, decreased clinical responsibilities

Curriculum development and scenarios

- Pilot in apex institutions and share curriculum with other institutions
- Collaborate with international bodies
- Create a pool of scenarios to be banked
- Develop national conferences on medical simulation, to bring together all trainers

Cost

- Pool resources. There are many large simulation labs which are not fully utilized
- Encourage realistic low-cost simulation
- Utilise Virtual reality, in situ and Standardised patient simulation modalities
- Develop 3-Dimensional printing and silicone casting
- Conduct research into developing indigenous low-cost high technology manikins
- Reserve high-cost manikins for specific learning circumstances

Large number of students, limited time

- Use classrooms for didactics followed by simulation so students can take turns learning by observation as well as participation.
- Encourage Virtual Reality
- Develop a library of simulation scenarios that can be re-used, so that subsequent simulation development takes less time

Research

- Form a national central governing body to supervise, encourage and fund simulation research
- Collaborate with organizations already working in this field like INSPIRE, SSH, PediSTARS.
- Publish national medical student simulation education journals

INSPIRE:International Network for Simulation-based Pediatric Innovation, Research and Education; SSH: Society for Simulation in Healthcare; PediSTARS: Pediatric Simulation Training and Research Society.

implemented to preserve psychological safety for learning.

A Framework to Implement Simulation-based-training in Pediatrics

MCI 2018 guidelines describe several competencies in the pediatric curriculum for medical students [4]. A stepwise approach starting with simpler skills in year 1, and adding more complex skills and scenarios in subsequent years would allow learners to build on skills they have developed (***Fig.* 3**). This will also allow trainers with specific skill sets to support skill training and reserve highly trained simulation educators for more complex simulation scenarios.

It is desirable to start with the highest priority competencies, such as identifying a sick child, performing basic procedures such as cannulation, intraosseous (IO) access, handwashing, aseptic precautions, waste disposal, and communicating effectively with families. Other competencies can be gradually integrated as a multistep process. Simulations such as history taking, airway management, basic life support (BLS), lumbar puncture, newborn examination, and nutritional assessment can focus on individual learning. However, emergency scenarios such as management of respiratory distress, cardiac arrest, septic shock, and seizures, and dealing with challenging families should be conducted as team training exercises so students can also develop skills in leadership, role allocation, calling for help, resource utilisation and providing clear instruction to colleagues [20].

Challenges

Faculty comfort will be a major challenge, because of the huge volume of students, the need for specialized training in simulation and a lack of time. Faculty development, manikin availability, cost, and access to space can be a

burden unless management and infrastructure support is available. Psychological safety for the students is extremely important to ensure learning from simulation, and this also applies to faculty who are developing their own simulation skills. Without psychological safety, both the learner and the program may be damaged.

Overcoming Barriers

A previous publication [1] called for exploring and embracing SBE in Indian subcontinent. After 4 years, it is exciting to witness incorporation of simulation by MCI in undergraduate curriculum and watch the breakthrough happening at some of the leading institutions in India. India is one of the most cost-effective countries when it comes to healthcare [24]. It is only a question of time for SBE to be applied across the country in medical education.

Creating a pool of highly trained faculty, optimizing low cost simulation opportunities, sharing resources, combining simulation with didactic classroom lectures [25,26], encouraging development of 3D printing, virtual reality [27], collaborating with simulation training organizations [28-30], and research into the impact of high-quality simulation-based training are some of the answers. Indian students deserve the best education platforms. ***Table*** **I** provides some insights into how we can make substantial progress.

CONCLUSION

It is now time for the much-needed paradigm shift – the time to incorporate simulation in medical education countrywide. It is no longer acceptable for our medical students to learn and practice on real patients, without first learning and training on simulated patients and situations. Simulation will never replace learning based upon exposure to real patients but will increasingly supplement and augment medical education in India. We need to think differently and be constructively disruptive as we develop simulation-based medical student curricula. The cost of integrating simulation into medical student education is modest compared to the potential number of lives saved and the joy of learning provided to our new generation of caring, able, deserving, and intelligent doctors.

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Half a Century With Pediatric Viral Encephalitis

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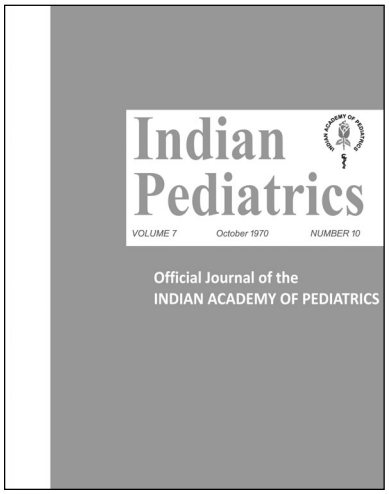
Periodic outbreaks of acute encephalitis regularly occur across India, leading to substantial mortality [1]. Japanese encephalitis (JE) has been the leading cause for the same [2,3], but the incidence of non-JE etiologies has been steadily increasing as well [1,4]. Even half a century back, pediatricians were struggling with this disease entity. We came across two articles from *Indian Pediatrics* archives dating back to 1970, and endeavor to describe the change in epidemiology and approach to viral encephalitis, over the past five decades.



THE PAST

Soon after Independence, there were many outbreaks of acute encephalitis in India. In 1954, Dr. Khan, while working at Tata Main hospital, Jamshedpur, described an epidemic, from Uttar Pradesh, Bengal and Bihar, of an acute encephalitic disease process, that predominantly affected children and had a high mortality rate. He undertook this work with Dr. Seal (Kolkata) and Dr. Work (Pune) [5,6]. This was the first reported epidemic of encephalitis from India.

Indian pediatricians have always been intrigued by this disease entity. During 1966-68, Balakrishnan, *et al.* [7] came across 72 consecutive pediatric cases of viral encephalitis. They published their experience in the April, 1970 edition of *Indian Pediatrics* [9]. They presented a case series of 19 clinically diagnosed pediatric viral acute encephalitis syndrome (AES) from Pondicherry. Cerebrospinal fluid examination was normal in a third of their cases, while echovirus-7 was isolated from CSF in 37% cases. Treatment offered by them 50 years back, was quite similar to what we offer today, including rehydration, nutrition by intravenous/enteral routes (nasogastric), antibiotics (tetracycline) and corticosteroids. But unfortunately, their mortality rate was quite high (79%).

Later, the same year (October, 1970), Athavale, *et al.* [8] published their experience with 125 children, who presented with meningoencephalitis, from erstwhile Bombay. Infectious etiological agents reported, included coxsackie (B4/B6) (12.8%), and echovirus (19/21) (12.8%). Their patient population had fever (91.2%, 45.8% high grade), altered sensorium (98/125) and convulsions (91/125) (1/3rd had persistent seizures). They observed that both presence of meningeal signs and absence of altered sensorium were associated with a better prognosis. They also defined a unique entity, acute fulminant meningoencephalitis (AFE) (disturbance in sensorium within 24 hours of onset), which was associated with terminal outcome.

Since then, acute encephalitis, predominantly attributed to Japanese encephalitis, has been reported from almost all states in India [3]. Enteroviruses [7,8] and Kyasanur forest disease [7] have also resulted in several outbreaks since independence.

THE PRESENT

This disease rattles the best brains even today. Worldwide, AES incidence varies between 3.5 and 7.4 per 100,000 patient-years [9]. But the mortality rate, has fortunately come down, to around 6% (National Vector Borne Diseases Control Programme (NVBDCP,2018) [3].

Across half a century, the etiology of AES is still predominantly viral. JE has continued to remain active, with recent outbreaks in Malkangiri [2012], Manipur (2016) and Delhi (2011) [10]. Amongst non-JE etiologies, enteroviruses (EV-71, coxsackie, echoviruses) [11,12], Nipah [13], Chandipura [14] and even dengue virus [12] are on the rise. Herpes simplex virus (HSV), the commonest cause of sporadic encephalitis worldwide, is still not as common in India [15]. Non-infectious causes have also been identified, as due to consumption of plant toxins (seeds of *Cassia occidentalis*, Cassia beans) (*kasondi* plant associated acute hepatomyoencephalopathy

[16] and litchi fruits (containing hypoglycin A and MCPG) (Muzaffarpur encephalitis) [17].

Pinpointing an etiological agent for acute encephalitis continues to be challenging, and may remain inconclusive in many cases. A detailed history, thorough physical examination focusing on level and localization of brain function, laboratory investigations, especially lumbar puncture, are very important in the treatment of the disease [15]. Nowadays, techniques such as enzyme-linked immunosorbent assay, molecular techniques like polymerase chain reaction (PCR) and dot blot hybridization are being increasingly used [18]. Advancement in radiological imaging has tremendously helped clinical decision making. Computed tomography scans in emergency situations, and magnetic resonance imaging when patients are more stable (especially with a diffusion weighted imaging and a gadolinium enhanced study), can help identify cerebral edema, and point towards a specific diagnosis.

Since viral encephalitis has a substantially high morbidity and mortality rate, primary prevention through immunization, holds a far greater promise than targeted therapy after disease infliction. Subsequent to the longest epidemic of JE in Gorakhpur (2005), mass vaccination against the same was introduced in endemic districts [10]. NVBDCP, launched in 2003-4, focusses on training staff at ground level (PHCs and CHCs) for early diagnosis and management. It also focusses on source reduction, especially vector control measures as water and hygiene practices, fogging, space spraying and antilarval measures [3].

THE FUTURE

Newer techniques as matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), unbiased high-throughput sequencing (HTS) and VirCapSeq-VERT (virome capture sequencing for vertebrate viruses) may hold promise for the future, in providing accurate and rapid epidemiological and virological data for acute meningoencephalitis patients [20,27]. More research is still needed for development of more robust vaccines with improved immunogenicity. Further strengthening of NVBDCP programs and surveillance measures will contribute towards controlling arboviral encephalitis.

Though, over past half century, we have progressed and reduced case fatality, the basic tenets of medicine, a good clinical history, and detailed serial neurological examinations and testing as CSF examination, remain the backbone for treating viral meningoencephalitis.

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Identification, Evaluation, and Management of Children With Autism Spectrum Disorder: American Academy of Pediatrics 2020 Clinical Guidelines

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The American Academy of Pediatrics recently published clinical guidelines for evaluation and management of children and adolescents with Autism Spectrum Disorder (ASD), nearly 12 years after the previous version. This article outlines salient features, highlights significant differences from the 2007 version, and discusses implications for Indian professionals dealing with affected families.

Keywords: *Dignostic tools, Investigations, Neuroimaging, Screening.*

The American Academy of Pediatrics (AAP) recently released clinical guidelines for the evaluation and management of children and adolescents with autism spectrum disorder (ASD) [1]. The previous 2007 guidelines covered both separately [2,3]. Many changes have occurred over the last 12 years: increasing prevalence; revised nomenclature and diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [4,5]; greater understanding of clinical profile [6], neurobiology and etiopathogenesis; advances in genetic testing [7]; evidence-based interventions; and a paradigm shift to family-centred therapy and holistic management throughout life. Understandably, there was a strong need for an update.

