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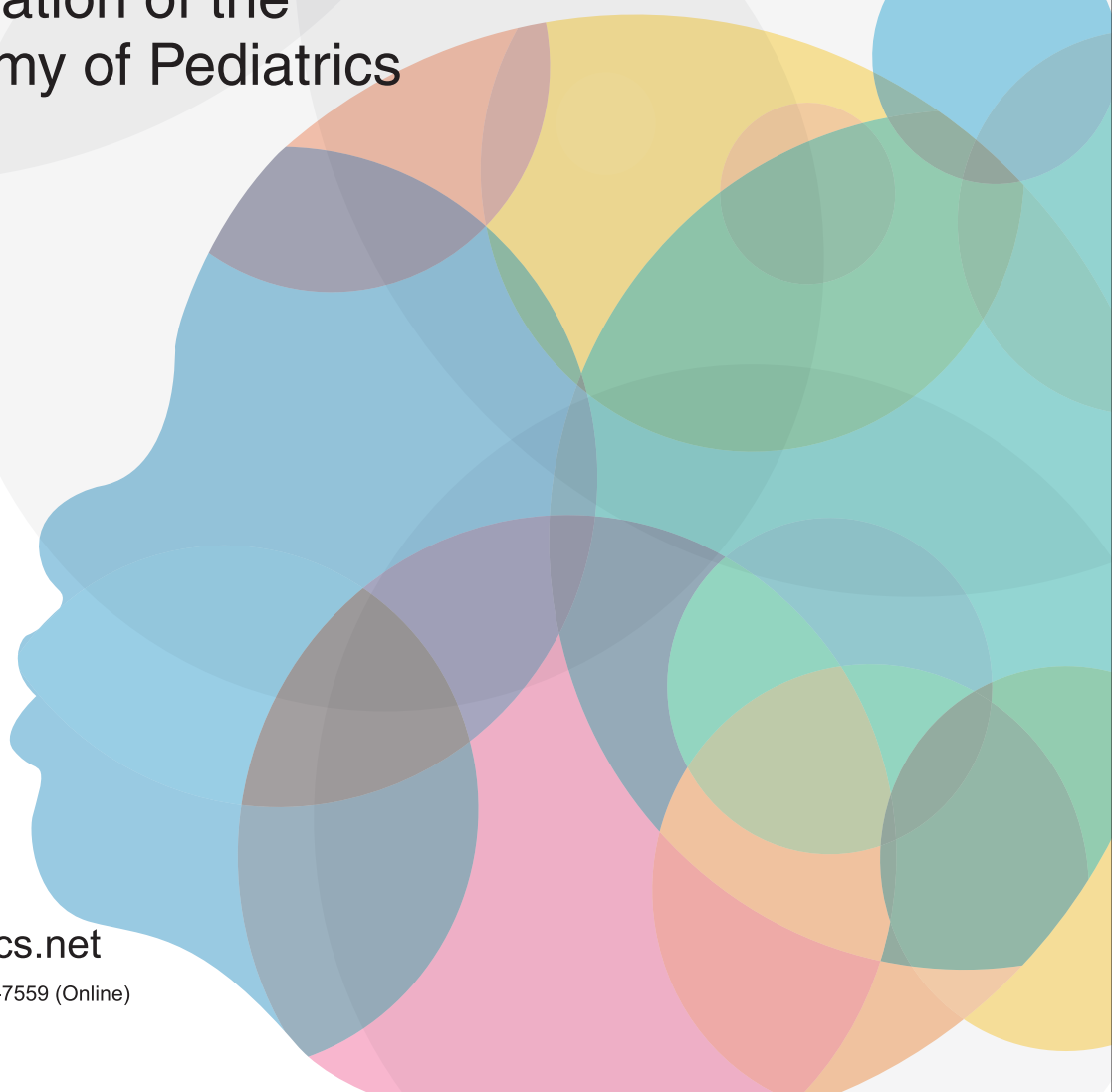

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Pediatrician-Friendly IAP Growth Charts for Children Aged 0-18 Years

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Growth is the fundamental physiologic process that characterizes childhood. Secular trends in growth patterns are followed as indicators of children's health on a population level. Growth can be worrisome along two variables: height (short stature) and velocity (growth failure). Anthropometry is an invaluable tool in the hands of a pediatrician to monitor growth.We must get into the habit of regularly plotting these anthropometric data on the appropriate growth chart until the age of 18 years, as this will help in picking up the reason for failure to thrive early and thereby help to reduce expensive investigations.

Growth charts are invaluable tools in the assessment of childhood nutrition and growth. Indian Academy of Pediatrics (IAP) produced and recommended IAP 2015 Growth charts for monitoring Indian children between the ages of 5 and 18 years, and recommended simplified World Health Organization (WHO) growth charts for monitoring of children under the age of five years. A combined WHO-IAP height and weight chart allows us to monitor growth from birth to 18 years on a single chart, and the relation between the child's height and the mid-parental height (MPH) can be readily observed on the same chart even for children younger than 5 years, which is not possible on the split chart (separate charts for under-5 and older children).

IAP 2015 body mass index (BMI) charts were designed to define overweight and obesity at 23 kg/m^2 and 27 kg/m^2 adult-equivalent BMI cut-offs, and overweight and obese lines were color coded as orange and red, respectively. However, deriving BMI involves a calculation (weight in kg/height in meters squared) which takes time and hence is often omitted by a busy practitioner. Prevalence of overweight and obesity increases in children as they get older, especially beyond the age of 8 years. A quick BMI screening tool based on weight for height that eliminates the need to calculate BMI will help to rapidly decide if a child is overweight, obese, normal or underweight. The tool has three lines which depict obese (OB), overweight (OW) and underweight (UW), the overweight line is orange and obese line is red (same color code as the IAP BMI charts). Based on where the child's weight lies on y axis for the height on x axis, the child can be classified as having BMI within the normal range (between UW and OW lines), overweight (between OW and OB lines), obese (above the OB line) or underweight (under the UW line).

MPH is necessary to understand a child's genetic potential so that the current height percentile can be checked against MPH percentile. MPH is based on parents' heights, but again involves a calculation and plotting at 18 years to know the mid parental percentile. MPH calculation is gender-specific and the formula is father's height+mother's height divided by 2, and then subtract 6.5 cm for a girl or add 6.5 cm for a boy. Pediatricians find this cumbersome and hence MPH assessment often gets omitted. Here we present a MPH percentile lookup tool which was designed in such a way that by joining the father's height on left to the mother's height on the right (both in cm) gives the MPH percentile (on the middle line) for that specific gender *e.g.,* joining mothers' height of 150 cm to father's height of 170 cm gives an approximate value of 25th percentile of MPH on both scales. Using formula for a boy the MPH is 166.5 cm and for a girl it is 154.5 cm. These correspond to 25th percentile of height both for boys and girls at 18 years, confirming the accuracy of the lookup scale.

We present user-friendly growth charts for everyday use by pediatricians (charts available at *https://iapindia.org/pdf/4422_Pediatrician-friendly-growth-charts-for-0-18-year-old-Indian-children-Dr-Bakul-Parekh-and-Dr-Vaman-khadilkar.pdf*). No calculations are involved while using these charts, neither for BMI nor for MPH. In a busy clinic, lesser the calculations the pediatrician performs, the better. Both these important parameters can be read-off directly from the tools provided on the chart.

An important reason for the popularity of United Kingdom Royal College of Paediatrics and Child Health (RCPCH) growth charts is that along with the standard

percentile lines, many tools such as the MPH percentile calculator, lower percentile lines and BMI z score look up tool are provided, which eliminate calculations. No such attempt has been made to incorporate all these tools in the IAP growth charts so far; although, it is the need of the hour. We believe that this need will be fulfilled by these user-friendly charts.

The percentile curves for height and weight in children below the age of 1 year are placed too close together, making it cumbersome to plot and despite using statistical smoothing, a small blip is evident at junction of 5 years (where WHO and IAP charts meet). We hope to improve these shortcomings in future charts.

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NOTES AND NEWS

Modifications to Instructions for Authors

Changes w.e.f. 1 January, 2021
(All manuscripts submitted after 1 November, 2020)

Text

- There is no need to provide the location of manufacturer of drugs, equipment and devices in the text.
- Avoid the terms mutation and polymorphism, instead use sequence variant, sequence variation, alteration or allelic variation. Similarly, use SNV (single nucleotide variation) instead of SNP (single nucleotide polymorphism).
- There is no need to expand CI or IQR either in text or in tables.
- There is no need to italicize foreign words which are commonly used in English like e.g., etc., viz., et al, a priori, post hoc, vs/versus.
- Additional guidelines for preparing a manuscript for the systematic review section have been provided at the website.

Tables

- For footnotes in tables, use small case letters sequentially in superscript.

References

- *Citing documents with multiple authors*: If there are six authors/editors or less, include the names of all authors/ editors. If there are more than six authors/editors, include the first three names followed by et al.
- In references, the URL of web-based references should be the last item in the citation and should not be followed by a period (full-stop).
- Do not provide DOI/PMID/PII numbers.
- There is no need to provide location of the publisher for books and reports in references.

The updated Instructions for authors are available at the website (www.indianpediatrics.net).

PERSPECTIVE

Ancillary Services in Pediatric Departments of USA

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It is well known that prolonged hospitalizations and medical procedures have adverse psychological impact on children. Ancillary services in the pediatric departments help in mitigating stress, improve patient satisfaction, reduce procedural time, and improve the quality of life. This can be translated to measurable outcomes such as less doctor's visits, fewer symptoms, early discharge and fewer medications. Other benefits include conserving staff time and energy, thereby increasing productivity, staff retention and decreasing burnout. As more free-standing children's hospitals emerge, the ancillary services will gain more recognition and popularity to give the best patient care experience.

Keywords: *Art, Clowning, Health, Hospital, Music, Pets*.

In the eighteenth century, physician George Armstrong expressed concerns on the psychological impacts of hospitalization in young children and that separation of sick children from their mothers had adverse outcome on the well-being of these children [1]. However, it was not until 1946 that pediatrician Sir James Spence established the first mother and child hospital [2]. In 1986, the American Academy of Pediatrics mandated that any facility with ten or more pediatric beds must actively address the psychological needs of patients, through implementation of appropriate programs [3].

Recently, there has been a rapid expansion of ancillary services and complimentary medicine in healthcare in pediatric settings world-wide. It is estimated that >50% of children in North America who have chronic diseases use some form of complementary therapy every year. Another study conducted in 20 European countries involving 68% of the European population, showed that complementary medicine (example acupuncture) was offered in private practices in all the countries [4]. Recently a large national survey with an 84% response rate, conducted in the USA reported that 74% employed a massage therapist, 53% a music therapist and 22% an art therapist [5]. A systematic review on the prevalence of use of complementary/ alternative medicine varied from 9 to 65% [6]. In 2020, a survey on music therapists working in pediatric medical settings in the United States found that such services have become a standard of care in many pediatric hospitals across the United States [7]. Currently all children's hospitals and community hospitals with medium and large pediatric units in the United States provide various services like – Child life specialist, art and music therapy, massage therapy, acupuncture, medical clowning and many more. Further, many pediatric units have school teachers to help children catch up with missed homework and earn credits with the work done during hospitalization.

In the following sections we will discuss each of the ancillary services in detail to appreciate their roles in a hospitalized child.

Child Life Specialist

Child life specialists (CLS) are individuals, working in a pediatric hospital setting, who are specialized in child psychology and development. Their goal is to provide emotional and spiritual support, educate and advocate children in a manner appropriate for the development of the child [8]. Along with other team members, they help to build rapport with the patient and the family and help in strengthen the role of parents in a family centered care model [8-10]. The admitted children may be exposed to two kinds of trauma which could impact their welfare-trauma of sickness and the trauma of hospitalization [11]. CLS help in reducing fear and allay anxiety by employing unique strategies tapered to the needs of the child. It may be as simple as giving a box of Lego to a 6-year-old to divert his attention during a physical examination or as complicated as to extract history from a sexually abused 5-year-old girl using play therapy. They also form an integral part of pediatric palliative care team – by identifying non-verbal pain, recognizing the needs and emotions at the end of life, conveying them to the palliative care teams and help in building legacy [8]. Interdisciplinary CLS teams work together focusing

on the quality of life, addressing the psychosocial needs, while respecting the traditional cultures and religious customs [10-12]. They work at times that are convenient for the child, help restructure the day, and prepare children for medical procedures [10,13]. They may decorate the hospital room to make it as comfortable and familiar as the home environment and have traditional ''Friday family game nights.'' They play board games; bring in movies, and electronic gadgets, helping children stay in touch with their classmates. They encourage patients and families to continue to maintain a semblance of normal life in the hospital setting [8,12,14]. The CLS work in both out-patient and inpatient pediatric settings including in the pediatric intensive care units, behavioral and rehabilitation facilities [15]. Most hospitals have a ratio of 1 CLF for every 10-15 patients, but the ratio may vary depending on the severity of illness and the emotional state of each patient [8,12].

Art and Medical Music Therapy

Art and health have been at the center of human interest since early times [12]. Creative art therapy is the use of expressive media including music, dance, poetry and fine arts which blend together in providing support during medical interventions [8,14,16]. It is well known that music can provide analgesia in painful procedures [13,17]. In addition, creative art therapy assists patients to express thoughts, feelings, and access the subconscious when words are difficult [14,17].

Art therapy is especially effective in pediatrics where primary communication is non-verbal [10,14]. It is well known that, the prefrontal cortex and anterior cingulate cortex are under-activated and amygdala is over-activated in children with mental trauma resulting from chronic debilitating medical illness, death of parents or abuse [18]. Self-expression through art therapy allows the creator to depict emotional experiences by creation of images and provides insight into how these experiences affect thoughts and behaviors [10,12,14,17]. These activities assist in making mind and body connections such as creating a map which can depict their emotions using shapes and colors [14,19]. Creative art therapists provide comfort and support at the community meetings through active listening at times of emotional distress [14,17]. The pediatric psychiatric unit implements a behavioral modification plan that is facilitated by creative art therapists which consists of earning points on a scale of 0-4. Most children are motivated to maintain positive behavior to earn privileges, such as not wearing a hospital gown or getting a special treat [19]. It is often seen that many sick children are more open to the creative art therapists as opposed to their physicians or nurses [19,20]. There is evidence that patients taking part in visual and performing arts interventions, had earlier discharges compared to those not doing so [12,14]. Furthermore, it also shows that complimentary medicine is effective in decreasing the incidence of apnea in premature infants, shortening length of stay in NICU by 3 days [21]. A study in 29 children found that that those receiving music therapy coped better with immunization procedures than those receiving traditional care [22]. One group was randomly assigned to have a music therapist present during immunization, while the second group received traditional care [22]. It has also been reported that music significantly increases levels of oxygen saturation and salivary IgA [23]. Studies show that parent's participation in music therapy helped in improving their interactions with their child. However more studies are needed to explore the type and duration of art-based therapies that are effective in specific conditions.