The increasing worldwide prevalence of ASD means primary care service providers (PCP) and pediatricians will encounter ASD routinely. Not only should we be competent enough to recognize, evaluate and establish diagnosis, we should be empowered to counsel, help families in decision making, and provide continual support. After outlining salient features of the 2020 guidelines and highlighting differences from the last one (***Tables*** **I** and **II**), implications for Indian professionals will be discussed.

Previously, increasing prevalence was attributed to growing awareness, improving surveillance and less misdiagnoses [2]. The present status (1in 59) of ASD in the US is also probably due to broadening of phenotype by DSM-5, universal surveillance and increased availability of services. Whether biological risk factors contribute to etiopathogenesis remains uncertain [1]. Earlier diagnosis is more common in higher socio-economic strata who have better access to services, while later identification is associated with milder manifestations. Clinical symptoms include core symptoms and co-existing conditions (medical, genetic, neuro-developmental, psychiatric and/or behavioral), the cumulative effect of which influence extent of social and functional impairment. The guidelines described these in-depth. They also emphasize the need for holistic evaluation and management to achieve best possible outcomes.

SCREENING AND DIAGNOSIS

The USA health system practices universal developmental surveillance with ASD-specific screening at 18 and 24/30 months. Earlier screening is indicated in high-risk individuals or when red flags for ASD are identified. Suspicion or parental concerns warrant in-depth evaluation. Establishment of diagnosis is primarily clinical, based on parental interview, personal observations and DSM-5 criteria. Though diagnostic tools are not mandatory, they help in extracting clinical information. Structured evaluation of behaviour, cognition, language, adaptive function, motor function, hearing, vision and sensory processing is recommended. Diagnoses established by the aforementioned comprehensive assessment in children under 30 months remain stable in ≥80% in adulthood.

Etiologic evaluation comprises of detailed history-taking and examination (anthropometry, dysmorphism, skin, neurologic and systemic). The indications for

Table I American Academy of Pediatrics Guidelines for Autism Spectrum Disorder (ASD)

Identification and evaluation; AAP, 2007 [2]	*Identification, evaluation and management; AAP, 2020* [1]
Clinical symptoms	
Cognitive impairment in 50%. Secondary ASD (10%) due to medical/genetic or environmental factors (more when severe delay and dysmorphism). Co-morbid conditions: seizures, gastrointestinal and sleep disorders, and challenging behaviors.	Cognitive impairment and minimally verbalin 30% each. Additional co-morbidities, other developmental/psychiatric (ADHD, motor coordination disorder, anxiety, mood disorders) and behavioral disorders (food refusal, pica, self-injury and aggression).
Screening and diagnosis	
Developmental surveillance existed, but few (8%) PCP practiced it. M-CHAT used.	Surveillance increased (75%). M-CHAT-R/FU used. Tools listed for younger ages.
Clinical diagnosis by DSM-4. Focus on category of severity, functional impairment & etiology (mainly by experts).	Clinical diagnosis by DSM5. ADI-R, ADO-S, CARS-2, SCQ and SRS may be used. Evaluation (*see text*) by PCP and experts.
Etiologic evaluation	
• High resolution karyotype; • DNA tests for FXS in all cases with GDD/ID; • *MECP2* analysis in Rettsdisorder.	• Discuss chromosomal microarray; • Discuss tests for Fragile X Syndrome; • Consider *MECP2* sequencing, if applicable • Consider WES and genetic referral.
Recurrence rate 2-8% in idiopathic ASD, higher/lower in secondary ASD.	Empirical, 4-14% if one previously affected child, 32-36% if ≥2 affected children.

Prepared from Hyman, et al. [1] and Johnson, et al. [2].ADHD Attention deficit hyperactivity disorder; ADI-R Autism diagnostic inventory-revised; ADOS-2 Autism diagnostic observation schedule, 2nd edition; CARS-2 Childhood autism rating scale, 2nd edition;, M-CHAT: Modified checklist for autism in toddlers, R/F Revised with follow-Up;MECP2: Methyl CpG-binding protein 2; SCQ: Social Communication Questionnaire; SRS: Social responsiveness scale; WES: Whole exome sequencing.

magnetic resonance imaging (MRI), electroencephalography (EEG) and metabolic testing remain individualized, with provision of more details. Genetic evaluation is recommended in all. The advantages of establishing genetic etiology include accuracy in counselling, possible specific therapy, avoiding unnecessary testing, and increased family acceptance.

Interventions

The goals remain minimizing core deficits, eliminating maladaptive behaviour, and maximizing functional independence. Intervention should be "individualized, developmentally appropriate and intensive" [1]. Periodic documentation of performance is required for monitoring response. The caveat that all interventions should be evidence-based has been added, with enumeration of characteristics of effective intervention.

Some sections *i.e.*, models of early intervention and education, psychopharmacology and complementary alternative therapy (CAM) are quite technical, since the basics were extensively explained in the previous guidelines. Hence, non-experts may not understand them unless they read the earlier version. Management of medical conditions, social skill instruction, speech and language therapy, motor therapy (including occupational therapy) and sensory therapies (the supportive evidence of which is still low) are given in greater detail.

Evaluation of maladaptive behavior and psychiatric conditions are separate and described with respect to the atypical development of ASD. The psychopharmacology section details principles of prescription and lists medications according to behavior-symptom cluster. The emerging role of psycho-pharmacogenetic testing is mentioned. According to the new guidelines, if a family opts for CAM, safety and effectiveness requires monitoring.

Working with Families

The USA'Medical home' model for primary care aims at "accessible, continuous, comprehensive, family centred, coordinated, compassionate, and culturally sensitive health care for all children and youth, including those with special needs" [8]. Though recommended for ASD since 2007, the process was not well-defined. The latest guidelines aim at better PCP and caregiver partnership, revolving around shared decision-making. Resources have been developed for pediatricians to enable them to deal with emerging issues, counsel effectively, provide parents with information and direct them towards advocacy and support groups. It is envisioned that this will result in easier handling of challenges, smoother transitions during adolescence (higher education/vocation, sexuality) and

Table II American Academy of Pediatrics Guidelines for Autism Spectrum Disorder (ASD)

Management; AAP, 2007 [3]	*Identification, evaluation and management; AAP, 2020* [1]
Interventions	
Principles, components and curricula used in early intervention are well explained.	This continues without alluding to the basics and hence may appear more technical.
Educational models have been named but not explained. Differences between programs by age (younger *vs* older) given.	More details are presented. Emphasis is on classroom models, less restrictive settings and development of social skills.
Speech and language approaches named but not explained. Brief mention of occupational and sensory therapy.	Details of language behavior and techniques included. Stress given to developing skills for conversing. Motor component new.
Management of concurrent medical conditions like seizures, gastrointestinal symptoms and sleep problems detailed	Management of feeding disorders, obesity, pica, dental health, wandering and motor disorders have been added
Challenging behaviors were included as a sub-group of medical problems and also in the section of psycho-pharmacology.	Behavioral and psychiatric disorders well described.Screening for behavioral and emotional problems (including depression > 12 y) advised.
Clinical approach to psycho-pharmacology explained step-wise.	Focus is on principles of prescription and drugs listed by behavior-symptom cluster.
CAM categorized as biological and non-biological groups	CAM grouped as natural products, mind and body practices, and others
Working with families	
PCP responsibilities include provision of longitudinal support to families, handling crises, providing emotional support and referring them for counselling, medical and/or mental health services if required.	Approaches have been devised at various levels for capacity building of PCP and promotion of professional-family partnership to provide patient and family centered care as well as promoting research.
Research and service needs	
Not included in the previous guidelines	Seven broad research areas identified

Prepared from Hyman, et at. [1] and Myeos, etal. [3]. CAM: Complementary alternative medicine; PCP: primarycare service provider.

adulthood (employment readiness, medical care, legal guardianship and living arrangements), and better understanding of ASD related rights and laws.

Research and Service Needs

Key areas identified to direct focus of funding include, basic and translational science (genetics, epigenetics, neurobiology, psychopharmacology), clinical trials for focussed interventions, epidemiological surveillance and implementation research for health care services.

Implications for the Indian Setting

These guidelines have brought our existing lacunae to the forefront. Few pediatricians routinely practice developmental surveillance. Though DSM-5 and indigenous Indian tools are used for diagnosis, and intervention centres have been established all over the country, there is wide variability in skills and availability of multi-disciplinary professionals dealing with ASD, inconsistency in practice protocols, and minimal quality checking. National Trust workshops are infrequent and primarily related to disability certification. Consensus statements and clinical practice guidelines framed by expert bodies [9,10] sensitize professionals, but do not focus on capacity-building.

Given these challenges, the provision of easily accessible, family centred, individualized and intensive, multi-disciplinary intervention according to these recommendations (but tailored to Indian settings) to all affected families is still a distant goal. The need of the hour is planning and implementing evidence-based concrete strategies that will enable professionals dealing with ASD to provide global standards of care to these children and their families.

Quality improvement, collaboration and integration is required among the health, education, social welfare and public health systems to provide evidence-based, universal care to children/adolescents and families affected by ASD. The 2020 guidelines outline strategies for capacity building of PCP to support this vulnerable population from suspicion of ASD, through diagnosis and service provision, to adulthood.

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A Preliminary Report of COVID-19 in Children in India

We describe the profile of COVID-19 in children from India in this multicentre observational study from tertiary care hospitals in West Bengal. Data of children up to 12 years presenting with positive results on SARS-CoV-2 RT-PCR test were included. The median (IQR) age of the 41 patients included was 1 (0.42-5.0) year. Eleven (26.8%) patients, including 6 neonates, never showed any symptoms. Fever was seen in only 9 patients (21%), and co-morbities were found in 61% of patients. There was one death.

Keywords: *Co-morbidities, Course, Management, Outcome.*

The clinical profile of Corona Virus Disease 2019 (COVID-19) infection in children is variable, and information from developing countries is not readily available, except for China [1]. We report a series of pediatric cases of COVID-19 from eastern India.

We collected data of children younger than 12 years admitted in tertiary care institutes, including COVID designated hospitals, of West Bengal. The children were included after obtaining parental consent, if they had a positive RT-PCR test report for SARS-CoV-2. The study was conducted from March, 2020 to June, 2020. Ethical permission was sought from the institutional ethics committee.

RT-PCR for SARS-CoV-2 in an Indian Council of Medical Research (ICMR) approved medical laboratory, data regarding clinical details, exposure history, hospital course and outcome were collected in pre-designed proforma. The records were entered and updated by pediatric residents and subsequently reviewed by a senior pediatric faculty of the institute. Data were compiled in Microsoft Excel spreadsheet and summarized.

We studied 41 patients (24 boys) with the median (IQR) age of 1 (0.42-5.0) year. Majority of the cases, 40 (97.6%) were successfully discharged, with one death. We had 6 neonates with COVID-19, all of whom were born to SARS-COV-2 positive mothers and were asymptomatic. Of the rest, five patients never showed any symptoms throughout the period of isolation, while 14 (34%) were mildly symptomatic in the form of common cold and rhinorrhea. Fever, which is perceived to be a major presenting feature of COVID-19, was seen only in 9 patients (21%).

Two cases had multi-system involvement in the form of an atypical Kawasaki disease-like presentation. Almost 61% of the cases had associated co-morbidities (***Table* I**). Eleven (26.8%) patients needed no active management, 34% mildly symptomatic children needed nasal drops and anti-histaminics, 24.4% required oxygen inhalation, 4.9% were put on high flow nasal canula (HFNC) and 4.9% needed mechanical ventilation. Six (15%) patients required intensive care. Of the study population, only 63.4% had a positive contact history. One child died in this series due to type II respiratory failure with septic shock in a case of post adenoviral bronchiolitis obliterans and hypoxic brain injury.

Our study found that the clinical course of COVID-19 in children appeared to be less severe than that reported in adults, which is consistent with other reports published on COVID-19 in children. We also found that co-morbidities were more prevalent (61%) in the 41 children hospitalized with COVID-19 [2]. Comorbidities among children with COVID-19 were reported in all patients from China [3] but in 83% of those in US and Canadian intensive care units [4].

Some studies [5] have raised concerns about the appearance of a novel severe Kawasaki-like disease in children in association with SARS-CoV-2 infection [6]. Our study also

Table I Characteristics of Children With COVID-19 (*N*=41)

Characteristics	*No. (%)*
Age group	
<28 d	6 (14.6)
28 d -<1 y	12 (29.3)
1-5 y	15 (36.6)
6-10 y	6 (14.6)
>10 y	2 (4.9)
Symptoms[*]	
Asymptomatic	11(26.8)
Mildly symptomatic	14 (34.1)
Respiratory distress	13 (31.7)
Fever	9 (21.0)
Cough	5 (12.1)
Diarrhea	3 (7.3)
Rashes	2 (4.9)
Co-morbidity	25 (60.9)
Malignancy	8 (19.5)
Hematological disorders	5 (2.2)
Congenital heart disease	4 (9.7)
Neurological abnormalities	4 (9.7)
Chronic lung disease	2 (4.9)
Multiple congenital anomalies	2 (4.9)
Respiratory support	
Oxygen	10 (24.4)
High flow nasal cannula	2 (4.9)
Ventilation	2 (4.9)

[*]*Shock, convulsions and sepsis like illness were present in one child each.*

had two such cases with multi-system involvement in the form of an atypical Kawasaki - like presentation, similar to previous Indian reports [7].

In a recent meta-analysis, Meena, *et al*. [8] analyzed data from 27 different studies (4857 patients). They showed that even among the symptomatic COVID-19 cases, severe manifestations are fewer in children. They found that fever and respiratory symptoms are most common, although many children had gastrointestinal manifestations [8].

The study has its share of limitations of small sample size and lack of long term follow up of co-morbidities after discharge. In spite of these shortcomings, this study provides preliminary data on characteristics and outcomes of COVID-19 in children from India.

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Effect of Robot-Assisted Gait Training on Selective Voluntary Motor Control in Ambulatory Children with Cerebral Palsy

This pilot study investigated the efficacy of a four week robot-assisted gait training in twelve children with spastic diparesis. Short-term results and a 3-month follow-up showed statistically significantly increased selective motor control, walking farther distances, gross motor score, and decreased joint contractures.

Keywords: *Cerebral palsy, Gait, Joint range of motion, Lokomat, Motor control*,

Cerebral palsy affects movement and posture, resulting in a limited activity that is attributed to non-progressive disturbances occurring in the fetal or infant brain [1]. Since robot-assisted gait training (RAGT) induces changes in the brain plasticity, it appears promising in improving gross motor control of CP children with cerebral palsy [2-4].It could be hypothesized that RAGT can affect impaired selective voluntary motor control (SVMC), which is the inability to activate muscles to achieve a voluntary posture or movement [5]. Therefore, this pilot study investigated the efficacy of RAGT as monotherapy on lower limb SVMC, joint range of motion (ROM), walking ability, and gross motor measures.

The study received ethics committee approval from participating institutions. All parents and children provided written informed consent for participation. Twelve children [mean (SD) age, 10.9 (3.3) year; 2 girls] were tested at the baseline, after four weeks of intervention, and at 3-month follow-up. Children with spastic diparesis with toe-walking and/or scissoring patterns aged between 5-17 years were recruited. Only children who could attend the 4-week RAGT program regularly were enrolled. Children were excluded if

they had used any muscle relaxants within the previous 6 months or had orthopedic surgery within the last year [2-4].

Standardized, validated questionnaires and evaluations [5-8] were used: goniometry, Selective Control Assessment of Lower Limbs Evaluation (SCALE), D and E parts of Gross Motor Function Measurement (GMFM), 10-meter walk test (10MWT) and 6-minute walk test (6MWT). During walking tests, all children wore footwear and orthoses, if regularly used. For SCALE, children performed isolated movements of the hip, knee, ankle, subtalar, and toe joints. Scores were assigned as: normal - joints moved selectively within at least 50% of the possible ROM, and at a physiological cadence; impaired - movement performed slower below 50% of ROM, with mirror and/or synergistic movements; or unable - no joint movement performed or synergy patterns present. Pre-post intervention goniometry and SCALE evaluations showed bilateral asymmetries in lower limbs across all children. Asymmetries were recorded as 'more impaired limb (MIL)' and 'less impaired limb (LIL)'.

The Lokomat Pro device (Hocoma AG, Volketswil, Switzerland) was used [9]. Children attended 20 sessions scheduled on 20 consecutive working days. Therapy ranged 30-45 minutes and progressively increased by at least 3 minutes every other day [mean (SD), 39 (6) minute]. Walking speed [mean (SD), 1.4 (2.38) km/h] was set individually. The walking distance [mean (SD), 969 (172) meter] was gradually increased every other day by at least 50 meters. All children had an initial level of 50% body-weight support [mean (SD), 14.8 (4.76) kg], which was gradually decreased every other day for each child until the knee did not start to collapse into flexion during the stance phase.

Data were analyzed in MatLab (Mathworks Inc., USA). Shapiro-Wilk test (0.05 significance level) showed abnormal data distribution. The Wilcoxon sign rank test was used for the LIL and MIL, separately [10]. Spearman correlations were calculated for the following: goniometry/SCALE, GMFM D, E/10MWT, and GMFM D, E/6MWT.

Hip joint flexion contractures decreased bilaterally by 10° (P=0.004). Internal hip rotations decreased by 10° in LIL and 15° in MIL (P=0.002). Ankle dorsiflexion improved bilaterally by 10° (P=0.001). SCALE scores increased by 1.5 in LIL and 2.5 points in MIL (P=0.001). The 6MWT walking distance increased by 75 meters (P=0.001). 10MWT showed no significant change (P=0.89). GMFM-D improved by 8% (P<0.001) and GMFM-E by 6% (P=0.002). Correlations were found only between GMFM D, E scores and walking tests (rho=-0.614-0.784;P<0.05). Increased GMFM scores correlated with decreased time in 10MWT, and increased walking distance in 6MWT. There was no significant difference in short-term and 3-month follow-up data (P>0.05) across all measures.

Since active training seems to be more effective than passive training for motor learning and cortical reorganization in central motor impairments [2-4,9], RAGT likely improved motor control of CP children due to active training performed with a high-repetition-rate of guided movements in the most neutral pelvis and lower limbs position. To the best of our knowledge, this is the first study suggesting that RAGT improves SVMC and decreases hip joint internal rotation contractures. We support the previous results that CP children increased walking distance following RAGT [2-4]. It has been shown that the combination of RAGT and physiotherapy improves GMFM D,E scores [2-4].

Our outcomes suggest that although expensive (~300,000 Euro), RAGT, which is primarily used in rehabilitation centers, can improve D, E scores even when used as a stand-alone therapy. Although this study provides a foundation on which future studies can be built on, RAGT should be investigated over longer periods in different populations to further determine its effectiveness.

Ethical Approval: (*i*) Charles University, Prague, the Czech Republic (number 120/2015) dated August 12, 2015, and (*ii*) University Rehabilitation Institute, Ljubljana, the Republic of Slovenia on October 5, 2015.

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Pediatric Papilledema at a Tertiary Care Ophthalmological Center

Pediatric papilledema is usually asymptomatic and is diagnosed on routine screening. We conducted a retrospective study to evaluate pediatric papilledema with respect to presentation, etiology and treatment at the neuroophthalmology clinic of a tertiary care eye institute.19 of the 24 children studied had Idiopathic intracranial hypertension.This study stresses upon the interdisciplinary approach for prompt diagnosis and treatment of papilledema.

Keywords: *Diagnosis, Idiopathic intracranial hypertension, Management, Referral.*

Papilledema is defined as optic disc edema secondary to high intracranial pressure, the etiology for which may be known or unknown (idiopathic) [1]. Idiopathic intracranial hypertension (IIH) is typically defined by exclusion using modified Dandy criteria [2]. IIH typically affects obese women of childbearing age, but it may be seen in patients of any age or weight [3]. Obesity and weight gain appear to be risk factors during adolescence but not in pre pubertal age group [4]. Pediatric IIH is diagnosed in many asymptomatic children during a routine encounter [5].

Pediatric central nervous system tumors are the second most common childhood malignancies, and hence is a major etiology of pediatric papilledema. The purpose of this study was to evaluate papilledema in the pediatric age group at the neuro-ophthalmology clinic of a tertiary eye care center.

A review of hospital records of papilledema patients in the pediatric age group (<15 years) was done for the period January, 2016 – December, 2018. Patients with pseudo papilledema and those on previous treatment were excluded from the study. We reviewed the case records of all the patients and extracted information on age and symptoms at presentation, best corrected visual acuity, pupillary response, extraocular movements, diplopia, fundus biomicroscopy and optic disc findings at presentation. Body mass index was calculated for all the patients. Pre pubertal age was considered to be less than 11 years and pubertal between 11 and 15 years. Best corrected visual acuity was measured using Snellen optotypes and visual field was tested using Bjerrums kinetic perimetry. Neuro-imaging of brain (magnetic resonance imaging (MRI) or MR venogram) findings and serological evaluation including complete hemogram, thyroid function tests were recorded. Results of lumbar puncture and cerebrospinal fluid analysis were available for only one patient, due to lack of consent in others.

Twenty-four patients met the inclusion criteria and the mean age was 11.3 years, youngest was a 2-year-old child. Girls were more frequently affected (13, 54.1%). The commonest presenting symptom was headache **(***n*=12**)**, followed by double vision (*n*=7), and defective vision (*n*=6). Few patients presented with sudden onset of ocular deviation (*n*=2), pain on eye movement (*n*=2), radiating neck pain (*n*=2) and frequent blinking (*n*=1). Best corrected visual acuity remained 20/20 in 18 of our patients in both eyes, while 6 (25%) patients presented with visual morbidity. Of those, three had IIH and others were due to secondary causes. Pupillary examination and color vision remained normal in all our patients except in one diagnosed with craniopharyngioma. Sixth nerve palsy was seen in 12.5% (*n*=3) of patients,and 87.5% (*n*=21) patients had enlarged blind spot on visual field assessment. Overall, 23 (96%) patients had bilateral disc edema and one had unilateral disc edema on fundus examination. The most common etiology in our population was found to be IIH in 79% (*n*=19), intracranial tumors in 12.5%, and the rest falling under infective etiology and obstructive hydrocephalus (***Table*I**).