Pediatric Massage Therapy

The first written records of massage therapy (MT) were found in China and Egypt, as long back as 2700 BC. In United States, MT became popular in the hospitals in the 1850's [24]. Many studies have shown that MT can relieve both emotional and physical discomforts by decreasing anxiety, fear and stress associated with chronic conditions such cancer, asthma, sickle cell disease in children [25]. Pediatric massage therapy (PMT) decreases cortisol level, reduces anxiety and improves the pulmonary function in patients with cystic fibrosis [25]. PMT increases the ability of children with ADHD to focus, helps the autistic child to tolerate touch, and relieves post-traumatic stress disorder [25,26]. The therapists offer their services in a variety of settings like NICU, oncology units, and adolescents clinics [26,27]. Growing evidence has shown that neonates feel the same pain intensity as older children and adults. The lack of verbal skills and cognitive limitation to recognize pain such as in vaccination (commonest source of iatrogenic pain in children) among infant and younger children is more challenging compared to older children. One interes-ting study found that massage therapy reduced vacci-nation pain (mean pain scores of 3.05 ± 0.13 and 5.03 ± 0.03 in the study and control groups, respectively) [27]. More studies are needed to understand the frequency, style, and duration that have maximal benefits in children.

Aromatherapy

Aromatherapy is the use of aromatic plant extracts and essential oils in massage or baths, which potentially induces self-healing in hospitalized children by reducing stress and promoting relaxation. The use of such essential

oils for therapeutic, spiritual, hygienic, and ritualistic purposes dates back to ancient civilizations in Chinese, Indian, Egyptian, Greek, and Romans who used them in cosmetics, perfumes and drugs [28]. Variable effectiveness has been seen in pediatric cancer patients [29]. On the other hand, a systematic review found that aromatherapy had superior results in reducing anxiety and improving quality of life compared to massage therapy [30].

Acupuncture

Acupuncture, originating in China in 100 BC, is a form of alternative medicine in which thin needles are inserted into the body [31]. It is still not clear whether acupuncture works through release of neurochemicals such as endorphins or through direct effect on the sympathetic and parasympathetic nervous system [10]. One study showed that it is effective and well tolerated in acute post-operative pain as well as in chronic pain [32]. Further, acupuncture promotes relaxation and sleep [32], thereby decreasing the stress of hospitalization. The biggest challenge in pediatric acupuncture is addressing children's fear of needles. To deal with this issue, the acupuncturist may spend hours with their first-time patients and families to make them completely comfortable with the procedure. They explain and demonstrate the process on their own hands or on the child's toy animal**.**

Overall, studies have shown good results regarding the efficacy of acupuncture, especially in reduction of pain and vomiting in the pediatric oncology population [33]. It is worthwhile to mention that, acupuncture is safe with less than 0.05% serious adverse event rate [34]. However, more studies need to be done to establish its role in pediatric patients.

Pet Therapy

Pet therapy involves bringing domestic animals into the hospital to interact with patients. Pet therapy was first reported in 1792, to help people with mental illnesses at York Retreat in England, while the first documented use of animal therapy was in a convalescent hospital in New York in 1942 [35,36]. It is not clear when pet therapy was introduced in the pediatric patients. Many studies have shown that pet therapy has an important role in hospitalized children by improving satisfaction, decreasing stress, boosting the morale of patients and their parents as well as reducing post-operative pain, improving pleasure in pediatric palliative care patients [37,38]. The commonly used animals in pet therapy are dogs, which are trained for interacting in medical settings. However, there are concerns regarding risks of potential allergic reactions and occasional aggressiveness of pets in hospital settings. More studies need to be done to explore type, time and preconditions of pet therapy in the pediatric population.

Hypnosis

Hypnosis is the induction of a state of consciousness in which a person apparently loses the power of voluntary action and is highly responsive to suggestions or directions [40]. It is not clear when hypnosis was used for the first time in the pediatric population, but it has been used in the treatment of a wide variety of childhood disorders. A systematic review done in 2010 suggested that hypnosis works by changing the perception and sensation [41]. Another study showed that hypnosis may activate certain brain areas resulting in changes in arousal, visual imagery perception and reinterpretation [42]. To measure the sensitivity of the child to hypnosis, many scales have emerged, with 'The Shorter stanford clinical scale' being the most commonly used [43]. According to studies, hypnosis has a positive impact in pediatric cancer patients in reducing anxiety, pain, nausea, vomiting and stress. Studies have also indicated that hypnosis is superior to standard therapy of controlled breathing, games or distraction [44,45].

Educational Services for Hospitalized Children

Hospital school program provides hospitalized children with their educational needs to enable a smooth transition back to school [46]. The teachers of the hospital school program are state certified. They are provided with curriculum and instructional materials aligned to the common core learning standards [46,47]. The children have a choice of attending the class in a group or may opt for individual bedside teaching, Science and Maths are taught in a large class setting. Along with academics, children are also taught coping skills and how to work with small peer groups in art projects [47]. They are given incentives like scented pencils, erasers, and highlighters for completing the educational tasks. Attending home school, while being hospitalized, helps children maintain their academic standing, especially during prolonged absence from school [46-48]. In addition, the children may take the examinations required for promotion. Thus, the hospital school program ensures children feel comfortable and less stressed, brightens their spirits during the hospital stay, and facilitates a smoother return to school.

Hospital Clowning

Hospital clowning is a program where specially trained clowns visit health care facilities with an aim to bring some joy and brighten up the everyday life of the

otherwise mundane hospital environment [48]. Since its introduction in the US in 1986, by professional clown Michael Christensen, medical clowning has been widely used in hospitals worldwide [48].

Hospitalization can be a frightening experience for both parents their children. Thus, the so called 'red nose doctors' pitch in to help alleviate family fears and anxiety [10,48]. The Nonprofit organization 'Red Noses' founded in 2003, comprising of 'red nose doctors' or the 'clown doctors' serve the inpatient, intensive care, out-patient units and acute care waiting areas, touching the lives of hundreds of children and their families every year. The clowns use performances such as 'red nose transplants', 'kitty cat scans', funny bone exams, music, and magic tricks to demystify even the most complicated medical treatments, and support the emotional wellbeing of children and their families [48,49]. They reduce the children's pre-operative anxiety and the pain during an invasive procedures like venous blood draws, allergy skin prick tests, and aid in healing respiratory infections [48-50]. According to a recent meta-analysis, clowning was found to be as effective in reducing children's preoperative anxiety as midazolam or the presence of parents [48].

CONCLUSIONS

The invaluable role of ancillary services in managing a hospitalized child cannot be overemphasized. They improve patient satisfaction and have a positive outcome on the quality of life, which can be translated in to measurable outcomes such as reducing time for procedures, less doctor's visits, fewer symptoms, early discharge and fewer medications. These services help in conserving staff time and energy thereby increasing productivity, staff retention and decreasing burnout [50].

The services can be implemented depending on the geographic location, hospital tier, and availability of the providers. All services need not be available in one facility, but they may be shared between different hospitals within a commutable range. As more free-standing children's hospitals emerge, the ancillary services will gain more recognition and popularity to give the best patient care experience.

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EDITORIAL COMMENTARY

Reducing Perinatal Deaths: A Distant Dream But on the Right Path!

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"*In God we trust, all others bring data!*"

The phrase emphasizes the importance of 'data' to understand a problem, identify the causes, implement preventive and therapeutic activities and specially to plan health programs that concern public health issues. Data collection is an ongoing systematic process of gathering, analyzing and interpreting various types of information from relevant sources. Quality assurance and quality control are two important components of any data. Quality assurance starts before the data collection and quality control occurs during and after data collection. The study by Kumar, *et al.* [1] published in the current issue of *Indian Pediatrics,* the authors evaluated the quality assurance aspect of a perinatal mortality audit. They evaluated the available resources including manpower (public and private hospital staff), protocols (registries, case-sheets, certification), training and reporting (reports generated) required for audit of perinatal mortality. The study shows major gaps in the documentation and reporting of peri-natal deaths. The reasons for lack of quality assurance on perinatal mortality audit from the current study include recent introduction of facility based CDR (child death review) or community based CDR of neonatal deaths and absence of any policy on still birth review till recent times [2]. Inclusion of many private hospitals in the audit also seems to be a major reason for identifying wider systemic gaps. The present study as well as other Indian studies have highlighted the poor engagement of private sector in maternal and infant death reviews, although the private sector contributes to 43% of deliveries in urban areas and 22% deliveries (NHFS 4) in rural areas [3].

Perinatal mortality (PMR) includes still births and early neonatal deaths. As the cause of mortality for these components are closely related to maternal antenatal and intrapartum care, PMR is considered one of the important health indicators of quality of care around delivery. The current PMR of the country is 36 per 1000 pregnancies (NFHS -4). Although reduction of PMR is not addressed directly, the health programs in the country are largely directed to reduce still births and neonatal deaths. India newborn action plan (INAP) targets to reduce still birth rate (SBR) and neonatal mortality rate (NMR) to a single digit by 2030 [4]. Annually approximately 6 lac still births occur in the country and of these nearly 45% occur during delivery. As per the estimates published in Lancet in 2011, the SBR in India is 22 per 1000 total births [5]. The portal of the Health management information system (HMIS) published by the Ministry of health and family welfare, Government of India (GOI), reported 3,03,857 stillbirths for the period 2015-16, which seems to be a gross under-estimate [6]. A sentinel still-birth surveillance program launched by GOI in June 2016, not only provides an opportunity to count stillbirths but also helps to review the circumstances, risk factors and leading determinants resulting in a still born baby [6]. Data from this surveillance will be of immense use to meet the India newborn action plan (INAP) target of single digit SBR by 2030. However, the known causes of stillbirths are largely addressed in the existing health and other social sector programs directly or indirectly. Janani suraksha yojana (JSY) program ensures registration of all pregnant mothers, encourages antenatal visits, and institutional delivery with cash incentives. The success of this program is visible in most states as institutional deliveries in public sectors hospitals improved signifi-cantly over the last decade. Also, NFHS-4 revealed that the proportion of institutional deliveries (public or private) almost doubled from 39% in 2005-06 to 79% in 2015-16 [7]. The Dakshata program, a skill oriented, evidence-based, woman- and baby-friendly training ensures essential interventions that need to be in place to reduce reproductive, maternal, newborn and child mortality and morbidity and promote reproductive health. In addition to JSY and the Dakshata program, the Labour room and quality improvement initiative (LaQshya) and the Pradhan mantri surakshit matritva abhiyan (PMSMA) would contribute significantly to reduce SBR [8].

Neonatal mortality and early neonatal mortality are adequately addressed in the current health programs of

the country. Facility based death review (FBDR) and Community based death review (CBDR), under the National health mission are important policy decisions to account for neonatal deaths. Appropriate implementation and feedback of these would help in improving community awareness, reduce the gap between facility and the pregnant mother, improve services to cater to the care of newborn and also integrate other social services such as sanitation, nutrition and availability of potable drinking water. Navjaat shishu suraksha karyakram (NSSK), a capacity building program implemented in collaboration with Indian academy of pediatrics (IAP), backed with a scheme like Janani shishu suraksha karyakram (JSSK) and state of the art infrastructure in the form of Special newborn care units (SNCUs), Newborn stabilization units (NBSUs) and the Newborn care corners (NBCCs) across the country have contributed significantly in reducing the newborn deaths due to asphyxia, prematurity and sepsis [8]. There is still a great need to improve newborn care further across different tiers of health facilities to achieve the INAP targets by 2030.

In conclusion, the present paper brings out glaring deficiencies in documentation, record keeping and reporting of perinatal deaths as on 2015, but a significant change is visible in the last five years with the inclusion of child death review in NHM, and also the start of a sentinel surveillance of stillbirths. We sincerely hope that the upcoming National digital health mission (NDHM) will ensure that these deficiencies wouldn't exist in coming years [8]. Since neonatal mortality rate is an INAP indicator, and is closely monitored under current national programme, there are instances to (mis)classify early neonatal deaths as stillbirths so as to keep the neonatal mortality low. This makes a strong case to begin monitoring the perinatal mortality rate across the country and expand the scope of CDR to include stillbirths. Nodal officers for CDR should be made more responsible for perinatal death reviews at state, district and sub-district Level.

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RESEARCH PAPER

Documentation and Reporting of Perinatal Deaths in Two Districts of Karnataka, India: A Situational Analysis

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Objectives: In Karnataka state, perinatal mortality rate is almost equal to infant mortality rate. This preliminary study was conducted in two districts of Karnataka to study potential problems to start of perinatal death audit. **Methods**: Hospitals providing maternal and child health care services, which met study inclusion criteria, in Dakshina Kannada and Koppal Districts were included. Following variables were studied: (*i*) Documentation and reporting systems in these hospitals; (*ii*) Role of health care personnel in documentation and reporting (*iii*) Existing system of audit, if any. **Results**: Totally 94 hospitals met our criteria with Dakshina Kannda District having 63 (67.02%) and the rest in Koppal District. Documentation and reporting was poor in Koppal District and inadequate in Dakshina Kannada district. Health care personnel were apprehensive about perinatal death audit. **Conclusion**: Problems identified need to be addressed before starting perinatal death audit.

Keywords: *Death audit, Infant mortality, Perinatal mortality*.

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Karnataka has shown a reduction of infant mortality rate (IMR) from 71 in the year 1980 to 35 in the year 2011 [1]. The perinatal mortality rate (PMR) has also decreased from 40.2 in the year 1980 to 33.4 in the year 2011 [1]. But the contribution of PMR to IMR in Karnataka has varied from 60 to 70% during this period of time. For reasons that are not clear, the contribution of PMR to IMR in Karnataka has increased from 95 to almost 99% from the year 2011 to 2013 [1]. An audit of perinatal deaths could help in understanding and rectifying the causes for perinatal deaths. However, there is no perinatal death audit system in India. To start a perinatal death audit system, it is essential to carry out a preliminary study exploring the issues and problems that exist to start perinatal death audit. Thus, a preliminary study would help understand the problems that need to be addressed to start a perinatal death audit system.

The maternal and child health care facilities are not uniformly developed in Karnataka; the northern districts lag behind the southern districts [1]. The issues and challenges to starting a perinatal death audit in a relatively backward northern district of Karnataka may not be the same as compared with a better developed southern district. We conducted this study to enlist the problems, if any, in starting a perinatal death audit in two different districts of Karnataka.

METHODS

This descriptive study was a part of a three-year interventional project conducted in two districts of Karnataka in the year 2015. The initial pre-interventional survey was carried out over one year. Dakshina Kannada district located in southern Karnataka is well developed with much better facilities as compared with Koppal district from the northern part, which is considered as one of the five backward districts of Karnataka [2,3].The entire system involved in documentation and reporting perinatal care in both the districts of Karnataka were explored and documented. All government hospitals and those private hospitals which provided maternal and child health services with any one or more facilities for conducting: (*i*) normal delivery (*ii*) high-risk delivery, and (*iii*) normal and high-risk neonatal care were included for the study.

Editorial Commentary : Pages 1004-05.

The components of perinatal care documentation system included for the study were documentation and reporting systems (like documentation of the case related information, and reporting system); and the role of healthcare personnel involved in perinatal care in documenting and reporting of perinatal deaths. Details of the documentation and reporting systems considered for the study were as follows: Presence of registries for

documenting deaths, death certificates, person filling the death certificates, case sheets, person preparing the case sheets, registries for documenting data from field area covered by that government hospital, routine reporting (like weekly reports, monthly reports, nil reports), and maintenance of records in the hospitals.

Apart from the information available about the components mentioned above, some non-governmental organizations (NGOs) in both the districts were also contacted. These NGOs have a system of tracking infant deaths by gathering information from house-to-house visits. This helped to cross-verify the information about perinatal deaths from the government and private hospitals.

Semi-structured checklists were developed to record all the components of the documentation and reporting systems mentioned above. These semi-structured checklists were pre-tested in neighboring district of Udupi to know the feasibility and appropriateness for use. Some open-ended items were introduced so that any other relevant observation could be documented.

Permission was obtained from the Government of Karnataka to conduct the study. The district commissioners of the two districts were directed by the state government to provide the necessary administrative support for the study. Four qualified medical social workers who were trained to fill the checklists collected the data by visiting the health care facilities. They filled the semi-structured checklists by a combination of observation and interaction with the doctors and support staff present in the hospitals. The filled checklists were scrutinized by the investigators. In case of any queries, the healthcare facilities were approached more than once to collect the data.

The filled forms were studied, and discussions conducted by the investigators to arrive at solutions for improving the documentation and reporting of perinatal deaths. The qualitative data is presented in numbers and percentages.

Table I Details of the Government and Private Hospitals that Met the Study Criteria in Two Districts of Karnataka

Type of health-care facility	*Koppal district (n=63)*	*Dakshina Kannada district (n=31)*	*Total*
Government hospitals			
PHCs	4	7	11
CHCs	1	3	4
District hospital	1	1	2
Private hospitals	25	52	77

**PHCs: Primary health centres; CHCs: Community health centres.*

RESULTS

The details of the institutions that met the study criteria are presented in ***Table* I**. Most hospitals in Koppal (29, 93.5%) did not maintain case sheets. Most hospitals in Dakshina Kannada maintained case sheets (60, 95.2%), but in majority the records did not have clinical information necessary to carry out the audit. When present, the details in case sheets were not legible.

In Koppal district, the documentation was almost non-existent in private hospitals; most (21, 67.7%) did not document any perinatal deaths. Based on the information collected from the NGOs of that area, when the hospitals were asked about such deaths, they verbally confirmed it. But there were no written/documented details. As the hospitals did not document these, they did not report to the authorities. Government hospitals also did not have adequate information. They did not report all the neonatal deaths. Register for documenting first information report (FIR) of neonatal deaths in Koppal district hospital was not available. In Dakshina Kannada district, documentation was much better and the district hospital maintained death registry for documenting FIR of perinatal deaths.

Table II Functioning of Existing Neonatal Death Audit System in Both the Districts

Indicator of functioning of existing audit system	*Dakshina Kannada district*	*Koppal district*
Statistics and line listing of deaths at district level	Maintained	Maintained
Proceedings of death audit meetings, (if any)	Not available	Not available
Feedback sent after the audit, (if any)	Not available	Not available
Number of FBDR carried out in the hospitals	No data available	No data available
Reports received from private and public institutions and copies of the FBDR	No data available	No data available
Registries maintained in district health officer (DHO) office	Yes	No
Guidelines for FBDR received from Government of Karnataka maintained in the DHO office	Yes	No

FBDR: Facility based death reviews.

Most of the doctors in both the districts were not aware of the existence of a separate death certificate for documenting perinatal deaths. Medical officers in charge of government hospitals did not pay attention to weekly or monthly reporting of neonatal deaths, still births and perinatal deaths. Some of them had delegated the responsibility of filling the registries to the nursing staff.

At the time of start of this study, there was no perinatal death audit system in both the districts. However, neonatal deaths were audited as part of infant death review as per National Health Mission (NHM) guidelines. Verbal autopsies were done to some extent. There was no auditing of fetal deaths in antenatal period. However, the facility-based death review (FBDR) began much later after our study project was underway. FBDR was introduced by the government as a part of child death reporting. According to it following activities had to be undertaken: (*i*) the deaths are expected to be discussed at all the facilities, (*ii*) report sent to the district health office, and (*iii*) district health office collects verbal autopsy reports and sends the summary for line-listing of neonatal deaths to the state health department. These activities were not being done fully. The functioning of existing neonatal death audit system in both the districts is shown in ***Table* II**.

Box 1 Suggested Solutions for Starting Perinatal Death Audit

Improving documentation at the hospitals

- It should be made mandatory for the doctors to fill all the case sheets pertaining to maternal and neonatal care provided in the hospitals.
- Maintenance of separate file for keeping copies of all the case sheets pertaining to perinatal deaths
- To maintain a registry with contact details of the parents would help in cross-verification and clarification if needed.
- Prompt weekly / monthly reporting of all the perinatal deaths in hospitals to the District health officer (DHO) would be required.

Improving the role of health care personnel

- Doctors should be trained to fill the separate perinatal death certificates.
- Doctors should fill all the details in the case sheets.
- In private hospitals, nurses should be made in charge of maintaining registries and sending routine reports.
- In government hospitals clerks should be in charge of maintaining registries and routine reporting to the District health officer.
- About perinatal deaths occurring in the community, nurses in government hospitals who are in charge of covering the population in the field area (designated for that hospital) should prepare and provide a First information report (FIR) to the hospital of all the perinatal deaths that occurred in their field area.
- Information about perinatal deaths occurring in the community (outlined above) could be used to update the registries in the government hospitals.

Improving the reporting system in the district

- District health officer (DHO) (alternatively known as Civil surgeon) should make it mandatory for all the hospitals to report at least once in a fortnight including nil reporting.
- DHO should designate a Taluka medical officer (alternatively called Block Medical Officer) to scrutinize all the death certificates and case sheets. This should preferably be done by Medical officer in charge of implementing Reproductive child health programme in the district.
- This officer should also seek and obtain information from all the NGOs tracking infant deaths in the district. · A clerical staff member should be designated to update the registries and prepare monthly reports of all the reported perinatal deaths in the district.
- Proceedings of all the facility-based death reviews carried out every month should be documented and kept in a separate file. Copy of feedback, if any, sent to the hospitals (Government or private) should be kept in the DHO office.

Enhancing compliance with reporting system at the district level

- Training programme covering perinatal death auditing, writing death summaries, filling perinatal death certificates and reporting formats doctors.
- At the time of training, apprehensions about implications of auditing among health care personnel should be addressed. This will help remove fear and improve compliance.

WHAT THIS STUDY ADDS?

Improvements in documentation and reporting systems are required to initiate the perinatal death audit system in the Districts covered in this survey.

DISCUSSION

The documentation and reporting of perinatal deaths in Dakshina Kannada and Koppal districts was found to be sub-optimal in this study. A review of studies on under-reporting indicates that, while both live births and neonatal deaths may be underreported, fetal deaths are much more likely to go unreported [4,5]. Reports from developed countries show that incomplete reporting of vital events varied from 10-30% [6-8].

Based on the problems identified by this study, we identified four categories of solutions for starting perinatal death audit (***Box* 1**). Starting a perinatal death audit would help in knowing causes, identifying problems that need to be solved and help arrive at solutions. Such a system would help identify 'preventable' perinatal deaths. Targeting and reducing preventable perinatal deaths should be a priority. Though neonatal mortality declined from 31 in 2011 to 24 in 2017, it has reduced just one point per year [9], and we do not know what proportion of these were preventable perinatal deaths. A survey of maternal and neonatal care facilities in these two districts has revealed deficiencies in managing high risk cases [10]. Even though efforts are being made to improve health care infrastructure under National Health Mission (NHM), poor healthcare infra-structure and inefficiency in the healthcare delivery in rural areas has been reported [11]. Considering the fact that deficiencies exist for managing high-risk cases, it is certain that some perinatal deaths are preventable [10]. The prerequisites *i.e.*, documentation, record keeping, and reporting would help to start perinatal death audit and identify preventable perinatal deaths, apart from providing inputs for planning intervention strategies.

This study was limited to only two districts of Karnataka. As most of the hospitals in Koppal district did not document and report, further details like errors in filling up of case sheets and death records could not be identified. However, inclusion of one district from well-developed southern part and one from backward northern part of Karnataka shows that the problems identified are similar.

Our findings suggest that the healthcare personnel have to be trained for documentation and reporting, before introducing perinatal death audits.

Contributors: HK, PK, SB, NK, SR: took part in drafting the protocol; HK, SB, PK: organising the data collection and supervising field work; SB, PK, NK, SR: cross-checking of the filled forms; HK: statistical analysis; HK, SB, PK: writing the paper.

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Competing interest: None stated.

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RESEARCH PAPER

Epidemiological and Clinical Profile of Pediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARS-CoV-2 (PIMS-TS) in Indian Children

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Background: We describe the demographic, clinical and laboratory findings along with the treatment and outcomes among children meeting the case definition of Pediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS).

Methods: We analyzed the clinical and laboratory findings of children who presented with PIMS-TS during an 8-week period from May 4, 2020 to July 8, 2020.

Results: We report 19 children with a median age of 6 year (IQR: 13 months-16 years), who met the case definition of PIMS-TS. All of them presented with fever. Multi organ involvement (79%), mucocutaneous involvement (74%), cardiovascular symptoms (63%) and gastrointestinal symptoms (42%) were the other features. Elevated levels of C-reactive protein was found in all of them and the majority of them had evidence of coagulopathy; intensive care admissions were needed in 12 (63%) and vasoactive medications were given to 6 (31.5%) children. There were no deaths.

Conclusion: Children with PIMS-TS present with a wide range of signs and symptoms. Fewer children in this series had coronary artery abnormalities, and there was a low incidence of RT-PCR positivity with high presence of SARS-CoV-2 antibodies.

Keywords: *COVID-19, Hyper-inflammatory syndrome, Kawasaki disease, MIS-C, Toxic shock syndrome*.

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The impact of the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been widespread. Initial reports worldwide showed that most children are asymptomatic or have mild or moderate disease [1-3]. However, there are now several reports of the pediatric multisystem inflammatory synd-rome associated with COVID-19 (PIMS-TS) in children globally [4-11].

In early May, the first published report of PIMS-TS or multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) was reported from India from our center. [11]. We hereby describe the demographic, clinical and laboratory findings of a series of cases of PIMS-TS seen since then in our center, so as to provide Indian data related to this syndrome.

METHODS

This study was conducted at a tertiary care children's hospital in Chennai, India. We analyzed children presenting to our hospital from May 4, 2020 to July 8, 2020 (8 week period), who satisfied the case definition of PIMS-TS as defined by Royal College of Paediatrics and Child Health (RCPCH) [12]. Retrospectively, four children admitted during the month of April, 2020 were also included, as they met the criteria specified by RCPCH PIMS-TS definition. Data on the following parameters were collected: demographics, clinical findings, radiological findings, underlying comorbidities, echocardiographic findings, laboratory investigations, treatment received including intensive care interventions and outcome. This data is a part of a larger COVID-19 study in children presently undergoing at our institution, and was approved by the ethics committee. All children were included in the study after written informed consent of the caretaker.

Confirmed COVID-19 was defined as either positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) performed by Indian Council of Medical Research (ICMR) approved laboratories or positive antibody test performed with ICMR-approved YHLO SARS-CoV-2 IgG and IgM antibody titer assay kits (Shenzhen YHLO Biotech Co. Ltd.) as per manufacturer's instructions.

Designated doctors and the study nurse collected all details in standardized and approved case report forms, which were then entered into to the Microsoft Excel spreadsheet. Vital signs (tachycardia, tachypnea and hypotension) were classified according to normal values for the age [13]. Data on various laboratory markers were collected and elevated levels were defined in relation to the normal levels for the age [14,15]. Cardiovascular involvement was described as children needing any of the following: fluid bolus (>20 mL/kg) with or without vasoactive medications, an echocardiogram showing decreased left ventricular function (EF <55%), coronary artery abnormality, pericarditis or pericardial effusion, electrocardiogram (ECG) evidence of arrhythmias with or without elevated levels of troponin or pro BNP.

Statistical analyses: Data are presented as median (IQR), numbers and proportions. Statistical analyses were performed using SPSS version 24.0.

RESULTS

A total of 19 children with a median (IQR) age of 6 years (13 months-16 years) who met the criteria of PIMS-TS were included in this series. Between May 1 and July 8, 2020, 15 children were identified and four children were identified in April, 2020.

The male to female ratio was 1:1.4 and 9 children (47%) were younger than 6 year. Of the 19 children, 15 (79%) were tested for COVID 19 by RT-PCR and serological assays and 11 (58%) were identified as confirmed cases of COVID-19. SARS-CoV-2 was confirmed by RT-PCR alone in three children (16%), one child (6%) had evidence from both RT-PCR and serological assay, 7 children (47%) had positive serological assay alone whereas RT-PCR and serological assay was negative in 4 (27%) children (***Table* I**).

RT-PCR and/or serological assay negative or COVID-19 status unknown children were included as they met the criteria as specified by RCPCH PIMS-TS definition. All children (100%) presented with fever of more than 3 days and six (31%) presented with lymphadenopathy. Multi-organ involvement was seen in majority of the children (15/19, 79%). Cardiovascular symptoms were reported in 12 (63%) children, of which three had coronary artery abnormality at presentation (***Table* I**).

Elevated CRP (median (IQR): 118 (73-298) mg/L) was noted in all 19 children (100%). Coagulation parameters (PT, APTT and INR) were abnormal in 11/15 children (73%) and D-dimer (median (IQR): 4,250 (339 - 7328) ng/mL FEU) was elevated in 13/14 (92.8%) children (***Table* II**).