IIH in children and adolescents is relatively uncommon and may be associated with puberty and resulting hormonal changes

[6]. In pre-pubertal children, IIH appears to be even less frequent;we found three girls and three boys each in the pre-pubertal age. Children with IIH are reported to have an equal sex distribution [7], though we found a male female ratio of 1:2. Affected adolescents of IIH tend to be overweight, but obesity and weight gain do not appear to be risk factors [8]. In our series one girl was obese, two were overweight; one of whom was in pubertal age. Acute headache and double vision were the common symptoms on initial presentation and none of our patients were picked upon routine examination. We had three patients with sixth nerve palsy as false localizing sign, who presented with sudden squinting.

Visual loss has been reported to occur in children with IIH. Pediatric IIH is just as threatening to vision as the adult form [6], in our study we encountered visual morbidity in three of our patients. Enlarged blind spot, which has been reported to occur in virtually all eyes with papilledema,was found in our patients also. Accurate visual field testing in children is sometimes difficult to perform, and hence difficult to rely on as the only accurate test. We suggest performing a kinetic perimetry in young and uncooperative children. Symmetric papilledema was recorded in eighteen children and one boy had unilateral papilledema.In this series, all our patients were referred to neurophysician and medically managed with oral acetozolamide and responded well to treatment. None of our patients needed Optic nerve sheath decompression.

Brain tumors with the greatest direct threat to the visual pathways are tumors that involve the optic pathway, parasellar tumors, and cerebral hemispheric tumors [8].We had one patient with pilocytic astrocytoma, the commonest cerebral hemispheric lesion which causes vision loss due to secondary optic atrophy following papilledema. Craniopharyngioma, the most common supratentorial tumor of childhood exhibits a bimodal age distribution. In our series, it was diagnosed in a 15-year-old boy with chronic visual deficit in one eye with papilledema [9].Though tuberculosis is common in India, tuberculous brain abscess is rare [10].Our patient with multiple tubercular cerebral abscess and midline shift had papilledema as the primary manifestation and was treated with anti-tuberculous therapy and recovered completely.

In summary, IIH is a common cause of papilledema in Indian children, and they are mostly symptomatic during presentation and respond well to medical management. Prompt diagnosis and proper management can prevent needless blindness resulting from secondary optic atrophy and also play a significant role in saving the life of children. This study emphasizes that ophthalmologists play a key role in monitoring for visual morbidity following papilledema and also stresses upon the interdisciplinary approach for prompt diagnosis and treatment of papilledema.

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Noonan Syndrome in Thai Children

This study describes clinical features of Noonan syndrome and gene mutations, including *PTPN11, SOS1*, and *BRAF* in the Thai population.Widely spaced eyes were the most common finding from the digital facial analysis technology used in this study.

Keywords: *Facial analysis technology, Gene mutation, PTPN11*.

Noonan syndrome is a genetic disorder with an estimated prevalence of 1 in 1,000 to 2,500 live births [1]. The typical facial features include ptosis, widely spaced eyes, down slanted palpebral fissures, and low set ears [2]. Early and accurate diagnosis of NS is essential as each patient needs an individual treatment regimen, and has distinct recurrent risk and prognosis [3]. Due to limited resources for genetic testing for the disorder, facial analysis technology may be useful to identify new cases. The digital facial analysis technology has previously been used to identify individuals with Noonan syndrome from 20

countries. The sensitivity and specificity of the test for Noonan syndrome in the Asian population was reported to be 0.95 and 0.90, respectively [5]. This study reports common physical findings with the facial analysis technology evaluation and genetic testing in children with Noonan syndrome in Thailand.

Participants were enrolled at Chiang Mai University Hospital including patients with clinical features of Noonan syndrome, and those without these features as controls. Informed consent was obtained from all participants. Medical records were also reviewed, and photographs of patients were sent to the Children's National Hospital for analysis *via* secure encrypted email.

Participants were 12 children (4 females) with clinical features of Noonan syndrome. The mean (SD) age was 5.19 (4.53) year (range 3 month – 17 year). Nine children were further evaluated by the digital facial analysis technology (Case No.1-9) and 7 cases (Case No.1-4 and 10-12) were identified by gene sequencing. The details of 12 individuals are shown in ***Web Table* I**.

Hypertrophic cardiomyopathy (HCM) was the most common cardiac defect found in this study, followed by pulmonary valve stenosis (PVS) and atrial septal defect (ASD). Novel gene mutations were found in 57.1% cases with gene sequencing identification. Three genes that carried mutations were *PTPN11* (71.4%), *SOS1* (14.3%) and *BRAF* (14.3%).

The most common phenotype from the digital facial analysis technology in this study is widely spaced eyes, which is consistent with a previous study [5]. Significant different texture features of Thai patients with normal controls were the texture at upper eyelid (P=0.004), nose apex (P<0.001), cupid's bow (P=0.005), oral commissure (P<0.001), center of ala of the nose (P=0.003), and nostril (P<0.001).

The frequency of cardiac defect is different from a previous report from China [6], which found ASD as the most common defect (50%), followed by PVS (20%). Isojima, *et al*. [7] found that PVS was the most common cardiac defect in Japanese patients (52.6%), followed by HCM (27.3%) and ASD (21.4%) [7]. Despite these variations, the three common defects in Noonan syndrome are HCM, PVS, and ASD [8].

Most patients had *PTPN11* gene mutation, similar to the study by Tartaglia, *et al*. [9]. De novo mutations account for 57.1% of cases, consistent with a previous study, which found 60% of cases with novel mutations [10].

As identification was done by clinical features, only severe phenotypes were included in the evaluation by the facial analysis technology or gene testing. Lastly, complete genetic testing for all cases with the facial analysis technology would provide more information adding to the clinical features.

This study describes clinical features of Noonan syndrome and gene mutations in the Thai population. The feature of widely spaced eyes was the most common facial appearance found by digital facial analysis technology. This may be a helpful clue in suspecting Noonan syndrome by clinicians.

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COVID-19 in a Child With Diabetic Ketoacidosis: An Instigator, a Deviator or a Spectator

We report severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) precipitated diabetic ketoacidosis in a child with newly diagnosed type 1 diabetes mellitus with mild hyperinflammatory syndrome leading to fluid responsive shock.

A 15-year-old previously asymptomatic girl presented to the emergency department in the first week of May, 2020, with complaints of acute onset of abdominal pain and vomiting. At the referring hospital, she was noted to have hyperglycemia and severe metabolic acidosis (pH 6.9, bicarbonate 2 mEq/L). She was initiated on a fluid bolus and was referred to our center.

On admission to the pediatric intensive care unit, the child was observed to be lethargic (GCS-14). On clinical examination, she had normal blood pressure with heart rate of 140/minute, cold extremities, tachypnea (respiratory rate 40/minute) and Kussmaul breathing. She had short stature (with a height of 145 cm, <-2 SD) normal body mass index (19 kg/m^2), and nofeatures of insulin resistance. Systemic examination was unremarkable except for mild generalized abdominal tenderness. Her blood investigations revealed random blood sugar of 414 mg/dL, neutrophilic leukocytosis, and serum potassium was 2 mEq/L. Her urine showed 4+ ketones, and arterial blood gases were suggestive of severe compensated metabolic acidosis (pH=7.03). Her HbA1C was 13.5%.

Fluid deficit replacement followed by insulin infusion at 0.1unit/kg/hour was initiated. Over the next 6 hours, the blood sugars began normalizing at a rate of around 50 mg/dL per hour; however, severe metabolic acidosis persisted. This was accompanied with a clinical deterioration of sensorium and onset of shallow breathing pattern with a rapid rise in partial pressure of carbon dioxide (pCO_2) and oxygen desaturation on arterial blood gas, requiring the initiation of non-invasive ventilation. A chest radiograph at the time revealed low volume lung with mild bilateral haziness. In view of the possibility of cerebral edema, 3 mL/kg of 3% sodium chloride was infused over 20 minutes, and fluid intake was optimized. With these measures, sensorium, pCO_2 and oxygen saturation improved. The nasopharyngeal swab reverse transcriptase polymerase chain reaction, done as per institutional protocol for all inpatients, was positive for SARS-CoV-2. Oral hydroxy-chloroquine (6.5 mg/kg twice daily for 1 day followed by 3.25 mg/kg twice daily for 4 days) was added to the treatment regimen. She had a low grade fever on the second day of admission, which was managed symptomatically.

By the third day, the child's sensorium had significantly improved and glycemic control had been achieved and she was weaned to high flow nasal cannula. However, during the course of the day she developed tachycardia, decreased urine output and sudden onset hypotension requiring two normal saline boluses of 20mL per kg to restore her circulatory status. Following the fluid resuscitation, there was worsening of the base line tachypnea without the requirement of supplemental oxygen. A rise in creatinine to a maximum of 2 mg/dL from a baseline of 0.4 mg/dL was also documented which took two days to normalize despite optimal fluid status maintained by intravenous fluids and nasogastric tube feeds. Despite good control of blood sugars and resolution of ketonuria, the child was noticed to have persistent severe metabolic acidosis and hyperchloremia which gradually improved over the next four days. By day 5, acidosis and appetite improved, hence she was switched over to 3-hourly subcutaneous insulin according to a sliding scale for the first day followed by basal bolus regimen and was discharged after 14 days of hospital stay.

There have been many reports on new onset diabetes in SARS-CoV-2 positive patients as well as worsening of glycemic control in those with preexisting diabetes mellitus [1]. However, majority of the world wide data point towards type 2 diabetes, with only a few anecdotal reports of COVID-19 infection in individuals with juvenile diabetes [2]. The expression of angiotensin converting enzyme 2 (ACE-2) receptors on pancreatic β cells can lead to direct injury to pancreatic beta cells and decreased insulin secretion which might then precipitate ketoacidosis [3].Similar cases have been reported in the viremic phase of other viral illnesses like H1N1 too [4].

Multiple questions regarding the association of COVID-19 and diabetic ketoacidosis remain unanswered such as precipitation in a child with previously undiagnosed diabetes (suggested by a highly elevated HbA1c level); the cause of circulatory collapse despite adequate initial fluid resuscitation, and the mechanism of renal injury (prerenal) seen in the child. Although GAD antibodies were negative, absence of obesity, markers of insulin resistance and negative family history favored the clinical diagnosis of type 1 diabetes.

The COVID infection most probably also triggered the hyperinflammatory response in the child leading to third spacing and the fluid responsive shock with subsequent early acute tubular necrosis and mild acute kidney injury [5]. The circulatory collapse was observed to occur in the first 4-5 days of illness in the patient which probably coincides with the peak of viremia. The increased work of breathing during the fluid resuscitation also points towards the need of slower and judicious fluid resuscitation in diabetic ketoacidosis or shock, especially in the setting of COVID- related pulmonary capillary leak. Lastly, the hyperchloremic metabolic acidosis took more than 96 hours to get corrected in spite of tailoring the chloride content of iv fluid which is an unusual and atypical pattern. The

above clinical presentation may fit into a pediatric inflammatory multisystem syndrome (PIMS) associated with COVID-19 [6]. However, further data is required to shed light on the complex and varying presentations of coronavirus infection in children with and without associated co-morbidities.

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Managing Children with Special Needs in COVID-19 Times

Children with special needs are facing additional predicament of understanding and dealing with the challenges brought about by the ongoing pandemic due to their unique health conditions. We herein, underscore some of the important issues.