Chest radiography was performed in 15 children, of which 5 showed evidence of lobar consolidation (unilateral). Ultrasound scan of abdomen was performed in 5 children of whom one was suggestive of as possible appendicitis. CT chest and abdomen was performed in the same child, which showed evidence of right lower lobe consolidation. Coronary artery abnormality (dilatation without aneurysm, *Z* score <2.5) was seen in three children with one of them having evidence of minimal pericardial effusion.

Of the 19 children, 5 (26%) received intravenous immunoglobulins (IVIG) alone, whereas three children (16%) were treated with steroids alone; 8 children (42%) received both IVIG and steroids, and one child received IVIG and tocilizumab. Aspirin was given in 16 (84.2%) children and two children were not given any immunomodulatory agents. All 19 children received broad-spectrum antibiotics at presentation, which were discontinued after negative culture results. No organisms were isolated from blood cultures.

Only one child had underlying co-morbidity (global developmental delay) and one child presented with features mimicking appendicitis along with positive SARS-CoV-2 antibodies. Median length of hospitalization was 6 days (IQR 3-13 days) and 12 (63%) children required PICU support. There was no mortality in our series.

DISCUSSION

This study is the first series from India describing children presenting with PIMS-TS. Consistent with published data from Europe and US, children in this study also presented with signs and symptoms mimicking complete or incomplete Kawasaki disease (KD), toxic shock syndrome (TSS), hemophagocytic lymphohistiocytosis (HLH) and/or macrophage activation syndrome (MAS) [4,5,10]. Although, cardiac dysfunction is the most commonly reported organ dysfunction [5,7,12], a notable finding in our series was that a fewer number of children were identified to have echocardiographic evidence of coronary artery changes (3/19, 16%), though a significant number of children (57%) developed hypotension requiring admission to the PICU for vasoactive medications. Likewise, when compared to the available data, fewer children (42%) in our series presented with gastrointestinal symptoms as against up to 80% in literature [4-6,16], and more than two-third (74%) presented with mucocutaneous manifestations.

Clinical presentation, epidemiology and pathogenesis of PIMS-TS are still unclear and evolving, but cases of PIMS-TS seem to appear few weeks after the COVID-19 peak in the population [5,17,18]. The COVID-19 peak in

Table I Demographic and Clinical Characteristics of Children With PIMS-TS (*N*=19)

	All children	*^RT-PCR / Serology*	
		Positive (n=11)	*Negative/unknown (n=8)*
Age, median (range)	6 y (1y 1m-16y 9m)	8.2 y (2y 10m-16 yr 9 m)	4.2 y (1yr 1 m - 11y 1 m)
Male	8 (42)	4 (36)	4 (50)
Comorbidity	1/19 (5.2)	1/11 (9)	0
RT-PCR positive	4/15	4/11	4 negative, 4 not tested
Serology positive	8/15	8/11	4 negative, 4 not tested
Fever	19 (100)	11 (100)	8 (100)
Lymphadenopathy	6 (31.5)	1 (9)	5 (62.5)
GI symptoms	8 (42)	6 (54.5)	2 (25)
Abdominal pain	8	6	2
Vomiting	6	4	2
Diarrhea	3	3	0
Mucocutaneous	14 (74)	6 (54.5)	8 (100)
Rash	12	4	8
Edema	10	4	6
Congested conjunctiva	9	3	6
Oral mucosa involved	9	2	7
CVS symptoms	12 (63)	9 (81.8)	3 (37.5)
Hypotension	10	9	1
Acute kidney injury	3 (16)	3 (27.2)	0
Respiratory symptoms	8 (42)	5 (45.4)	3 (37.5)
Neurological symptoms	6 (31)	3 (27.2)	3 (37.5)
Meeting KD criteria	7 (36.8)	1 (9)	6 (75)
PICU admission	12 (63)	10 (91)	2 (25)
Mechanical ventilation	0	0	0
HHFNC	1	1	0
Nasal cannula oxygen	4	4	0
Fluid bolus (>20 mL/kg)	10 (52.6)	9 (81.8)	1 (12.5)
Vasoactive support	6 (31.5)	6 (54.5)	0
IVIG used	15 (79)	7 (63.6)	8 (100)
Steroids used	11 (58)	8 (72.7)	3 (37.5)
Tocilizumab (8 mg/kg) used	1 (5.2)	1 (9)	0
Aspirin used	16 (84.2)	8 (72.7)	8 (100)

PIMS-TS: Pediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2; All values in no. (%); GI: gastrointestinal, PICU: Pediatric intensive care unit; HHFNC: High flow nasal cannula oxygen; IVIG: Intravenous immunoglobulin; CVS: Cardiovascular system; RT-PCR: Reverse transcriptase polymerase chain reaction; ^RT-PCR results available in only 15 children – 4/11 were positive in first group, and in second group 4/8 were negative and results were unknown in remaining 4.

the community is possibly yet to occur in several cities in India, and we postulate that we may also see a significant increase of PIMS-TS among children in the coming days.

A positive serologic assay for SARS-CoV-2 or RT-PCR has been a consistent finding in the literature [7,8]; although, there have also been published reports with negative results for SARS-CoV-2 [10]. Most of the children in this study (58%) had laboratory confirmed SARS-CoV2 infection. Serology testing or RT-PCR could not be performed in four children as they presented to us at the beginning of COVID-19 pandemic in Chennai. These four children had no microbiological evidence for other infections. They had multi-organ dysfunction with elevated inflammatory makers (CRP, D-dimer and ESR) in addition to neutrophilia and lympho-penia. However, we plan to perform serological assay in these children during their follow up to establish a link between their symptoms and SARS-CoV-2. PIMS-TS generally tend to occur in older children (reported median age 8 years) [5,6,10], which is

Table II Profile of Laboratory Markers in Children With PIMS-TS (*N*=19)

	All children	*^RT-PCR / Serology*	
		Positive (n=11)	*Negative/unknown (n=8)*
Elevated CRP	19 (100)	11 (100)	8 (100)
Elevated troponin (pg/mL)	1/6 (16.6)	1/5	0/1
Elevated NT pro BNP (pg/mL)	3/4 (75)	3/3 (100)	0/1
&Elevated fibrinogen	7/9 (77.7)	6/7 (85.7)	1/2 (50)
Elevated D-dimer (ng/mL FEU)	13/14 (92.8)	10/11 (91)	2/3 (67)
%Hypoalbuminemia (g/dL)	11/18 (61.1)	7/11 (63.6)	4/7 (57.1)
@Hyponatremia (mmol/L)	11/19 (58)	7/11 (63.6)	5/8 (63)
‡Elevated LDH (U/L)	7/13 (53.8)	4/10 (40)	3/3 (100)
Neutrophilia (per m^3)	13 (68.4)	6 (54.5)	7 (87.5)
Lymphopenia (per m^3)	7 (36.8)	6 (54.5)	1 (12.5)
^High ferritin (ng/mL)	3 (21.4)	3/10 (30)	0/4
Anemia (mg%)	6 (31.5)	5 (45.4)	1 (12.5)
Thrombocytopenia (per mm^3)	3 (15.7)	3 (27.2)	0
#Elevated ESR (mm/h)	9/11 (81.8)	4/5 (80)	5/6 (83.3)
Transaminitis (U/L)	5 (26.3)	4 (36.3)	1 (12.5)
Deranged coagulation	11/15 (73.3)	9/11 (81.8)	2/4 (50)
Abnormal chest *X*-ray	5/15 (33.3)	5/11 (45.4)	0/4
Coronary artery changes*	3	1¥	2
Three systems involved	7 (36.8)	4 (36.3)	3 (37.5)
Four systems involved	6 (31.5)	5 (45.5)	1 (12.5)

*PIMS-TS: Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2; #median (IQR) ESR: 86 (15-140) mm/h; ^median (IQR) ferritin 238 (220-1230) ng/mL; ‡median (IQR) LDH: 451 (307-751) U/L; @median (IQR) hyponatremia: 132 (130-139) mmol/L; %median (IQR) hypalbumenia: 3 (2.3-3.4)g/dL; &Median (IQR) Fibrinogen: 458 (228-669) mg/dL; PICU: Pediatric intensive care unit; CRP: C-reactive protein (>30 mg/l); Troponin: T (>4pg/mL); NT pro BNP: N Terminal PRO B Type Natriuretic Peptide (>180 pg/mL FEU), Fibrinogen (>400 mg/dL), D-dimer (>500 ng/mL FEU), Hypoalbuminemia (<3.5 g/dL), Hyponatremia (<135mmol/l), LDH (>460 U/l), Neutrophilia (>7700/mm^3), Lymphopenia (<1500/mm^3), Anemia (<9 mg%), Thrombocytopenia (<1.5l/mm^3), Ferritin (>500 ng/mL), ESR-Erythrocyte Sedimentation Rate (>40 mm/hr), Transaminitis- (Alanine amino transferase (ALT)/Aspartate amino transferase (AST) >40IU/l), PT: Prothrombin time; INR: International Normalized Ration >1.2; *Coronary artery changes-dilatation without aneurysms (z score < 2.5); ¥Evidence of minimal pericardial effusion in addition to coronary artery dilatation.*

slightly more than that seen in our patients. Laboratory testing in our group generally showed significant elevation of inflammatory markers, as reported earlier [6,19].

Currently there is no consensus regarding management of children with PIMS-TS; although there has been a recently published review suggesting a treatment flowchart [20]. IVIG (2 g/kg) has been most commonly used as first line therapy with many children receiving additional high-dose steroids [5-7,16]. Nearly half of the children (42%) in this series received both IVIG and steroids, with a few children requiring a second dose of IVIG and one child needing additional immuno-modulatory medication. The role of aspirin in children with hyperinflammation without KD is not yet described, though it has been used by many in PIMS-TS [10,11]. Lack of uniform guideline for management reinforces the fact that further studies are required to establish optimal treatment in PIMS-TS.

The main limitations of the study are relatively smaller number of patients and a shorter duration of study; hence, we are unable to provide data on long-term sequelae of PIMS-TS. Another limitation is absence of serological confirmation of SARS-CoV-2 infection in nearly one-fifth of the children.

Our study is one of the first series from Asia describing PIMS-TS in children. We report fewer coronary artery abnormalities, as compared to the existing data on PIMS-TS. Finally, we also report low incidence of RT-PCR positivity with increased presence SARS-CoV-2 antibodies. This study underscores the occurrence of PIMS-TS in children in India and will increase awareness of the disease among the clinicians, so as to enable early recognition and prompt management.

Ethics approval: CTMRF-KKCTH Ethics committee; No. ECR/676/Inst/TN/2014/RR-17, dated June 2, 2020.

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WHAT THIS STUDY ADDS?

- Lower age and lesser echocardiographic abnormalities were observed among children with PIMS-TS.
- Prompt recognition and treatment with immunomodulatory agents are likely to result in favorable outcome in PIMS-TS.

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RESEARCH PAPER

Multisystem Inflammatory Syndrome in Children With COVID-19 in Mumbai, India

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Objective: We describe the presentation, treatment and outcome of children with multisystem inflammatory syndrome with COVID-19 (MIS-C) in Mumbai metropolitan area in India.

Methods: This is an observational study conducted at four tertiary hospitals in Mumbai. Parameters including demographics, symptomatology, laboratory markers, medications and outcome were obtained from patient hospital records and analyzed in patients treated for MIS-C (as per WHO criteria) from 1 May, 2020 to 15 July, 2020.

Results: 23 patients (11 males) with median (range) age of 7.2 (0.8-14) years were included. COVID-19 RT-PCR or antibody was positive in 39.1% and 30.4%, respectively; 34.8% had a positive contact. 65% patients presented in shock; these children had a higher age (*P*=0.05), and significantly higher incidence of myocarditis with elevated troponin, NT pro BNP and left ventricular dysfunction, along with significant neutrophilia and lymphopenia, as compared to those without shock. Coronary artery dilation was seen in 26% patients overall. Steroids were used most commonly for treatment (96%), usually along with intravenous immunoglobulin (IVIg) (65%). Outcome was good with only one death.

Conclusion: Initial data on MIS-C from India is presented. Further studies and longer surveillance of patients with MIS-C are required to improve our diagnostic, treatment and surveillance criteria.

Keywords: *PIMS-TS, Kawasaki disease, Myocarditis, COVID-19, SARS-CoV-2.*

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Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 [1,2], also called as Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [3], is a hyperinflammatory syndrome occurring in close temporal association with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children. The initial cases from India were reported in May, 2020 [4-6], and as the number of COVID-19 cases has grown exponentially across the country, clinicians have started identifying this new entity more frequently [7].

We describe clinical features and management in children with MIS-C from the Mumbai metropolitan area, which had a high incidence of coronavirus disease 2019 (COVID-19).

METHODS

This is the preliminary analysis of an ongoing observational study from the Division of pediatric cardiology and Division of pediatric intensive care of four tertiary care hospitals in the Mumbai metropolitan region. Patients with MIS-C who fulfilled the WHO criteria [2] and were treated at the participating centers between 1 May, 2020 and 15 July, 2020 were included in this analysis. Other infective causes with similar presentation such as dengue shock syndrome and bacterial sepsis were excluded prior to diagnosing the patient with MIS-C. Institutional ethics committee approval was taken from all four hospitals. Data were extracted from hospital records and were entered on a Microsoft Excel spreadsheet. Variables studied included demographics, presence of positive SARS-CoV-2 antigen or antibody test or history of contact with a positive patient, clinical symptomatology, laboratory parameters, treatment given and outcome.

Based on the dominant clinical presentation, the cases were categorized into two subsets: Group 1 (MIS-C with shock), those patients requiring inotrope use and/or fluid resuscitation >20 mL/kg; and Group 2, MIS-C without shock. Mucocutaneous features such as skin rash, non-purulent conjunctivitis, changes in lips, oral

mucosa and extremity changes as defined by previous guidelines of Kawasaki disease (KD) [8] and MIS-C [2] were noted. Shock was defined as hypotension with poor peripheral perfusion requiring inotropic support and/or fluid resuscitation >20 mL/kg. Specific laboratory markers described for MIS-C were measured as per the treating physician's discretion and institutional protocols. This included total and differential white blood cell count, platelet count, acute phase reactants (C-reactive protein, ferritin, D-dimer, interleukin-6), renal and liver function tests and cardiac biomarkers (troponin, CPK-MB, N-terminal pro BNP). Laboratory parameters were labelled as elevated or depressed in relation to the age-specific normal ranges.

Echocardiography was used to assess ventricular dimensions, myocardial dysfunction and ectasia or aneurysm of the coronary arteries. All echocardiograms were done by the consultant pediatric cardiologists at the respective centers. Presence of arrhythmias and ischemia was assessed on electrocardiogram. Chest CT was not routinely done. Clinical myocarditis was defined as cardiac dysfunction with left ventricular ejection fraction (LVEF) <50% on echocardiography with elevated cardiac biomarkers. Patients presenting with shock with left ventricular (LV) dysfunction on echocardiography were classified primarily as cardiogenic shock. Patients with warm shock requiring inotropic support in spite of having normal left ventricular function were classified as vasoplegic shock. The coronary artery diameters were measured as per standard criteria [8] and indexed with *Z* scores [9]. Coronary *Z* scores of greater than 2.5 were considered as dilated [8].

SARS-CoV-2 infection was diagnosed by nasopharyngeal swab real-time reverse transcription-polymerase chain reaction (RT-PCR) and/or rapid antibody test for SARS-CoV-2 (Vitros Anti Sars Cov IgG antibody kit, Ortho Clinical Diagnostics) as recommended by Indian Council for Medical Research. Additionally, history of contact with a COVID19 positive patient was also considered positive as per the WHO criteria. Outcome was classified as discharged or death. Long term follow-up of these patients is ongoing.

Statistical analyses: Statistical analysis was performed using SPSS v 26 (IBM, USA). Chi-square test was used to compare categorical variables, student-t test was used to compare normally distributed data and Mann Whitney U test was used to compare data which was not normally distributed.

RESULTS

A total of 23 patients (11 males) with MIS-C were treated during the study period. Demographics and clinical presentation are detailed in ***Table* I** and laboratory findings and treatment are shown in ***Table* II**. Patients presenting with shock (group 1) were older and had significantly higher neutrophil count, lower lymphocyte counts, higher serum ferritin, NT pro BNP and troponin levels as compared to group 2. Of the patients in group 1 (*n*=15), 8 (53%) had LV dysfunction with cardiogenic shock; those with normal LV function who also presented in shock possibly had vasoplegic shock with the generalized hyperinflammatory state. Clinical myocarditis was diagnosed in 15 patients (65%) who had LV dysfunction and/or elevated cardiac biomarkers and coronary involvement was seen in 26% of the patients.

One six-year old girl with positive COVID contact with history of fever and loose stools, presented to the casualty in shock, died within two hours of presentation with pulmonary hemorrhage despite all management efforts (Shock management, steroids, IVIg, invasive ventilation, antibiotics). Her echocardiogram showed moderate LV systolic dysfunction (LVEF 37%). RT-PCR sent at admission was negative, and antibody testing could not be done.

DISCUSSION

MIS-C is a rare disorder, affecting only 0.6% of patients <21 years of age infected with SARS Cov-2 [10,11] and

Table I Demographic and Clinical Parameters in Children With Multisystem Inflammatory Syndrome in Children With COVID-19 (MIS-C)

Characteristics	*Total cases n=23*	*Group 1= Shock, n=15*	*Group 2= No shock, n=8*
^Age (y)*	7.2 (5.7-9.4)	7.8 (6-10.1)	5.2 (1.25-9.7)
Females	12	9 (60)	3 (37.5)
H/o contact	8 (34.8)	5 (33.3)	2 (25)
RT-PCR positive	9 (39.1)	5 (33.3)	4 (50)
Antibody positive	7 (30.4)	4 (26.6)	3 (37.5)
Symptoms			
Fever duration (d)#	5.2 (1.8)	5.5 (0.6)	4.75 (1.5)
Pain in abdomen	12 (52.1)	8 (53.3)	4 (50)
Diarrhea/vomiting	15 (69.5)	9 (60)	6 (75)
Breathlessness	11 (47.8)	9 (60)	2 (25)
Rash	14 (65.2)	9 (60)	5 (62.5)
Conjunctivitis	11 (52.1)	7 (46.7)	4 (50)
Oral cavity changes	4 (21.7)	2 (13.3)	2 (25)
Limb changes	3 (13.0)	2 (13.3)	1 (12.5)
SpO_2 (%)#	95.9 (7.1)	95.8 (8.7)	96.1 (3.4)

*All values in no. (%) except *median (IQR) or #mean (SD); ^P=0.05; SpO_2: Oxygen saturation.*

Table II Biochemical and Echocardiographic Parameters and Management in Children With MIS-C

Characteristics	*Total (n=23)*	*Group I (n=15)*	*Group II (n=8)*	*P value*
Investigations				
Total leucocyte count ($X10^9$), mean (SD)	15.0 (10.2)	16.2 (1.0)	11.3 (8.1)	0.26
Neutrophils percent, mean (SD)	80 (11)	83 (10)	67.1 (6.7)	0.007
Lymphocyte percent, mean (SD)	14.3 (9.1)	11.4 (8.0)	20.5 (8.5)	0.02
Hemoglobin (gm/dL), mean (SD)	10.4 (2.2)	10.1 (2.6)	11.2 (1.1)	0.18
Platelet ($X10^9$), mean (SD)	236.8 (155.9)	185.1 (133.8)	323.6 (165.2)	0.06
Serum glutamic pyruvic transaminase (U/L), median (IQR)	48 (23-89.5)	72 (38-209)	26 (14-35)	0.007
Creatinine (mg/dL), median (IQR)	0.47 (0.35-0.6)	0.5 (0.3-0.7)	0.37 (0.27-0.49)	0.17
Creactive protein (mg/L), mean (SD)	96.6 (67.03)	107 (72)	87 (57)	0.65
Serum ferritin (ng/mL), median (IQR)	596.8(282.2-1473.5)	875 (422-2338)	319 (85-515)	0.01
D-dimer (ng/mL), median (IQR)	4090 (1824.9-9958.7)	3160 (1827-10330)	5609 (1770-13765)	0.78
Interleukin 6 (pg/mL), median (IQR)	230.2 (95.5-498.7)	351 (172-635)	95.5 (33-359)	0.12
NT-Pro BNP (pg/mL), median (IQR)	410 (205.5-21277)	35000	205 (101-382)	0.05
Troponin (ng/mL), median (IQR)	33.4 (5.7-185)	79.4 (10.8- 360)	0.1 (0.01-0.1)	0.007
Echocardiographic features				
LV systolic dysfunction, *n* (%)	8 (34.8)	8 (53.3)	0	0.01
Coronary dilation, *n* (%)	6 (26)	3 (20)	3 (37.5)	0.3
Treatment				
Mechanical ventilation, *n* (%)	9 (39.1)	8 (53.3)	1 (12.5)	0.05
IVIG, *n* (%)	15 (65.2)	12 (80)	3 (37.5)	0.04
Steroids, *n* (%)	22 (95.6)	15 (100)	7 (87.5)	0.16
Tocilizumab/ infliximab, *n* (%)	3 (13.0)	3 (20)	0	0.17

MIS-C: Multi-system inflammatory syndrome in children; Left ventricular (LV) systolic dysfunction: Ejection fraction <50% as measured by M Mode echocardiography in parasternal long axis view; Coronary involvement: Z score >2.5 of either the left main coronary artery, left anterior descending coronary artery or the right coronary artery. NT Pro BNP: N terminal pro brain natriuretic peptide.

there are limitations in its recognition and diagnosis [11]. Within India, Mumbai was one of the early epicenters of the epidemic and we believe this is one of the reasons that this region has witnessed an early clustering of MIS-C. Testing guidelines with COVID-19 RT-PCR have now been streamlined in Mumbai and most parts of India. However, the antibody test reports are still not standardized, and IgM and IgG levels are not routinely reported. Hence, the requirement of either antigen or antibody positivity, or positivity in an immediate contact, is a potential problem in any COVID-related diagnosis, including MIS-C. In the absence of standardized uniform international diagnostic guidelines, there is high probability that clinicians are either missing the milder cases [11] or even over-diagnosing similar presentations of KD or toxic shock syndrome [5] as MIS-C.

Whitaker, *et al.* [3] have proposed three clinical patterns of PIMS-TS presentation *viz*, those with shock and cardiac involvement, those with fever and elevated inflammatory markers without features of KD, and those who fulfilled diagnostic criteria for KD. In our series, while only one patient fulfilled diagnostic criteria for classical KD [8], there was significant clinical overlap of several patients having few mucocutaneous features of KD, raised inflammatory markers, and presenting with shock. The most important clinical factor in our patients affecting treatment and outcomes was shock. As expected, the levels of NT pro-BNP and troponin were significantly elevated in the group with shock, and inotropic and ventilatory requirements were more. Additionally, neutrophilia, lymphopenia, elevated serum ferritin and liver enzymes were significant laboratory parameters observed in patients with shock. Use of IV immunoglobulin (IVIG) was significantly more in this group of our patients, possibly because they were sicker at admission. Shock, myocarditis and LV dysfunction were all more common in older children in our series.

Dufort, *et al.* [10] reported KD/ KD like illness in 36%,

WHAT THIS STUDY ADDS

- The clinical presentation, laboratory findings, response to treatment and outcome in children affected with MIS-C are reported.

myocarditis in 53%, shock in 10% and coronary aneurysms in 9% of their cohort of children with MIS-C from New York. In a recent study from Chennai, India, Dhanalakshmi, *et al.* reported hypotension requiring vasoactive medications in 57% of patients presenting with PIMS-TS, and coronary artery changes in 16% [7]. Previous authors have observed coronary involvement in all clinical groups of MIS-C, regardless of laboratory markers and whether diagnostic criteria of KD were met [3]. This observation is consistent with the present series as coronary involvement did not differ statistically with shock or age at presentation in our patients. This implies that all patients with MIS-C would need serial echocardiographic surveillance for coronary and myocardial involvement in the acute and convalescent phase of illness, even if the initial echocardiogram was normal [3,12], at least until definite guidelines for long term cardiac follow-up after MIS-C become available.

In classifying patients with MIS-C with Kawasaki-like illness, clinicians need to carefully differentiate this from classical KD in patients from COVID-19 endemic areas [6]. There is significant epidemiological evidence that MIS-C is distinct from KD. Children with MIS-C are older and sicker a compared with those of classical KD [3,10,12]. Feldstein, *et al.* [12] have observed 50% MIS-C patients presenting with cardiovascular shock leading to vasopressor or inotropic support as compared to only 5% of children with KD in the United States. Similarly, in our series, the median age of patients was 7.2 years, which is older than the age of presentation for KD.

There is a 2-4 week lag period for MIS-C presentation post COVID-19 infection, and we should expect to see more patients from across India in the coming weeks, based on present infection trends. In the US MIS-C series, IVIG (77%) and systemic glucocorticoids (49%) were used in most patients [12]. In the UK series, 71% received IVIG and 64% corticosteroids. Three patients received anakinra and eight received infliximab. Inotropic support was required in 47% [3]. In our series, 96% of the patients received steroids and 65% IVIg, and 65% required inotropic support. Biologicals such as tocilizumab/infliximab were used in 13%. The relatively lower usage of IVIg can be attributed to the high cost of this treatment, which unfortunately is often a deciding factor for treatment decisions in our population.

Based on our small numbers, we do not believe that at present, levels of acute phase reactants can reliably predict the subsequent clinical course of the child. The cardiac biomarkers (NT pro BNP, Troponin and CPK-MB) are of course indicative of myocarditis and can be used to predict clinical deterioration and shock. Generally, the short-term outcomes of MIS-C have been promising. Mortality in our series was 4.3%, which is comparable to international studies [11].

Our study is an ongoing analysis of hospital data. We were rigid in our case selection to include only those patients who themselves or whose immediate family contacts had confirmed SARS-CoV-2 antigen or seropositivity. The main prerequisite for these diagnostic criteria is universal and free availability of testing, which is often not the case. Hence, we may have missed mild cases or reallocated them to a diagnosis of KD due to this testing criterion. Additionally, we have only reported echocardiography and coronary findings at presentation. As we know from the KD experience, serial surveillance for coronary involvement with follow up echocardiography is essential to understand the mid-term and long-term sequelae of MIS-C in our patient population.

Our preliminary data is expected to add to the meagre data on this condition from India, and assist clinicians in identifying and managing MIS-C. Further studies and longer surveillance of patients diagnosed with MIS-C is required to improve our diagnostic, treatment and surveillance criteria.

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RESEARCH PAPER

Profile of Retinopathy of Prematurity in Outborn and Inborn Babies at a Tertiary Eye Care Hospital

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Objective: To study the profile of retinopathy of prematurity (ROP) among outborn and inborn babies at a tertiary-care centre. **Methodology**: In a prospective observational study from 2015-2016, outborn and inborn babies eligible for ROP screening were evaluated for ROP profile and treatment results. **Results**: 532 outborns and 38 inborns had ROP. Respiratory distress, sepsis and apnea were present in 81.3%, 51.5% and 36.2% of outborns with ROP and 68.4%, 39.4% and 36.8% of inborns with ROP. Type 1 ROP was noted in 49.2% eyes of outborns with ROP and 36.8% eyes of inborns with ROP. Type 1 ROP regressed with laser in 97.3% and 100% eyes of outborn and inborn with ROP, respectively. Stage 4, 5 and sequelae were noted in 5.2%, 22.8% and 4.6% eyes of outborns with ROP, respectively, but none in inborns. **Conclusions:** Quality neonatal care and timely screening ensured lesser ROP-related morbidity in inborns as compared to outborns.

Keywords: *Blindness, Referral, Screening, Surgery*.

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Improved neonatal care of preterm babies has led to a reduction in mortality, but due to unrestricted use of supplemental oxygen there is a significant increase in retinopathy of prematurity (ROP), the so-called third epidemic in middle income countries [1].

The quality of neonatal care, neonatologist-ophthalmologist coordination, timely ROP screening and management may prevent advanced ROP, with recent studies showing lower rates of ROP ranging from 20% to 30% [2-4]. This study was conducted to determine the difference in ROP profile of inborn and outborn babies with respect to risk factors, diagnosis at presentation, treatment given and outcomes.

METHODS

The study was conducted at our tertiary eye-care centre and Neonatal intensive care unit (NICU) associated with the same hospital, from May, 2015 to May, 2016. The study was approved from the Institutional review board and adhered to the Declaration of Helsinki guidelines. Informed written consent was taken from the parents to participate in the study.