Challenges: Interruption of requisite therapies can have long-term consequences on children with developmental disabilities. Cessation of regular physiotherapy may worsen functional ability and cause complications like hip dysplasia in children with cerebral palsy [1]. Lack of a daily schedule can be challenging for children with autism who require reliable routines, resulting in irritability and temper tantrums. Lack of understanding of the effects of pandemic, resistance to change and inability to adapt to new strategies can lead to pre-existing behavioral problems intensifying or development of novel ones in these children, especially those with autism and intellectual disability. Children with attention deficit and hyperactivity disorder (ADHD) and learning disorder may not be able to make effective use of online school sessions due to poor attention span or difficulty in comprehension [2]. Additionally, children with disabilities are at a greater risk of contracting Covid-19 because of their health-related challenges and inability to understand and follow recommended measures for infection control [3,4].

Parents of these children are also facing tough times. Their children's health related stress, which was earlier shared between parents, schools and therapy centers, has to be dealt with by them alone. Perception of delay in child's progress, inaccessibility to remedial services along with economic constraints due to lockdown and inability to engage children in activities throughout the day may impose a huge mental burden. Thus, mental health counselling for parents is an additional intervention required.

Suggestions for care: Since children with special needs may not be able to follow the standard respiratory etiquette like wearing of masks and social distancing due to their health conditions and behavioral issues, parents can create a circle of protection for their children by stringently following safety measures. Visual charts for hand hygiene and social distancing may help children with autism and intellectual disability. For children with visual impairment clear verbal instructions along with physical prompts can help [4]. Along with this, disinfection of the adaptive devices like wheelchairs, orthotics, hearing aids etc. should be stressed upon.

Parents should try to maintain some schedule for their children by following online school sessions and engaging them in fun based household chores. Wherever possible, these children should be encouraged to continue social interaction through supervised telephonic and video calls. Avoiding extra demands and unrealistic expectation from children during these times may help in eluding frustration and behavioral issues.

As far as possible, clinical focus of specialised treatment should shift to telehealth services and 'virtual first' approach must remain standard practice [5]. Tele-intervention is a viable service model for continuing intervention in children with disabilities. Apart from questionnaire-based assessments and guided therapies, it can be helpful for giving psychological support to the families and thus reduce chances of abuse and neglect.

To summarize, during the current pandemic when accessibility to essential services is difficult, children with disabilities and their parents are a high-risk group for various physical and mental health issues, and need appropriate guidance and support.

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Diverse Pathophysiology of Sudden Unexpected Death in Epilepsy in Children

We read with interest the review article by Garg and Sharma [1] on sudden unexplained death in epilepsy (SUDEP) in the pediatric population. We have the following comments.

A pathophysiological mechanism of SUDEP not considered by the authors is Takotsubo syndrome, also known as stunned myocardium or broken heart syndrome. Takotusbo syndrome is an acute onset, usually reversible cardiomyopathy, mainly of the left ventricle, morphologically and functionally characterized by focal or global dyskinesia, hypokinesia, or akinesia of the left ventricular myocardium, resulting in low output failure [2]. Though the outcome is usually fair, it can be fatal in isolated cases, particularly in those with the global type. The syndrome is triggered by physical or emotional stress, associated with a massive dumping of catecholamines (catecholamine storm). It is considered that the sudden overstimulation of adrenergic receptors on the surface of cardiomyocytes results in contractile dysfunction and thus acute heart failure [2]. Epilepsy is the most frequent central nervous system trigger of Takotsubo syndrome [2]. Since it can be complicated by ventricular arrhythmias [2], patients experiencing Takotsubo syndrome may not only die suddenly from acute heart failure but also from asystole or ventricular fibrillation [2].

A second pathophysiological mechanism not considered is neurogenic pulmonary edema (NPE) [3]. NPE is characterized by acutely developing pulmonary edema within minutes or hours following an acute lesion of the central nervous system [3], which usually resolves spontaneously within 24-48 hours after onset [4]. Central nervous system triggers of NPE so far reported include enterovirus 71-associated brainstem encephalitis, subarachnoid bleeding, intracerebral bleeding, traumatic brain injury, stroke, hypoxia, hydrocephalus, or epilepsy, usually with generalized tonic-clonic seizures [3]. NPE may occur after a single seizure or multiple seizures. In a retrospective study of 47 patients, NPE was found on computed tomography scans of the lungs in 19% of the patients experiencing a generalized tonic clonic seizure [5].

Overall, patients with epilepsy, particularly those with poor seizure control, polytherapy with anti-seizure drugs, poor compliance, and multiple comorbidities, should be prospectively screened for cardiac and pulmonary disease by electrocardiographic monitoring, echocardiography, stress tests, and pulmonary function tests. Epilepsy patients at risk of cardiac or pulmonary disease should receive primary prophylactic treatment to lower the risk of SUDEP.

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AUTHORS' REPLY

We thank the reader for their interest in our article [1], and for addressing additional putative pathophysiological mechanisms that may contribute to Sudden unexpected death in epilepsy (SUDEP). The authors suggest a potential role of Takotsubo syndrome. Although it has been well recognised that seizures may trigger this syndrome in adults, the role of this entity in SUDEP in general continues to be debated and in pediatric SUDEP, is definitely uncertain. In a review including 74 patients who developed Takotsubo syndrome in association with a seizure, the age range was 18-82 years [2]. Of these, a fatal outcome occurred in only two (3%) patients. This is similar to mortality reported in the International Takotsubo registry [3]. Considering the rarity of fatality, in association with the aforementioned age range, Takotsubo syndrome seems an unlikely contributor to SUDEP pathogenesis in children. Autopsy studies in SUDEP patients indicate that cardiac pathology comprises interstitial fibrosis, myocyte hyper-trophy as well as vascular wall thickening [4]. However, whether these are the effects of multifactorial influences such as anti-seizure medications or even epilepsy itself, or the cause of SUDEP remains unclear. Moreover, none of these features are pathognomonic of "active catecholamine myocarditis" pathology observed in TTS [5].

The authors also suggest a role of neurogenic pulmonary edema (NPE) in the pathogenesis of SUDEP. NPE has been consistently noted in patients with epilepsy and serves almost as a pathological biomarker for SUDEP. However, the reported degree of pulmonary edema has only been to a mild extent, as observed on autopsies in the MORTEMUS study [6]. Additionally, NPE following a seizure tends to be short-lived. Hence, both ante-mortem and post-mortem evidence suggest that NPE following seizures is a common but mild finding, making the link between SUDEP and NPE as a causative factor tenuous.

We agree with the authors' suggestion that underlying cardiac and pulmonary diseases in persons with epilepsy, particularly among those who are refractory to medical

therapy, should be treated. However, whether this strategy generates a reduction in SUDEP occurrence necessitates more prospec-tively collected data, particularly among children and adolescents.

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Telephonic Triage and Telemedicine During the Peak of COVID-19 Pandemic – Restricting Exposure to Healthcare Professionals

We read with interest the article by Mahajan, *et al*. [1] on the use of telemedicine during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The authors have well summarized the pros and cons of tele-health service. We would like to share our experience with telemedicine used with forward triaging that helps mitigate some of its major limitations and protects healthcare workers (HCWs) from potential exposure.

The guidelines for telemedicine have been eased to enable continued care of non-COVID illnesses [2]. However, it is the chronic illnesses that require holistic care by an entire team,which have taken a backseat in the current scenario. Telehealth needs to be part of routine practice, and not just during emergencies [3]. This focuses on creating a more sustainable model of care, and a telehealth-ready workforce, incorporating telemedicine training even in the medical curriculum [3].While many countries are using telemedicine to triage COVID suspects, we planned to develop it into a system of care even in the post-pandemic phase [4,5].

Following our initial experience with use of telephonic consults, a new platform that incorporated telemedicine into the existing Hospital Information system (HIS) was launched on 8 June, 2020. A teleconsultation was provided as per schedule, once a telemedicine appointment was taken by the patient, using a simple feature phone, any video calls or images are shared through WhatsApp (Business). Referral to other specialties was also possible to ensure comprehensive care. The prescription was sent to the patient as a PDF document. After a telemedicine consultation, in case the physician felt the need of an in-person visit, the same is again indicated in the online system and patient is allowed physical entry into the OPD after screening on the appointed date and time.

In our hospital, telephonic-only consults were provided to 2477 patients over a period of 45 days (21 April to 7 June, 2020) while the new system has enabled provision of care to 10,625 patients over the same time span (8 June to 16 July, 2020) (***Fig.* 1**). Physical consultations constituted only 29% of the consultations in this period. This also reflects the proportionate reduction in exposure of healthcare staff to potential SARS-CoV-2 carriers.

The system mitigated the limitation of telemedicine by

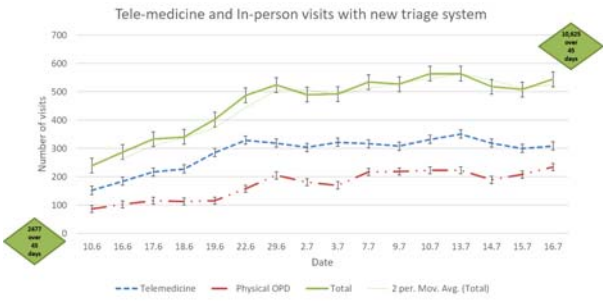

Fig. 1 *Line diagram showing the number of patients seen through new OPD system. The red line indicates the number of patients provided in-person visit after telemedicine triage. The green diamonds shows the number of patients cared for- 2477 patients were provided tele-consult before the launch of new platform over 45 days which increased to more than 10000 patients in next 45 days.*

allowing physical examination after adequate triaging in selected patients. Although, rural India is poor in individual digital literacy, there is a wide network of e-mitra kiosks, ASHA workers and teachers who have come forward to help navigate the system and move through the process. The benefit arising out of limited physical visits to the hospital for patient are already described but restricting the exposure of doctors and patients to someone who is potentially infected is of vital importance.

For a major impact to be seen, an operational telehealth network is required, and infrastructure needs to be scaled up. It also requires a behavior change of not just an individual or an institute but an entire health system as well as patients. We have tried to curtail these limitations and made a beginning while making use of the COVID-19 crises as an opportunity to introduce the system that will stay for future.

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Proximal Limb Girdle Weakness, Joint Hyperlaxity, and preserved Deep Tendon Reflexes: A Distinctive Phenotype

A 9-year-old girl presented with mild motor delay and progressive proximal limb-girdle weakness. Socio-cognitive milestones were normally attained. Examination revealed normal head size and intellectual functioning, proximal limb girdle weakness, mildly prominent calves, and preserved deep tendon jerks (including both ankles). She had hyperlaxity of finger joints and both elbow joints (Beighton score 4/9). She also had polyminimyoclonus. Creatine kinase levels were elevated (790 IU/L) while electrocardiogram revealed tremor (***Fig.* 1**). Nerve conduction studies revealed motor axonal loss with sensory sparing while electromyography (EMG) was suggestive of abnormal spontaneous activity (fibrillations and fasciculations) signifying active denervation. She was not cooperative for voluntary EMG assessment. Multiplex ligation-dependent probe amplification (MLPA) revealed homozygous deletion of exon 7 and 8 of *SMN1* gene confirming the diagnosis of spinal muscular atrophy type 3 (SMA type 3).

Important differential diagnosis for progressive limb girdle weakness presenting in late childhood (with onset beyond infancy) include muscular dystrophies (especially Duchenne muscular dystrophy and limb girdle muscular dystrophies) and SMA type 3. It may be difficult to differentiate these conditions based on deep tendon jerks and creatine kinase levels because these are often misleading. Deep tendon reflexes may be preserved in SMA type 3 [1]. Joint hypermobility and hyperlaxity, although an overlooked feature of SMA, if present favors a diagnosis of SMA over muscular dystrophy [2,3]. The caveats include early-onset muscle disorders such as congenital muscular dystrophies and congenital myopathies [2]. In SMA,

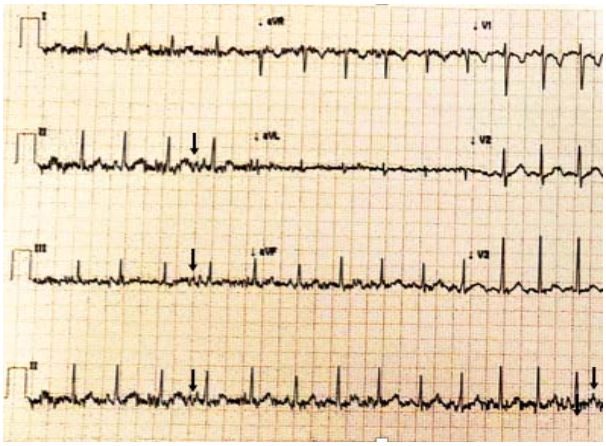

Fig. 1 *Electrocardiogram of the index patient showing the high frequency (30-40 Hz) tremor (arrows) due to muscle fasciculations (seen predominantly in limb leads).*

anterior horn cell loss begins in early infancy and may possibly account for distal hypotonia and hyperlaxity. Hyperlaxity, especially of upper limb joints may persist till adulthood in more than half of patients [4]. It is perplexing to see that this finding was not captured in major prospective cohorts of SMA type 2 and 3, which predominantly addressed the weakness and ambulation. This finding needs to be further confirmed in large cohorts not only because of diagnostic significance but also for rehabilitation point of view, considering the improved outcomes with newer therapies in SMA.

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NeoBox - A Multipurpose Aerosol Box for Neonatal Care DuringCOVID-19 Pandemic

Safety of the newborn and the protection of healthcare workers (HCWs) from aerosol exposure are extremely important during the current severe acute respiratory illness coronavirus 2 (SARS-CoV-2) pandemic. Use of personal protective equipment (PPE) has been shown to be associated with a reduced risk of infection [1]. As per WHO guidelines, it is mandatory to use personal protective equipment (PPE) while performing aerosol-generating procedures like suction, intubation, chest compression *etc*. [2,3]**.** However, despite the use of PPE, there remains a possibility that aerosols can contaminate nearby surfaces [4]**.** An aerosol box acts as a physical barrier against the aerosol spread [4,5]. PPE with a barrier enclosure like an aerosol box can be an effective measure to minimize aerosol spread and exposure during this pandemic [2,4].

Recent literature reports that when an aerosol box was used for airway management, the inner surface of the box and the laryngoscopist's gloves and gowned forearms were observed to be contaminated [4], but no macroscopic contamination outside the box was observed [4]. Unlike adult resuscitation, the focus of newborn resuscitation is effective ventilation of baby's lungs which includes aerosol-generating procedures like suction, PPV, using continuous positive airway pressure, intubation, chest compression, etc. [6,4]. To see the feasibility of using the standard aerosol box as a barrier enclosure while performing aerosol-generating procedures on neonates, a novel simulation session integrating a newborn delivery of a suspect or confirmed COVID-19 mother with a subsequent need for neonatal resuscitation was developed. The 15-minute simulation was run with two resident doctors, an embedded simulation nurse, and a low fidelity manikin in the delivery room setting. The 'newborn' was a low fidelity simulator (Laerdal Medical). During simulation sessions, accessing the neonate and performing resuscitation steps in the squared aerosol box was observed to be impossible. After completion of each session, the learners were debriefed using the PEARLS Healthcare Debriefing Tool with plus/delta and advocacy enquiry format by a trained simulation leader [8,9]**.** Difficulties were encountered at all steps of resuscitation like - attaching pulse oximeter, performing positive pressure ventilation, intubation, chest compression and umbilical catheterization, etc. These difficulties were addressed and the need for a modified aerosol box for neonates was informed to the biomedical department of our institute. The box underwent multiple modifications based on the feedbacks received. The final design specifications were given (***Web Table* I**) and the NeoBox was developed (***Fig.*1**).

The NeoBox is made up of a transparent polycarbonate (3 mm thick). The material required was procured and necessary fabrications were done by the local acrylic / polycarbonate sheet fabricator. The average time required to make one NeoBox was approximately 4 hours. The cost was Rs 6500. An alcohol based disinfectant (Ethanol 70%) with a contact time of minimum 1 minute is used to clean the NeoBox [10].

The NeoBox was primarily designed as a physical barrier to prevent aerosol exposure and spread while performing aerosol-generating procedures during resuscitation in delivery room. While running simulation sessions, its wider application for neonatal care like transporting a suspected or confirmed COVID-19 neonate from one place to another (intra hospital transport) and caring for them in the neonatal intensive care unit (NICU) while performing aerosol-generating procedures was recognized. Use of NeoBox in addition to PPE helped boosting HCWs confidence for managing suspected or confirmed COVID-19 neonates. We found that the NeoBox would require training before use in the treatment of patients. Wearing PPE is

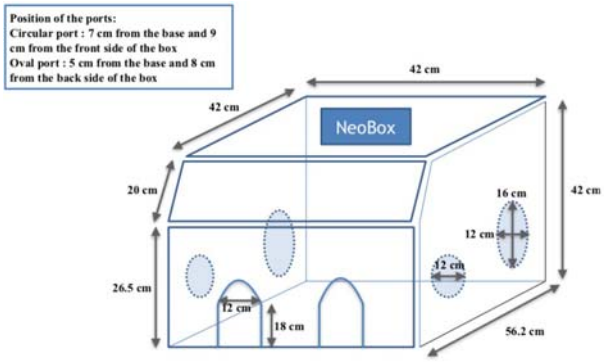

Fig. 1 *NeoBox with dimensions.*

Fig.2 *NeoBox in delivery room – resuscitator managing airway.*

must for HCWs while performing aerosol-generating procedures in a suspected or confirmed COVID-19 neonate. NeoBox works as a physical barrier to prevent aerosol spread. However, in case of difficulty it is advised to remove the NeoBox and perform intubation.

We propose the NeoBox as an additional protection, and suggest that it may be considered to be an adjunct to standard PPE for managing suspected COVID-19 newborns in delivery room (***Fig.* 2**). It can also be used as a barrier enclosure during intrahospital transport and while performing aerosol-generating procedures in the NICU.

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An Infant With Isolated Motor Delay

An 11-month-old male infant, first born of a non-consanguineous marriage was brought with concerns of delayed motor milestones. He had an uneventful antenatal and perinatal period. He achieved head control at 6 months of age and rolling over at 10 months of age. He had normal social and cognitive milestones. None of the family members in a three-generation pedigree had symptoms suggestive of any neuromuscular illness. On examination, he had peripheral hypotonia, diminished deep tendon reflexes in both upper and lower limbs, without any tongue fasciculation or signs of facial, extraocular, bulbar, and cardiac muscle involvement. Serum creatinine phosphokinase was found to be elevated (2568 IU/L). A clinical possibility of Pompe disease, congenital muscular dystrophies and congenital myopathies (central core and multiminicore myopathy) was considered. Muscular dystrophy and congenital myopathy genetic panel revealed a hemizygous pathogenic nonsense variation in exon 61 of the *DMD* gene (ChrX:g:31366736G>A), confirming a diagnosis of Duchenne muscular dystrophy (DMD). The observed variation was confirmed by sanger sequencing. It found to be previously reported in patients with DMD and has been classified as pathogenic in ClinVar database. The *in silico* prediction of the variant was damaging by Mutation Taster 2. He was started on oral prednisolone (0.3mg/kg/day) and physiotherapy and parents were counseled about the nature and prognosis of the disease.

Duchenne muscular dystrophy (DMD) is the commonest muscular dystrophy having an incidence rate of one in every 3500 male infants [1]. Indian data suggests that exonic deletions and duplications are found in around 67% and 6% boys with DMD, respectively. Most of the cases become symptomatic between 2 to 6 years of age, with frequent falls during walking, difficulty in getting up from sitting or squatting position, and waddling gait [1]. However, few recent studies have revealed that a proportion of children with DMD had a delay in the attainment of motor milestones from infancy [2]. Although some of these parents often express the developmental concern of their children in toddler years, differential diagnosis of DMD is rarely considered in these children because of the absence of muscle weakness [2]. In the existing literature, the youngest age at which diagnosis was established in symptomatic DMD cases was 3 years of age, although new-born screening and screening of affected siblings have detected asymptomatic cases in infants [2]. The common causes of peripheral hypotonia with elevated CPK levels in infants include congenital muscular dystrophy (CMD), congenital myopathies (central core and multiminicore myopathy), and metabolic myopathies like Pompe's disease [3]. Children with congenital muscular dystrophy usually have much higher serum CPK levels with hypotonia, while children with secondary merosin deficient CMD often have epilepsy, cognitive impairment to some extent and brain malformations. Children with congenital myopathies have predominantly ocular, facial and bulbar involvement along with mildly elevated serum CPK. Infants with Pompe disease have hepatomegaly and cardiomyopathy along with peripheral hypotonia and elevated CPK levels. Infantile polymyositis is another rare possibility in such cases, which unlike older children, may sometimes present with isolated motor delay and elevated serum CPK without any fever or systemic features.

Early diagnosis of DMD often provides an opportunity for timely institution of treatment including drugs like steroids, ataluren and eteplirsen, physiotherapy and genetic counselling of parents for subsequent conceptions [4]. Early institution of glucocorticoids in low doses, as soon as the diagnosis is established, has been shown to improve the outcome at the cost of tolerable side effects, although not able to cure the disease. Glucocorticoids were initiated in the index case after discussing risks and benefits with parents.

To conclude, while evaluating an infant with raised CPK levels, clinicians should consider DMD as one of the differential diagnosis apart from CMD and few selected congenital myopathies. Early diagnosis and initiation of steroids may improve the outcome at the cost of tolerable side effects.

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Therapeutic Clowning in Pediatric Practice: A Novel Concept to Think About in India

Therapeutic or medical clowning is a new concept across various healthcare settings around the world [1]. It is a para-medical practice in which clowns are associated with healthcare system to mitigate anxiety, stress, fear and sadness in admitted patients, thereby augmenting the healing process [2]. They create a more positive and constructive hospital environment and trust between patients and medical teams. Research has concluded that medical clowns have a significantly positive effect in adults [3]. A consistent observation has been seen that clowns are always appreciated by pediatric patients [4].

Idea of medical clowning was conceptualized by Michael Christensen in 1986, in the United States. At a physiological level, laughing stimulates release of endorphins modulating immune system. Laughing also replaces negative feeling with positive ones at and emotional level. Clowning distracts the child from the current situation at the cognitive level. Socially, laughing stimulates better interaction between children and health care personnel [4,5].