We studied the risk factors for ROP, demographics and screening referrals of ROP from the discharge summary or by interviewing the caregivers. Records were requested from the NICU, if unavailable. Outborn babies (referred from other health facilities to our centre) were screened for ROP as per the National Neonatology Forum (NNF) of India guidelines (<1750g; <34 week or 1750-2000 g or 34-36 week in babies with co-morbidities) [5], and inborn babies (born at level 3 nursery of our hospital) were screened as per our hospital NICU protocol (<1500g; <32 week or 1500-2000 g or 32-34 week with co-morbidities).

The babies were examined with indirect ophthalmoscope and Retcam wide field imaging system. Diagnosis at presentation was documented as per International classification of ROP (ICROP), 2005 [6]. The treatment was given as per early treatment of ROP (ETROP) guidelines [7]. As per these guidelines, type 1 ROP includes (*a*) Zone 1 any stage with plus disease; and (*b*) Zone 1 stage 3 without plus disease and (*c*) Zone 2 stage 2/3 with plus disease; and requires intervention. Type 2 ROP includes (*a*) Zone 1 stage 1/2 without plus disease, and (*b*) Zone 2 stage 3 without plus disease; and requires observation [7]. Advanced ROP cases such as stage 4 and 5 ROP underwent surgical management.

The data were entered in a predesigned proforma and analyzed using SPSS Version 23 (SPSS Inc. Chicago, IL, USA). Due to variability in baseline characteristics, risk factors were evaluated separately for ROP cases in outborns and inborn babies. The categorical risk factors were subjected to the Pearson chi-square test for

comparison between the groups.

RESULTS

A total of 722 outborn babies were referred among which 532 (73.6%) babies had ROP; 22.6% (*n*=38) of 168 inborn babies screened in NICU developed ROP.

The mean (SD) birthweight [1354.8 (376.3) g *vs* 1122.2 (271.2) g; *P*=0.0002] and gestational age [30.7 (2.7) week *vs* 29.6 (2) week; *P*=0.014] were higher/similar between outborn and inborn babies with ROP, respectively. Respiratory distress syndrome (RDS), sepsis, and apnea of prematurity (AOP) were the most commonly associated risk factors in both inborn and outborn ROP babies (***Table* I**).

Among the outborn group, type 2 ROP or less was seen in 192 (18%) eyes which spontaneously regressed on follow up. All the eyes with type 1 ROP (524 eyes, 49.2%) regressed following interventions like laser and anti-VEGF therapy. Out of 76 inborn eyes, 48 eyes (63.1%) were type 2 ROP or less and 28 eyes (36.8%) were type 1 ROP, which required only laser therapy and regressed (***Table* II**).

Median age for referral of outborns was 39 (range 29 to 316) weeks. Only 66.9% (*n*=483/722) babies had been advised ROP screening among outborns, out of which 219 (30.3%) were screened late. All inborn babies were advised timely ROP screening within 4 weeks by the pediatricians and were screened timely by the ophthalmologists.

DISCUSSION

The proportion of ROP was 22.6% with no case of severe/advanced ROP amongst the inborn babies. However, a much higher prevalence of ROP was found among outborn babies with a high proportion of advanced ROP due to the large number of referrals to our center.

Respiratory distress syndrome (RDS), sepsis and apnea of prematurity (AOP) were the main risk factors found in both the groups. These risk factors likely increase the chances of neonatal mortality, long NICU stay and high oxygen exposure, which increases the risk for severe ROP [8]. Although, a safe level of oxygen supplementation has not yet been defined, in our NICU we target a arterial oxygen saturation between 90-95% to avoid hyperoxia.

In our study, we saw a spectrum of ROP from milder forms to severe/advanced forms like type 1 ROP and stage 4 requiring immediate intervention (laser or anti-VEGF drugs or surgery). In our study, most outborn (97.3%) and inborn (100%) babies who underwent laser therapy as per ETROP guidelines had regressed ROP after the procedure. Anti-VEGF drug (Bevacizumab) was used in selected cases of zone I disease with informed parental consent. Though multiple studies have been done on efficacy of anti-VEGF agents in ROP, its safety profile has still not been fully established [9]. Operated stage 4 cases had good anatomical outcome while the outcomes were poor in stage 5 cases wherever surgery was attempted. Cases with sequalae were not operated in view of limited further visual potential. Though advanced ROP and its sequelae were not seen among the inborn babies due to timely treatment, a large number (32.7%) of outborn babies had advanced ROP or its sequelae. This clearly shows the importance of pediatrician-ophthalmologist coordination, early ROP screening and appropriate treatment to halt the progression of the disease to severe forms. Sicker babies who are not able to be screened and treated in peripheral cities are referred to tertiary eye care centres at a later stage and hence the ratio of severe cases among outborn and inborn babies is more [10].

Table I Neonatal Systemic Risk Factors in Babies Diagnosed With Retinopathy of Prematurity (*N*=570)

Risk factors	*Outborn babies with ROP (n=532)*	*Inborn babies with ROP (n=38)*
RDS	433 (81.3)	26 (68.4)
Sepsis	274 (51.5)	14 (36.8)
AOP	193 (36.2)	15 (39.4)
PDA	40 (7.5)	8 (21)
NEC	39 (7.3)	5 (13.1)
HIE	22 (4.1)	4 (10.5)
Seizures	20 (3.7)	3 (7.8)
TTN	11 (2.0)	14 (36.8)

All values in no. (%). RDS: Respiratory distress syndrome, TTN: Transient tachypnea of newborn, AOP: Apnea of prematurity, PDA: Patent ductus arteriosus, HIE: Hypoxic ischemic encephalopathy, NEC: Necrotizing enterocolitis.

Table II Profile of Retinopathy of Prematurity in Outborn and Inborn Babies (*N*=570)

Outcomes/treatment	*Outborn babies (n=1064 eyes)*	*Inborn babies (n =76 eyes)*
Type 2 ROP/Follow up	192 (18)	48 (63.1)
Type I ROP		
Laser	510 (47.9)	28 (36.8)
Laser plus anti-VEGF	14 (1.3)	0
Stage 4 ROP/Surgery	56 (5.2)	0
Stage 5 ROP		
Surgery attempted	88 (8.2)	0
Surgery not attempted	155 (14.5)	0
ROP sequalae	49 (4.6)	0

All values in no. (%); ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor.

WHAT THIS STUDY ADDS?

Inborn babies with appropriate neonatal care and timely screening/management of ROP did not develop or progress to severe/advanced stages of ROP, unlike outborn babies.

We found that 33.1% babies were never advised screening and 30.3% were screened late for ROP, showing the lack of awareness and structured protocol for ROP screening and referral in many centers. A pilot survey in Northern India showed that 34% of pedia-tricians never referred babies for ROP screening from their NICU and only 14.5% of pediatricians were following international guidelines for ROP [11]. Similar results were shown in another study conducted in stage 5 ROP where none of the babies were referred by their pediatricians for ROP screening [12]. Another study showed that the lack of awareness and compromise in screening and manage-ment leads to large number of stage 5 ROP cases being referred to tertiary eye care centres [13].

The major limitation of this study is the study design, which makes comparison between inborn and outborn cases difficult due to the missing information in outborn babies and their selective referral with higher stages of ROP. Since our center is a tertiary care referral facility, a larger number of babies are referred for advanced management which could account for a higher number of advanced ROP seen in the outborn group. A large multi-centre country wide study may be able to better estimate the true incidence and causal relationship between the risk factors leading to advanced ROP.

Superior NICU care and management practices can prevent development of ROP and reduce disease severity [14]. Health planners need to address the urgent need to establish effective ROP screening and treatment services as well as develop good neonatal services across the country.

Ethical clearance: Institutional Ethical Committee, AIIMS, New Delhi; No. IESC/T-01/21.01.2015, RT-18, dated April 1, 2015.
Contributors: PC, RA, MJS, RC, RV, AK: substantial contributions to the conception or design of the work; AS, DK, MJS, PC: acquisition, analysis, or interpretation of data for the work; AS, DK, PC, RA, MJS, RC: drafting the work or revising it critically for important intellectual content. All authors approved the final manuscript.
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RESEARCH PAPER

The Association Between Environmental Lead Exposure and Recurrent Respiratory Infections in Children Aged 3-7 Years in Shenyang, China

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Objectives: To investigate the lead exposure levels, and the effect of blood lead level (BLL) on recurrent respiratory infections in children aged 3-7 years in Shenyang. **Methods**: A case-control study including 78 children with recurrent respiratory infections and 141 controls was performed. Venous blood was obtained for BLL, and a questionnaire was completed. **Results**: The BLL was significantly higher in children with recurrent respiratory infections than that in the control group [Median (IQR): 2.56 (1.29-6.19) *vs* 1.99 (0.90-5.92) µg/dL, *P*=0.029]. Children with BLL ≥1.95 µg/dL were more likely to be suffering from recurrent respiratory infections (OR=2.328, 95%CI=1.228-4.413) than those with BLL <1.95 µg/dL. **Conclusions**: High lead level can increase the risk of respiratory infections in preschool children.

Keywords: *Humoral immunity, Lead toxicity, Predisposition, Risk Factors*.

Lead is harmful to children's health because of the dysfunction of various organ systems induced by lead, such as hematological, neurological, gastrointestinal, central nervous, renal and immune systems [1,2]. Studies showed that people exposed to occupational lead had impaired congenital and humoral immune responses and increased susceptibility to chronic infection [4,5]. However, there is little information about the effect of non-occupational lead exposure on humoral immunity.

At least 6% of children under 6 years old suffer from recurrent respiratory infections (RRI). We studied the blood lead and immunoglobulin levels among children aged 3 to 7 years in present study to study its relation with RRI.

METHODS

The study was done between September, 2017 and October, 2018. A case-control study was carried out in children aged 3 to 7 years. Among children diagnosed with RRI, 78 were chosen randomly from the inpatient department of our hospital, and the control group was 141 healthy children of matched age and gender who were chosen randomly from the physical examination center of the same hospital. Exclusion criteria for both case and control group were taking zinc, calcium, iron, vitamin A, vitamin D, or multivitamin supplementation in past 3 months; history of congenital malformation, such as heart disease and thoracic deformity; and history of disease associated with kidney, liver or immune system.

Ethics approval was granted by the institute ethics committee and informed written consent was obtained from the parents/caretakers of the participants. Parents/caretakers of 219 participants completed a questionnaire, including child's age, sex, BMI (kg/m^2), passive smoking and social economic status (low, middle, high income). If anyone in the family was smoking currently, it was defined as passive smoking. Children's medical histories were reviewed in particular with regard to the frequency of upper respiratory infections (cold, pharyngitis, laryngitis, tonsillitis, otitis media) and lower respiratory infections (tracheitis, bronchitis, bronchiolitis, pneumonia). RRI was defined as either upper respiratory infections at least six times within one year; or lower respiratory infections at least two times within one year [7].

The sample size was calculated according to the assumptions that alpha of 0.05, power of 0.8, odds ratio 2.5, and prevalence of exposure (lead poisoning) in the control group 20% [8]. The result was 77 children in the case group and 139 children in the control group.

Blood samples were collected in lithium heparin coated trace-metal free tubes and were transported on ice to Shenyang Harmony Health Medical Laboratory for analysis. Blood lead level (BLL) was determined by atomic absorption spectrometry through graphite furnace ionization techniques.

Since BLLs were non-normally distributed, statistical analysis was performed after logarithmic transformation. Student t-test and analysis of variance test (ANOVA) were used to evaluate the differences of indicators between different groups. Categorical variables were compared by chi-square test and Fisher's exact test. BLLs was categorized into two groups (<1.95 µg/dL and ≥1.95 µg/dL) for multiple logistic regression analysis. Data were analyzed by Statistical Package for the Social Sciences (SPSS 20.0). The results were considered statistically significant at 5%.

RESULTS

A total of 228 children were approached, of which, 5 refused to complete a questionnaire, while 4 met one of the exclusion criteria. The case-control study eventually included 78 children with RRI and 141 healthy controls (***Fig.* 1**). The percentage of passive smoking exposure was significantly lower in the control group than that of the case group (41.1% *vs* 56.4%; *P*=0.03) (***Table* I**). The median (IQR) BLL of case group was significantly higher than that of the control group [2.56 (1.29-6.19) *vs* 1.99 (0.90-5.92) µg/dL; *P*=0.029]. Children with BLL ≥1.95 µg/dL were more likely to be suffering from RRI, which was approximately 2.5 times more than those who had BLL <1.95 µg/dL.

Multivariate analysis of risk factors for recurrent respiratory infections showed that both passive smoking [OR (95% CI)=1.18 (0.98-3.20); *P*=0.057] and BLL of 1.95 µg/dL or higher [OR (95% CI) = 2.33 (1.23-4.41); *P*=0.010] had a higher risk of having recurrent respiratory infections.

DISCUSSION

Environmental lead exposure has always been one of the important public health issues in children, even at chronically low levels [5].

Table I Baseline Characteristics of Children With Recurrent Respiratory Infections and Controls

Characteristics	*Control group* (*n=141*)	*Cases* (*n=78*)
Child age		
36-47 mo	51 (36.2)	28 (35.9)
48-59 mo	31 (22.0)	26 (33.3)
60-71 mo	22 (15.6)	17 (21.8)
72-84 mo	37 (26.2)	7 (9.0)
Male gender	67 (47.5)	39 (50.0)
Passive smoking*	58 (41.1)	44 (56.4)
Socio economic status		
Low income	32 (22.7)	15 (19.2)
Middle income	103 (73.0)	57 (73.1)
High income	6 (4.3)	6 (7.7)

*All values in no. (%) except #mean (SD); All P>0.5 except *P=0.03.*

A value of 5 µg/dL US Centers for Disease Control and Prevention reference concentration) was considered as the clinical cut off for elevated BLLs [12]. This study show that the BLLs below 5 µg/dL are associated with an increased risk of RRI in preschool children. In addition, we observed that IgG levels of case group were lower than that of the control group, but the difference between these two groups was not significant (data not shown), which may be related to relatively small number of cases. The result also suggests that lead exposure may increase the risk of RRI by other means, such as by affecting cellular immunity. However, cellular immune indicators were not studied in the present study.

Previous studies [4,13,14] have shown that blood lead can affect the levels of immune cytokine, for example, reducing the production of IgG and IgM. The effects of lead on immune cytokine and other adverse

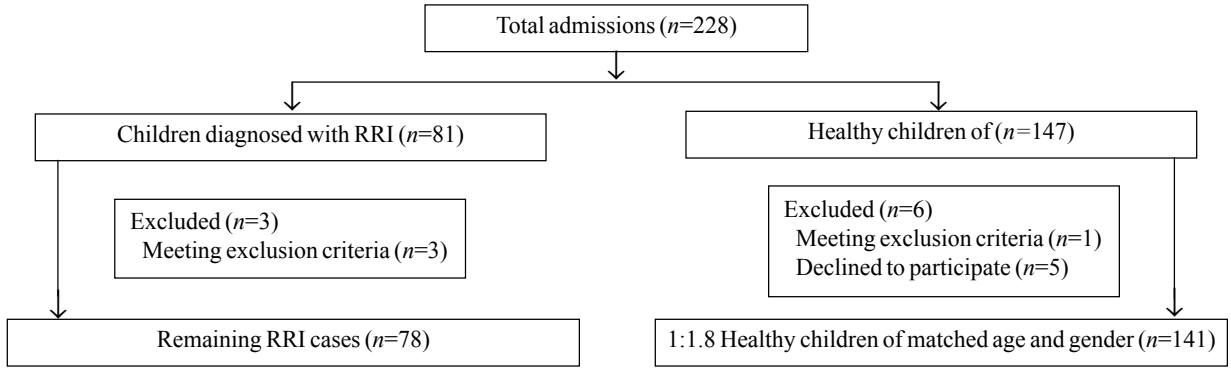

Fig.1 *Flow of participants in the study.*

WHAT THIS STUDY ADDS?

- Blood lead levels >1.95 µg/dL may increase the risk of recurrent respiratory infections in preschool children.

health are highly dose dependent. At present, the immunologic effects from low blood lead exposure (under 5 µg/dL) were poorly understood. The present study found that higher BLLs (≥1.95 µg/dL) increased the risk of RRI in preschool children, as also observed by other researchers [5]. In addition to lead exposure, some studies reported the association between other factors and RRI, such as socioeconomic status, passive smoking, air pollution, micronutrient intake of children [15,16]. Smokers often avoid children due to the increasing awareness of smoking harmfulness. So our results did not show a significant association between passive smoking and RRI.

Our findings highlight a potentially preventable cause of infectious disease in preschool-age children, findings indicate that it is necessary to control the source of lead pollution, and the harmful effects of apparently low levels of blood lead need to be further explored.

Ethics approval: The Fourth Affiliated Hospital of China Medical University; No. EC-2018-KS-053; dated December 17, 2018.

Contributors: X-NL: collection of data, study concept, analysis of data, revision of the manuscript; YL: collection of data, electronic preparation, revision of the manuscript, NH: collection of data, electronic preparation, revision of the manuscript; X-JC: collection of data and electronic preparation; LHJ: study concept, analysis of data, final revision.

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Competing interest: None stated.

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RESEARCH PAPER

Psychiatric Problems Amongst Adolescents Living With HIV at a Tertiary Care Centre in India

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Objective: To assess the prevalence of psychiatric problems among adolescents living with HIV (ALHIV). **Method**: Questionnaire-based cross-sectional study conducted at pediatric HIV clinic of a tertiary care hospital. **Participants**: 101 ALHIV between 10-18 years of age. **Results**: Of the 101 ALHIV, 12 (11.88%) met criteria for psychiatric disorders, of which dysthymi (5,41.6%) and oppositional defiant disorder (6,50%) were the commonest. Father of 7 (58.34%) and mother of 8 (66.6%) screen positive patients were dead as compared to 22 (24.7%) and 13 (14.6%) of screen negative patients (P=0.016 and P=0.0003, respectively). **Conclusion:** Psychiatric problems are common in ALHIV in the age group more than 15 years.

Keywords: *Depression, Dysthymia*, *Mental health disorders, Resilience.*

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Adolescence is associated with increased susceptibility to emotional and mental problems, and HIV can increase the probability of psychiatric problems among adolescents living with human immunodeficiency virus (ALHIV) [1]. With the effective and increased use of highly active antiretroviral therapy (HAART), children born with perinatal HIV infections are reaching adolescence and young adulthood in large numbers [2]. According to the report by UNICEF in 2018, nearly190,000 adolescents between the ages of 10 and 19 were newly infected with HIV [3]. Although India has an HIV prevalence of only 0.3%, with the adolescent group constituting around 22.8% of the total population, HIV among adolescents has a greater impact in terms of its prevalence and effects [7]. Limited studies from other parts of the world have shown that mental health problems affect around 12-44% of HIV-infected children [5,6]. The prevalence rate of psychiatric disorders in HIV-infected children and adolescents has uncommonly been reported from our country. An understanding of this problem is critical for improving their mental health and quality of life.

This study was conducted to study the occurrence of psychiatric problems in HIV-positive adolescents attending the HIV clinic at a tertiary care center in India.

METHODS

This cross-sectional study was carried out in the pediatric HIV clinic hospital from November, 2017 to March, 2019 after ethical clearance from institutional ethics committee. A sample size of 101 ALHIV with a 10% margin of error and a 5% level of significance was calculated based on the prevalence rates in previous studies [6].

ALHIV between 10 and 18 years were consecutively enrolled after taking written informed consent from them or the caregivers (either parent, or accompanying adult in case of orphans). Face-to-face interview was conducted with adolescents and their caregivers and detailed proforma was filled by the investigator. Information collected included socio-demographic data, World Health Organi-zation staging, route of HIV acquisition, and duration of treatment. Details of clinical examination, were recorded, and results of investigations including complete blood count, liver function test, kidney function test and CD4 count were collected from hospital records. The next part of the proforma included MINI KID questionnaire, in which questions were asked to adolescents and their caregivers from the modules addressing 19 psychiatric problems. The scale contained main diagnostic questions at the beginning of each module which if present, was further interviewed for details. All study participants who were positive for psychiatric disorders were referred to the psychiatry clinic at our hospital for further management.

Statistical analyses: Statistical analyses was done using Statistical Package for Social Sciences (SPSS) version

21.0. Quantitative variables were compared using Mann-Whitney test between the two groups as the data sets were not normally distributed. Qualitative variables were compared using the Chi-Square test/Fisher's exact test. A *P* value of <0.05 was considered statistically significant.

RESULTS

101 ALHIV (64.3% male), who were regularly attending the pediatric HIV clinic, were enrolled (***Table* I**). The mean (SD) age of the study group was 13.5 (2.28) years. All the patients were on ART. Of these, 26 (25.7%) were aware of the nature of their disease, its prognosis, and its effects on the body.

Twelve (11.8%) adolescents were screened positive for psychiatric disorders (***Table* II**); of which 5 (41.7%) were positive for two or more psychiatric disorders. The mean age of the screen-positive patients was 14.5 (2.0) years. No difference in proportion of adolescents with psychiatric disorder was according to age-group or sex.

Risk of being positive for at least one psychiatric disorder was higher in those whose parents were not alive [Father (24.1% *vs* 6.9%; *P*=0.02) or mother (38.1% *vs* 5%; *P*<0.001)]. Having knowledge about the disease was associated with a higher risk of positivity for a psychiatric disorder (26.9% *vs* 6.7%, *P*=0.006).

Ten (83.3%) screen-positive patients were in WHO stage 1 HIV while 2 (16.6%) belonged to WHO stage 3 HIV. Seven (53.8%) patients belonging to lower-middle socioeconomic class and 4 (6.3%) patients belonging to lower socioeconomic class were positive for psychiatric disorder as against 1 (4%) from upper-middle class (*P*<0.001). The mean duration of treatment for patients positive for a psychiatric disorder was 4 years [IQR:1.62, 8.25].

Table I Baseline Characteristics of HIV Positive Children (*N*=101)

Characteristics	*n (%)*
Age	
10-15 y	78 (77.2)
>15 y	23 (22.7)
Parents' HIV status	
Father positive	89 (88.1)
Mother positive	93 (92)
WHO stage	
I	93 (92)
II	1 (0.9)
III	7 (6.9)
Route of acquisition – Vertical	89 (88.1)
Duration of treatment	
<1 y	4 (3.9)
1-3 y	22 (21.8)
3-5 y	32 (31.6)
>5 y	43 (42.5)

Table II Psychiatric Disorders in HIV Positive Children (*N*=101)

*Psychiatric disorder**	*No. (%)*
Dysthymia	5 (4.9)
Conduct disorder	3 (2.9)
Oppositional defiant disorder	6 (5.9)
Adjustment disorder	3 (2.9)
Pervasive development disorder	3 (2.9)

**Other disorders like suicidality, (hypo) manic episode/ panic disorder, phobias, obsessive compulsive disorder, were also screened but no cases were found; One child (0.9%) each suffered from major depressive episode, post-traumatic stress disorder and attention deficit hyper-activity disorder; some participants had more than one disorder.*

DISCUSSION

The results of our study show that around 12% of ALHIV were suffering from psychiatric disorders of which dysthymia and oppositional defiant disorder were commonest. Further, it was seen that psychiatric disorders were significantly higher in ALHIV whose one parent had expired and in children who were aware of their disease status.

Various studies have shown that psychiatric illnesses are more common in children and adolescents living with HIV as compared to the general population [7-9]. Many of these studies have reported a higher prevalence (up to 50%) of psychiatric illnesses, much higher as compared to our study [2,10,11]. The lower prevalence in our study could be due to the lack of knowledge about the disease in the majority, lower stage of disease, appropriate HAART therapy, or cultural differences among communities.

The proportion of ALHIV with psychiatric illness was higher in older age group and in adolescents who knew about their disease. This was in contrast to previous studies [3,5] who found psychiatric morbidity to be common among patients between 10 to 15 years [2,11]. This might be due to a better understanding of the disease and associated stigma attached to the disease in older adolescents. Parental HIV status is known to affect psychiatric illness among CLHIV due to associated adversities of parental HIV and hence more common in children whose either parent had positive HIV status or whose either or both parents had died [12]. This was similar to other studies where the morbidities were

WHAT THIS STUDY ADDS?

- Psychiatric problems are common in adolescent with HIV who are older than 15 years, particularly in those who are aware of the disease or whose one of the parents has died.

common among those who had single mothers or single fathers or no parent [11,13].

Various other studies have also shown that depression was the major psychiatric problem in ALHIV [2,11,14]. In majority of these studies major depression was significantly associated with low CD4 count. The low prevalence of depression in our study may be due to higher CD4 counts in our cohort. Oppositional defiant disorder was observed similar to the previous studies [11].

According to the National Mental Health Survey 2016, the prevalence of mental disorders in 13 to 17 years' age group was 7.3%, most commonly depressive disorders; whereas, dysthymia and oppositional defiant disorder were commonest in our study [15].

The strengths of the study is the application of standard screening test by a single trained researcher. Since the study did not have a control group, the contribution of adolescent factors could not be separated out. Further, the age of disclosure of the diagnosis was not studied, which could have helped us to know the resilience of HIV positive patients.

The high prevalence of psychiatric problems in ALHIV emphasizes the need for screening of mental health illnesses, counselling, and referral during their visit to the HIV clinic. There is a need for larger studies to assess the psychiatric problems in ALHIV using definite psychiatric tools and study associated factors and course.

Ethical clearance: Institutional Ethics Committee of ABVIMS and Dr RML hospital; No.IEC/PGIMER/RMLH/446 dated October 30, 2017.
Contributors: AH, RPB: conceptualized the study and designed the protocol; RP: was involved in data collection, analysis, and literature search; SA: literature review and drafting the manuscript; SKA: critically reviewed the manuscript. All authors approved the final manuscript.
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RESEARCH PAPER

Factors Associated With Mortality in Toxic Encephalopathy Due to Shigellosis in Children

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Objective: To study the clinical characteristics and factors associated with mortality among children with *Shigella* encephalopathy. **Methods**: The data collection was done prospectively from January, 2018 to May, 2019 with retrospective data from June, 2016 to December, 2017. The study cohort consisted of 58 children <12 years of age with *Shigella* encephalopathy admitted to the pediatric intensive care unit. *Shigella* encephalopathy was confirmed if culture or real time polymerase chain reaction (PCR) of a stool sample or rectal swab was positive, with temporal association of diarrhea with seizures, altered sensorium or both. Association of mortality with risk factors was tested using chi square test, and the strength of association was estimated in terms of relative risk (RR) and 95% CI. **Results**: Seizures and altered sensorium were the predominant neurological symptoms. Shock occurred in 32 (55%) children, while blood in stools was a feature in only 6 (10%) children. *S. sonnei* was the commonest species identified on stool culture (19;33%). On univariate analysis, prolonged seizures, shock, prolonged altered sensorium, multi-organ dysfunction, lymphocytopenia at admission and need for mechanical ventilation were significantly associated with mortality. On multivariate regression, delayed presentation (presentation to the hospital 48 hours after the onset of symptoms) and prolonged altered sensorium (>12 hours) were found to be independently associated with mortality. **Conclusions:** Recognition of factors associated with mortality in Shigella encephalopathy may assist in better monitoring of sicker children and improved outcomes.

Keywords: *Diarrhea, Ekiri syndrome, Morbidity, Outcome, S. sonnei.*

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Shigellosis continues to be an important cause of diarrhea-related mortality in developing countries [1,2] with *Shigella flexneri* being the predominant species endemic in India [3]. The most common extra-intestinal complication in shigellosis is encephalopathy, presenting with seizures, headache, lethargy, confusion or hallucinations [4]. Over the last few decades, there has been a substantial reduction in deaths related to shigellosis [5]. Children with *Shigella* encephalopathy usually recover without any neurological deficits [4].

A recent study from Bangladesh has reported high case fatality in children with *Shigella* encephalopathy [6] We have also noticed an increase in mortality due to *Shigella* encephalopathy in our center which prompted us to analyze the hospital records which showed that there was only one death between 2013 and 2015 (unpublished data). Lethal toxic encephalopathy or Ekiri syndrome (a severe form of encephalopathy resulting in rapid prog-ression to coma and death) is reported in children with shigellosis from abroad but not from India [7]. The present study aimed to describe the clinical charac-teristics of *Shigella* encephalopathy in children and to identify factors associated with mortality.

METHODS

The study was conducted in the Pediatric Intensive Care Unit (PICU) of the Government Medical College, Kozhikode, a tertiary referral centre. Children between 1 month and 12 years of age admitted from 1 June, 2016 to 31 May, 2019 with a diagnosis of *Shigella* encephalopathy were included in the study. The data collection was done prospectively from January, 2018 to May, 2019 with retrospective data from June, 2016 to December, 2017. The study was approved by the institutional ethics committee.

Shigella encephalopathy was suspected based on

the temporal association of diarrhea with altered sensorium, seizures or both in children. Stool microscopy and culture were done in all cases, apart from other investigations including complete blood count, blood culture, cerebrospinal fluid analysis and culture, blood sugar, serum electrolytes, renal and liver function tests. The diagnosis was confirmed if *Shigella* spp. was isolated from a stool sample or rectal swab, or if polymerase chain reaction (PCR) from a stool sample was positive. Children with a negative stool culture or PCR, history of seizures poorly controlled with anti-epileptics, and those whose sensorium improved after correction of shock were excluded from the study.