This practice is still nascent at present in India. Sir JJ Hospital Mumbai has begun with medical clowning in pediatric wards recently. As a pediatrician, our primary responsibility is better health and quality of life of our pediatric patients, and hence, this novel idea of therapeutic clowning is worth trying, especially to begin with vaccination sessions. Further research is warranted to replicate its results in the Indian settings.

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Multisystem Inflammatory Syndrome in Children (MIS-C) - Recent Updates

We read the very timely article by Bhat, *et al.* [1] providing valuable insights into clinical epidemiology of multisystem inflammatory syndrome in children (MIS-C). We comment on the recent evidence to complement the information provided.

Recent clinical guidelines by American College of Rheumatology (ACR) elaborate on the most appropriate diagnostic and therapeutic steps for MIS-C at the present time, advising inflammatory markers and cytokine panel testing [2]. There is noteworthy discordance in interleukin levels of IL-1, IL-6 and IL-10 among patients with Kawasaki disease (KD) *vs* MIS-C [3]. While IL-1 is the main mediator of coronary artery inflammation in KD, inflammatory process in MIS-C is predominantly driven by IL-6 and IL-10, which may play a role in the myocardial dysfunction and higher severity of the 2019-nCoV infection [4].

We concur with the authors that the role for specific cytokine blockade including use of biologics in MIS-C is still lacking. The ACR guidelines advice immunomodulatory therapy for all severe/critical MIS-C patients with shock, significant respiratory distress, neurologic changes, dehydration, or features of KD. IVIG and glucocorticoid remain first line agents either alone or in combination. Anakinra is safe in severe infections among children with hyper-inflammatory syndromes. Although tocilizumab is effective in reducing mortality and ICU admission in patients with severe COVID-19 pneumonia [2], the clinical evidence is insufficient regarding its efficacy and safety for COVID-19 because of concerns regarding risk of secondary bacterial and fungal infections [5]. Aspirin (3-5 mg/kg/day) should be used in patients with MIS-C and KD-like features and/or thrombocytosis and continued until normali-zation of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis. Anticoagulation with enoxaparin should be added in patients with coronary artery aneurysm and *Z* score ≥10.0 or an ejection fraction (EF) <35% [2], but despite benefits, strategy based evidence is required due to high risk of hemorrhagic events or complications.

With the availability of these guidelines a standardized treatment plan for MIS-C involving multidisciplinary care

under pediatric cardiology, infectious disease, intensive care and rheumatology specialists can be designed. As the evidence base for COVID-19 and MIS-C treatment and care management is evolving rapidly, this guidance may change in future.

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Impact of the COVID-19 Pandemic on Retinopathy of Prematurity Practice: An Indian Perspective

The severe acute respiratory syndrome coronavirus 2019 (SARS-Cov-19) associated lockdown in India led to cessation of public transport and routine outpatient department (OPD) services. However, the need to screen to premature babies for retinopathy of prematurity (ROP) continued, with reduction in those actually getting screened. ROP requires urgent treatment and has been listed as an essential medical service during the COVID-19 pandemic by both the American Academy of Ophthalmology and All India Ophthalmological Society [1-3]. We discuss the impact of the COVID-19 pandemic on ROP services experienced at our center.

Impact on ROP screening: Following the guidelines issued by the All India Ophthalmological Society (AIOS) in conjunction with the Vitreo Retina Society of India (VRSI) and the Indian Retinopathy of Prematurity (iROP) Society, we continued to screen premature babies for ROP [2,3]. Being a tertiary care institute, we are the primary referral center for neighboring states. However, given the scarcity of trained ophthalmologists to perform ROP screening, we often end up as the first point of screening for majority of the regional neonatal intensive care units (NICU). There was a decrease in the number of infants screened both in the OPD (396 *vs* 87; *P*=0.001) as well as in the institute NICU (241 *vs* 169; *P*=0.001) during similar time periods pre (1st January, 2020 to 23 March, 2020) and post (24 March, 2020 to 31 May, 2020) COVID-19 lockdown. This could primarily be attributed to the lack transport facilities for patients to reach the hospital, despite this being permitted during the lockdown. In the pre lockdown period, the number of babies screened in the OPD were significantly higher than those screened inside the institute NICU/neonatal nursery (*P*=0.001), which was also reversed during the lockdown period.

Impact on ROP treatment: Laser photocoagulation was increasingly preferred (49 eyes) over intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents (2 eyes) as the primary treatment during the lockdown period. The main reason for this was the finite nature of laser photocoagulation compared to the risk of recurrences with anti-VEGF agents, which requires regular and extended follow-up [4]. We had at least three babies with aggressive posterior retinopathy of prematurity (APROP) who were given anti-VEGF injection prior to lockdown and missed follow-up for two months owing to movement restrictions during lockdown. While the disease regressed in two of these babies, one progressed to develop tractional retinal detachment in both eyes and required surgical intervention. In the pre-lockdown period, all laser treatments (for outborns as well as inborns) were done inside the neonatal nursery/NICU of our institute under monitoring by a neonatologist. This sometimes entailed a wait period of 24-48 hours depending on availability of a monitoring bed in the NICU. During the lockdown, there was shut down of most elective procedures such as cataract surgery. This allowed availability of more operation theatre (OT) tables for emer-gency procedures. We therefore arranged to perform all ROP interventions in the OT itself with the focus being on same day treatment. A pediatrician was available on call for monitoring in addition to the anesthetist. This helped reduce the contact of outborns with inborns as well as other NICU healthcare professionals in addition to reducing the waiting time. All lasers were performed under topical anesthesia using personal protective equipment as per the AIOS guidelines [2,5].

Impact on surgical rate: The proportion of babies requiring lens sparing vitrectomy (LSV) as the primary intervention increased from 1.1% in the pre-lockdown period to 2.9% in the post-

lockdown period. Majority had stage 4A ROP (1, bilateral stage 4B ROP). Delayed screening, delayed referral and travel difficulties were probably responsible for this advanced presentation. For bilateral cases, immediate sequential bilateral vitreous surgery was preferred over multiple sessions of surgery [6].

Impact on incidence of conjunctivitis: ROP screening and treatment requires frequent contact with the eyelids, both by the ophthalmologist as well as the parents. This increases the chances of conjunctivitis in these babies [7]. Prior to COVID-19 lockdown, 30 babies developed conjunctivitis while on follow up, including a cluster of 24 babies in the institute's NICU/ neonatal nursery. Post-lockdown, this number came down to three. Overall conjunctivitis infection rate reduced from 4.7% to 1.2% (P=0.01). This could primarily be attributed to the enforcement of frequent handwashing practices amongst both the doctors as well as the caregivers. We also reduced the points of contact of the baby once in the hospital. All babies for ROP screening were managed at a single dedicated room without going through the general ophthalmic screening OPD. Parents were educated and encouraged to dilate their babies' eyes themselves after performing hand hygiene while in the hospital waiting area. This helped reduce number of contacts with the health care professionals.

Implications for future: There were several important lessons learnt from the above experience. Firstly, there is a need to expand tele-medicine services for ROP throughout the country. Fundus photographs taken by a trained nurse/technician using portable, wide-field camera system scan be sent to a remotely placed expert and advice regarding the urgency of referral can be given. It will also be a good tool to educate parents regarding the condition of their child's eye. Low-cost imaging devices being made available now are a step in this direction [8]. Secondly, there is an urgent need to ensure adequate training for indirect ophthalmoscopy during residency at all medical colleges in the country which would help in bringing out more ophthalmologists who are confident in this field. Thirdly, laser photocoagulation for the treatment of ROP may be a better alternative in these times when there is a doubt on the ability of the patient to follow-up regularly. Lastly, some of the positive habits like frequent handwashing and use of masks may be a boon even in the post-COVID era, if reinforced regularly. They potentially helped reduce the conjunctivitis infection rate in our setting and could have similar implications in other healthcare settings. We hope our experience would assist other centers managing ROP, as we continue to experience the impact of the COVID-19 pandemic.

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Web Table I Difficulties Encountered by Learners During Simulation Sessions and Development of NeoBox

Simulation scenario	*Delta*	*Development of NeoBox*
Scenario 1	Size of the box was too big to fit under radiant warmer	NeoBox's base dimensions were determined by taking measurements of warmer bed (NeoBox base dimensions : Warmer bed length - 10 cm, Warmer bed breadth - 10 cm)
Scenario 2	Difficulty in accessing newborn's airway due to the straight front surface.	The aerosol box was flattened and angulated at the top to provide clear vision to the person performing intubation.
	Difficult to access newborn's airway due to it's inconveniently located ports	The lower border of two semicircular ports on the front side was lowered.
Scenario 3	Need for extra ports on both sides in case baby needs advanced resuscitation	Two ports were incorporated on either side of the box. The distal port was designed to be bigger (oval in shape) than the proximal one (circular in shape) for the easy access during procedures.
	Confusion in positions of the resuscitator while performing resuscitation	If the baby needs initial steps of resuscitation: The resuscitator stands at the head end and the assistant if any stands on the right side. If the baby needs advanced steps of resuscitation: (*i*) Instead of AMBU bag, T piece resuscitator will be used as the bag would need lot of space. (*ii*) Intubation will be performed from the head end. (*iii*) The resuscitator will shift to the left side while providing PPV through ET. (*iv*) Second resuscitator will provide chest compressions from head end. (*v*) Third resuscitator will perform umbilical catheterization from right side
Scenario 4	How to cover ports to minimize aerosol spread during intra hospital transport?	Polycarbonate flaps were prepared to cover side ports and a square polycarbonate sheet was made to cover front side. One can use polyethylene wrap to cover the ports and front side.

Infections in the time of the pandemic

The COVID-19 pandemic is an evolving natural experiment. There has been an unexpected windfall in this time of despair. Researchers from the Boston Children's Hospital have analyzed the rates of 12 common childhood infections in the same calendar period during 'social distancing' and in the 'pre-social distancing era,' using data of a primary care network which caters to 375,000 children. The infections they studied were acute otitis media (AOM), bronchiolitis, common cold, croup, gastroenteritis, influenza, nonstreptococcal pharyngitis, pneumonia, sinusitis, skin and soft tissue infections (SSTIs), streptococcal pharyngitis, and urinary tract infection (UTI). All infections showed a remarkable decline. Influenza, croup and bronchiolitis practically disappeared. The least decline was in the rates of UTI, which was as expected.

The decline in infections may have been due to decrease in prevalence or a choice not to seek medical care. However the trends of change in UTI suggest that the former was more predominant. It may give good pointers in developing strategies to reduce common childhood infections after the pandemic is resolved.
(Pediatrics 2 September 2020)

Deconstructing motherhood

Where in the brain is the center for nurturing? Catherine Dulac, a molecular biologist at Harvard, has won $3 million dollars as part of the Breakthrough Prize for work in this esoteric field. She has discovered the neural circuits which explain the unique parental behaviors in males and females. Close observation in mice showed that female mice show remarkable stereotyped behaviors when they see baby mice. Even when they are not the mother, they immediately retrieve the pups, groom them, build a nest for them and crouch around them. In sharp contrast in normal circumstances, male mice will attack baby mice.

Dulac's group found that the medial preoptic area of the hypothalamus releases a molecule called galanin which orchestrates the various parenting behaviors. Stimulating the galanin neutrons with light caused the male mice to show unusual maternal parenting behaviors. Destroying the preoptic areas in females resulted in non-nurturing behaviors in females.

The work is extraordinary because it is the first time such a complex social behavior like parenting has been explored to the cellular level. The biological underpinnings of social behaviors may open doors to therapeutics in many complex problems like post-partum depression, drug addiction and criminality.
(*Nature News 10 September 2020*)

Treading softly - CONSORT-AI guidelines

Artificial intelligence (AI) systems are sweeping across the landscape of medicine. And we stand mostly unprepared. Recently there has been a spate of randomized controlled trials using AI systems for diagnosis, but are these RCTs designed appropriately factoring in the complexities of AI and can we take their evidence at face value?

Guidelines for clinical trial protocols evaluating interventions with an AI component (SPIRIT- AI) and trial reports with AI (CONSORT- AI) have recently been published. One of the issues is random alerts by AI algorithms which will falsely over detect abnormalities compared to a clinician and be labelled as 'better'. Another major issue with AI are that many systems are self-learning and continually changing. Further the people who create the algorithms are not the clinicians who see patients. So they need to have a deeper understanding of medicine and clinicians need to have a better understanding of what these algorithms may or may not handle. The new guidelines have asked for clear detailing of the type of AI model being used, which version of the algorithm will be used, specific plans to identify and analyze performance errors etc.

Some paths in medicine are so byzantine, that even 'angels would fear to tread'. And the guidelines to rein in AI in medicine are certainly one of them.
(*BMJ 9 September 2020*)

AAP guidelines for resistance training in children

It is well established that muscular fitness in children is declining worldwide. On the other hand, competitive training in sports is starting at earlier ages and resistance training for body image development is not uncommon in some children.

The American Academy of Pediatrics has brought out guidelines to help pediatricians counsel parents in this regard. Resistance training/weights is now considered to have several benefits even in children e.g., improvements in motor skills, enhancement of bone mineral density and reduction in injuries. Supervision under a trainer is preferred. Children recover quickly from resistance training fatigue, hence shorter resting periods of 1 minute between sets initially and 2-3 minutes later is recommended.

Pre-habiliation is a term used for children in competitive sports. It means prophylactic exercises to prevent injuries. The other technique is plyometric exercises. This involves repetitive concentric exercises to rapidly build strength. Children as young as five can build strength with one-legged hops or frog jumps. For older children, lifting weights can be combined with aerobics or other sports to round out their activities. Children with uncontrolled hypertension may need prior medical evaluation.

The AAP also recommends 1-2 days off per week to prevent injuries due to over training. We also need to make sure that children take adequate fluids and calories required for the increased expenditure.
(*Pediatrics June 2020*)

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CLIPPINGS

Theme: Genetics

Exome sequencing aids in the treatment of a child with type I interferonopathy (*N Engl J Med. 2020; 382(3):256-65*)

Ubiquitin-specific protease 18 (USP18) deficiency [Pseudo-TORCH syndrome 2 (MIM# 617397)], due to homozygous or compound heterozygous variants in *USP18,* is a severe monogenic autoinflammatory disorder. USP18 restricts the access of Janus-associated kinase 1 (JAK1) to type I interferon receptor, thus preventing excessive interferon signaling. Individuals with USP18 deficiency present in the neonatal period with intracranial calcification, hemorrhage, liver dysfunction, septic shock, and thrombocytopenia, resembling congenital intrauterine infections. A Saudi Arabian boy, born to first-cousin parents, and diagnosed in the first month was treated with oral ruxolitinib, a JAK1/2 inhibitor. The child showed clinical improvement and was discharged from the intensive care unit at 9 months. At 3 years of age, this child is the oldest surviving individual with this rare condition. The case reiterated the importance of a rapid genetic diagnosis by ES, which specifically helped in initiating therapy and changing the course of the illness.

Genome sequencing in pediatric heart disease (*Genet Med. 2020;22:1015-24*)

Congenital heart disease (CHD) is one of the most common anomalies in humans. The Cardiac Genome Clinic was established in the Hospital for Sick Children, Canada, to assess the utility of genome sequencing (GS) in children with heart diseases. Individuals from 111 families with cardiac diseases like cardiomyopathy, laterality defects, and outflow tract obstructions were recruited from January, 2017 to December, 2018. Trio/ quartet (child and parents) GS was done and data were generated for 328 individuals from 111 families. Using a specific research protocol for variant prioritization, candidate variants were identified. Causative pathogenic or likely pathogenic variants were identified in 14 of the 111 families (12.6%). Seven families had *denovo* variants in genes like *ANKRD11* (KBG syndrome), *KMT2D* (Kabuki syndrome), *NR2F2* (NR2F2- related CHD), *POGZ* (White-Sutton syndrome), *PTPN11* (Noonan syndrome), *PTEN* (PTEN hamartoma syndrome), and *SALL1* (Townes-Brocks syndrome). Novel candidate genes for cardiac phenotypes identified in this cohort were *FGD5, CDC42BPA, VASP or TLN2, TRPM4, SMARCC1, TPCN1,* and *UBXN10*. Structural variants of sizes ranging from 9.1kb to 8.3Mb were also identified and the detection rate was more than chromosomal microarray. The evidence generated in this study is likely to pave the way for GS as a first-tier diagnostic test for pediatric heart disease.

Ultra-rapid exome sequencing in critically ill children with monogenic conditions (*JAMA. 2020;323:2503-11*)

This study was conducted in Australia to evaluate the utility of ultra-rapid exome sequencing in critically ill pediatric patients with suspected monogenic diseases. A total of 108 patients were recruited prospectively from neonatal and pediatric intensive care units from March, 2018 to February, 2019. Trio exome sequencing was performed in 105 families and singleton exome was performed in three families. The median age of study participants was 28 days (range 0-17 years). 62 patients were from NICU (57%), 36 from PICU (33%) and 10 were from other hospital wards. The majority of patients had neurological symptoms like seizures or hypotonia. The mean time from sample receipt to the generation of a report (primary outcome) was 3.3 days (95% CI, 3.2-3.5 days). Fifty-six genetic conditions were diagnosed in 55 patients (51%). Two novel candidate genes were identified. A change in clinical management after the report was observed in 44% patients. The diagnosis helped in targeted therapy in 12 patients (11%), palliative care discussions in 14 patients (13%), and surveillance plans in 19 patients (18%). The authors underlined the need for more evidence for assessing the clinical utility of ultra-rapid exome sequencing in other settings.

Genetic causes of neonatal encephalopathy (*Clin Genet. 2020 Jul 26.* 10.1111/cge.13818)

Neonatal encephalopathy is a common condition that presents in the newborn period with seizures, altered consciousness, poor muscle tone, and abnormal electroencephalogram, and magnetic resonance imaging of the brain. The authors recruited 366 neonates with encephalopathy from 2015 to 2017, and performed trio/singleton exome sequencing. A definitive molecular diagnosis was established in 43 neonates (11.7%), with pathogenic or likely pathogenic variants. The variants were identified in 30 genes which were classified into four different categories: epileptic (58.5%), metabolic (18.9%), mitochondrial (3.8%), and syndromic-related genes (18.9%). The most common genes to be involved were *KCNQ2* and *SCN2A*, causing epileptic encephalopathy. On follow up, it was observed that death rate and severe development delay were higher in neonates with a genetic diagnosis. Several personalized therapeutic interventions were possible in some of the genetic neonatal encephalopathies. Thus exome sequencing should be considered in the workup of neonatal encephalopathy.

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IMAGE

Targetoid Hemosiderotic Hemangioma

A 10-year-old boy presented with 1-year history of a gradually progressive non-tender, soft-to-firm, dome-shaped, brownish-black papule (6x6 mm) with a peripheral erythematous halo situated above the umbilicus (***Fig.* 1**). There was no history of preceding trauma, acute illness or any drug intake. Other mucocutaneous areas were uninvolved. Excision biopsy confirmed the clinical impression of targetoid hemosiderotic hemagioma (THH); no recurrence was noted on regular follow-up.

THH is an acquired benign vascular lesion presenting as a solitary, red-violaceous to brown targetoid papule with a hemorrhagic halo; usually adolescent onset. Classic histology shows biphasic pattern: dilated vessels lined by hobnail endothelial cells with intraluminal papillae in the papillary dermis; and angulated and slit-like vascular spaces dissecting the collagen bundles in the reticular dermis, with plenty of extravasated erythrocytes and hemosiderin deposition at the periphery (accounting for the targetoid appearance). They are often misdiagnosed as melanocytic nevus (coarse hair, absence of halo, presence of melanocytic nests), infantile hemangioma (bright red lobulated plaque with typical growth pattern), dermatofibroma (painful, positive dimpling sign), solitary angiokeratoma (no halo, hyperkeratosis and dilated vessels only in papillary dermis on histology) or melanoma (rare in pre-pubertal age, atypical melanocytic nests). Complete removal is sufficient to treat the condition.

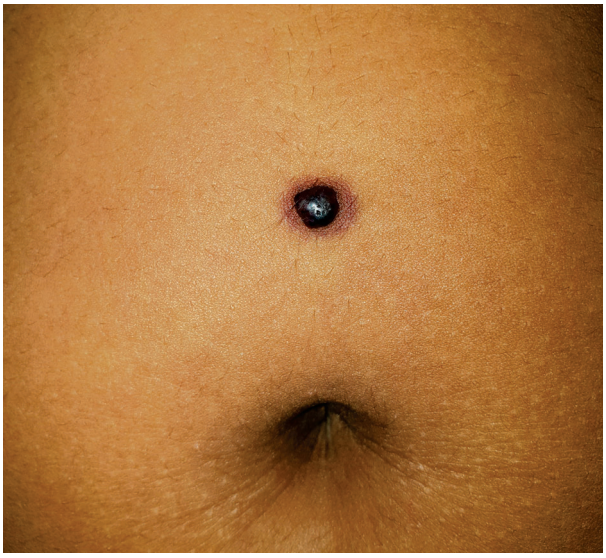

Fig. 1 *Targetoid hemosiderotic hemagioma characterized by a dome-shaped, brownish-black papule with surrounding erythematous halo.*

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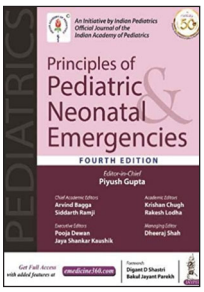
BOOK REVIEW



Principles of Pediatric and Neonatal Emergencies

Editor-in-Chief: **Piyush Gupta**
Chief Academic Editors: **Arvind Bagga and Siddarth Ramji**
Academic Editors: **Krishan Chugh and Rakesh Lodha**
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Pages: 1000, Price: Rs. 1995/-

The fourth edition of the Principles of Pediatric and Neonatal Emergencies is a much awaited revised and updated version after nine years. This book is of immense importance as pediatric emergency medicine is an upcoming sub specialty of pediatrics in India now.

The book has eight sections along with annexures of drug dosages. The chapters include all systemic emergencies along with syndromic approach of many life-threatening conditions. A separate section on surgical emergencies along with approach to injured child is relevant as most centers see many such cases in day-to-day practice. Emergency procedures are explained well along with pictorial assistance and ray diagrams.

This book is a 'must read' for all postgraduates and clinicians involved in the management of sick children.

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