The clinical characteristics were recorded and the factors associated with mortality were studied. The following definitions were chosen: Delayed presentation: Presentation to the hospital 48 hours after the onset of symptoms; Undernutrition: weight for age or weight for height below –2 z-scores on the WHO child growth standards; Fluid refractory shock: persistent shock despite administration of 60 mL/kg of fluid in first hour or development of fluid overload features like hepatomegaly or lung crepitations; Multi organ dysfunction: dysfunction of 2 or more organ systems other than the CNS; Prolonged seizure: seizures lasting for more than 30 minutes without the child regaining consciousness in between; Prolonged altered sensorium: altered sensorium lasting more than 12 hours; Hyponatremia: serum sodium concentration less than 135 mmol/L; Hypocalcemia: serum ionized calcium less than 1.1 mmol/L; Lymphocytopenia: Lymphocyte count below the normative value for the corresponding age.

All children were treated with ceftriaxone and other supportive measures, which included management of seizures and raised intracranial tension. Indications for mechanical ventilation included worsening respiratory failure, refractory shock and a score on the Glasgow coma scale of <8. Seizures were managed in accordance with the unit protocol which included a benzodiazepine, followed by fosphenytoin and levetiracetam or sodium valproate, depending on the response. Hypertonic saline (3%) was used as therapy for raised intracranial tension. Shock was managed as per standard protocol, including fluid boluses and inotropic support in fluid refractory shock. Appropriate intravenous fluids were used for rehydration and replacement of ongoing losses.

Statistical analysis: Qualitative variables were summarised as frequency and percentages and association of mortality with risk factors were tested using chi square test. A P value of <0.05 was considered to be statistically significant. Strength of association of risk factors with mortality was estimated in terms of relative risk (RR) and its 95% confidence interval (95% CI). A multivariate logistic regression was done to find out adjusted odds ratio of the variables. Those variables which were found to be significant on univariate analysis were selected for modeling using binary logistic regression to obtain an adjusted OR and its 95% CI. Statistical analysis was performed using SPSS V.16 (SPSS, Chicago, Illinois, USA).

RESULTS

Out of 158 probable cases, *Shigella* encephalopathy was confirmed in 60 children (***Fig.* 1**). Among them, 2 children had epilepsy with poorly controlled seizures and were not included for the analysis. The final sample consisted of 58 children with confirmed shigella encephalopathy. The prospective and retrospective data included 40 and 18 children, respectively (27 girls, age range 38 days-12 years). Stool culture was positive for shigella in 23 (40%) children while the rest had stool PCR positive for *Shigella* spp.

Nearly half (48%) of the diarrheal episodes occurred during the months of May and June. All except 5 children (53; 91%) were admitted to the PICU within 48 hours, and 45 (78%) of them on the first day of illness itself. The initial symptom was fever in 54 (93%) children and seizures, loose stools, vomiting and abdominal pain in one child each. Seizures and altered sensorium were the predominant neurological symptoms. Altered sensorium or seizures preceded loose stools in 16 (28%) children, while the majority (42, 72%) developed features of encephalopathy after the onset of loose stools (***Table* I**). *S. sonnei* was the commonest organism identified in stool culture (33%) followed by *S.boydii* (3%) and *S. flexneri* (2%). Blood culture was sterile in all cases.

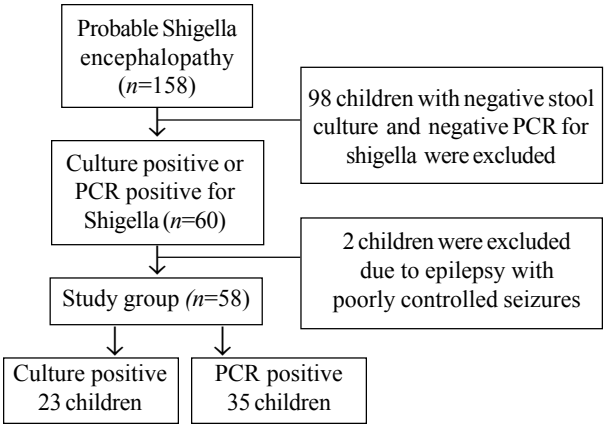

Fig.1 *Study flow chart.*

Table I Clinical and Laboratory Characteristics of Children With Shigella Encephalopathy (*N*=58)

Characteristic	*No (%)*
Fever as initial symptom	54 (93)
Seizures	51 (88)
Prolonged seizure (lasting >30 min)	10 (17)
Altered sensorium	27 (47)
Prolonged altered sensorium (lasting >12 h)	21 (36)
Headache	3 (5)
Blood in stools	6 (10)
Shock	32 (55)
Fluid-refractory shock	25 (43)
Lymphocytopenia	37 (64)
Hypocalcemia	12 (21)
Hyponatremia	28 (48)
Need for mechanical ventilation	13 (22)
Multi-organ dysfunction	11 (19)

The mortality in the present sample was 26%. More than half (9;60%) of the children who died were below the age of 5 years. Death occurred within 24 hours of hospitalization in (4, 27%) children and within 48 hours in 7 (47%) children. All 5 children who were admitted after 48 hours of onset died.

Among the children who died, prolonged altered sensorium occurred in 13 (87%), while 7 (47%) children had prolonged seizures. All the 13 children who had persistent low scores of <8 on the Glasgow coma scale died. Severe metabolic acidosis in the absence of shock or kidney injury was a feature in 2 (3%) children, and global developmental delay were present in 4 (7%) children. Computed tomography scans of the brain in two children and autopsy in one child showed severe cerebral edema. Stool culture for *S. Sonnei* was positive in 3 children who died.

On univariate analysis, prolonged seizures, admission to PICU after 48 hours of onset, shock, prolonged altered sensorium, persistently low score on the Glasgow coma scale, hyperglycemia at admission, multi - organ dysfunction, need for mechanical ventilation and lymphocytopenia at admission were significantly associated with mortality. On multivariate regression, delayed presentation to the hospital more than 2 days after the onset of any symptoms and altered sensorium for >12 hours were found to be independently associated with mortality (***Table* II**).

Table II Risk Factors for Mortality in Shigella Encephalopathy in Children (*N*=15)

Variables	*Adjusted OR (95% CI)*	*P value*
Prolonged altered sensorium (*n*=13)	18.23 (2.27 to 16.13)	0.006
Hyperglycemia (*n*=4)*	1.43 (0.09 to 21.16)	0.79
Shock (*n*=13)	4.64 (0.41 to 52.47)	0.22
Hyponatremia (*n*=5)*	0.46 (0.07 to 3.06)	0.42
Undernutrition (*n*=2)	13.13 (0.01 to 17042.92)	0.48
Lymphocytopenia (*n*=5)*	0.22 (0.03 to 1.61)	0.14
Delayed presentation (*n*=5)	8.74 (1.02 to 74.96)	0.05

**at admission.*

DISCUSSION

We studied the clinical characteristics and mortality in 58 children with *Shigella* encephalopathy during a period of three years. More than a quarter of the children died, possibly due to the occurrence of lethal toxic encephalopathy. Lethal toxic encephalopathy or Ekiri syndrome, first reported from Japan is a rapidly progressing fulminant encephalopathy associated with shigellosis in children [7-8]. In the present sample, children who died had a similar progress of encephalopathy with death occurring within 48 hours of the onset of the disease in 47% of cases.

The cause of death in lethal toxic encephalopathy is not yet well understood, although severe cerebral edema has been described and it is suggested that prevention will help to improve the outcome [7,9]. Entry of inflammatory cytokines into the brain in susceptible children, might be the reason for severe encephalopathy [10]. Our findings are also suggestive of the role of cerebral oedema.

In a large series from Israel, a disproportionate number of cases had developmental delay and intellectual disability, suggesting a possible increased susceptibility [9], though, we could not confirm the association. Although hypocalcemia and hyponatremia have been reported in children who died due to encephalopathy, they were not significantly associated with mortality in our series [7,9].

S sonnei was the commonest serogroup isolated in our series, although *S flexneri* has been reported as the most common serogroup in India [11-13]. Recent studies have reported increasing incidence of *S sonnei* infections in this region [14]. A shift towards *S sonnei* has been observed in other countries as socioeconomic conditions improve [15]. A significant association of *S sonnei* with encephalopathy has been reported earlier, suggesting increased virulence and might partly explain the increased mortality [6].

WHAT THIS STUDY ADDS?

- Delayed presentation more than 48 hours after the onset, and prolonged altered sensorium beyond 12 hours were the risk factors identified for mortality in Shigella encephalopathy in children.

Delayed presentation and prolonged altered sensorium were found to be independently associated with mortality, suggesting that timely initiation of antibiotics shortens the duration of illness and results in bacteriological clearance, as reported in literature [16]. One limitation of the present study is that the exact cause of rapidly progressing encephalopathy leading to death could not be identified in all children since we could not carry out brain imaging studies in all children and autopsy could be done in one child only.

The increased mortality in shigella encephalopathy in the present sample underscores the need for further studies on the changing virulence of *Shigella* organisms, as well as host-specific risk factors and optimal treatment.

Ethics Clearance: Institutional ethics committee of the Government Medical College, Kozhikode; No. GMCKKD/RP2018/IEC/15, dated 11 January, 2018.
Contributors: MPJ: designed study, collected the data and wrote the initial draft of the paper; MGG, PK: helped in writing the manuscript and interpretation of the data; VKG: patient management and helped in collection of the data; BG: expert in statistics who did the statistical analysis; PP, GA, PMA: conducted microbiological analysis.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Screen Time in Indian Children by 15-18 Months of Age

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Objective: To determine the prevalence and practices of exposure to screen-based media in children by 15-18 months of age. **Methods**: This observational descriptive study was conducted from March to August, 2019. Mothers of 370 healthy developmentally normal children (15–18 months of age) were enrolled during their visit to immunization clinic of a medical college affiliated hospital. Parental response to a semi-structured questionnaire was recorded to assess the initiation, frequency and duration of screen exposure, and related parental perceptions. **Results**: 369 (99.7%) children were exposed to screen-based media till 18 months of age, starting from median (IQR) age of 10 (8, 12) months. Smartphone and television were being viewed by 354 (96%) and 328 (89%) children, respectively. Screen time was >1 hour/day in 328 (88.7%) and >2 hours/day in 209 (56.5%) children (median (IQR): 120 (80, 180) minutes/d). Most (72%) parents were not concerned with their child's screen time. **Conclusions**: Almost all young children seem to be exposed to screen-based media by 18 months of age in the urban setting. Extensive use of screen-based media by young children calls for formulation of guidelines on toddlers' screen use and their dissemination to parents.

Keywords: *Computers, Smart phone, Television, Toddler, Video game*

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Screen exposure includes both traditional (like watching television) and new digital or social media (using smart phones/tablets, use of videos and computers for recreational activities, video and computer gaming, social media, mobile phone applications, internet use *etc*.) [1]. The prevalence of screen exposure in children less than 2 years of age range from 31-44% in China and Korea [2,3], and varies from 10-75% in other countries [4-6]. American Academy of Pediatrics (AAP) suggests avoidance of any type of screen-based media other than video-chatting for children less than 18 months [1]. Screen exposure leads to impaired quality of life of children and may have adverse outcomes markedly during early phase of development [7]. Increased screen exposure has been linked to language delay, depreciated motor skill development and delayed cognitive development [8,9].

Exposure of young children to screen-based media is a global concern, but the gravity of this situation has not been studied adequately in young children in the Indian setting. We conducted this study to determine the prevalence and practices of exposure to screen-based media in children 15-18 months of age and parental perceptions of the same.

METHODS

This descriptive study was conducted from March to August, 2019 in the Department of Pediatrics at a public hospital in Delhi, after obtaining approval from the institutional ethics committee. Sample size was based on an Australian study that showed 40% prevalence of smartphone use before 24 months of age [6]. Taking alpha error of 5%, absolute precision of 5%, and confidence level 95%, we planned to enroll 370 parent-child pairs.

Apparently developmentally normal healthy children between 15-18 months of age, born at term, were enrolled from the immunization clinic of our hospital. Children with severe acute malnutrition, sensory/motor impairment, acute or chronic illness, and those with restricted mobility were excluded. Enrolled mothers were administered a semi-structured questionnaire on one-to-one basis, after obtaining informed consent. Baseline information was obtained about the sociodemographic characteristics of the family. Screen-based media included (*i*) smartphone, (*ii*) television (TV) and (*iii*) other devices (desktops, laptops, tablet, video consoles, and portable video game device). Respondents were asked about household ownership of these devices, and number of family members owning smartphone devices. Mothers provided information on approximate age of initiation of screen viewing. Parents were also asked about what they used to offer to their child most commonly when they demanded attention/consolation. Frequency of use of screen-based media (minutes/day, and days/week) were also recorded

separately for each device. Screen time of last 24 hours was asked separately and recorded. Questions were also asked regarding the use of screen by the family. Frequency of screen viewing at dinner, for entertainment and academic activities (days/week), of the main caretaker was asked. Family accessibility to outside screen-based gadgets outside the home for gaming and entertainment was asked.

Parental perceptions of their child's screen time were also recorded. The responses for their concern on themselves or their child having excessive screen time were graded on a 5-point Likert scale. Parental awareness of any recommendations on screen viewing was also enquired. Their opinion on screen viewing and its impact on child health was also asked. They were asked for the various reasons of giving/showing screen-based devices to the children, and whether they restricted screen time for their children.

RESULTS

We interviewed 370 mothers-baby pairs (61% boys) with median (IQR) age 17 (16,18) months. Primary caretaker of toddlers in most families (99%) was mother; and only 8 (2.2%) kids were being sent to day care center. More than 90% mothers were homemakers (93%), and most (90.5%) families belonged to middle socioeconomic strata.

Most households had one television, and in 224 (68%) families television was placed in the room where child was sleeping. Of 361 families having smartphone, both parents owned separate smartphone in half of them (180, 49.9%). The use of other screen-based devices, including computer/desktop/laptop was low in this population and their access to outside screen-based gadgets for gaming and entertainment was negligible (***Table* I**).

All except one toddler (369, 99.7%) had been exposed to screen-based media till 18 months of age, starting from as early as 2 months of age (median (IQR) age at first exposure: 10 (8, 12) months) (***Table* II**). Overall, 48 (14.6%), and 39 (11%) toddlers were exposed to TV and smartphone, respectively, before 6 months of age. Presently, 328 (88.7%) were viewing screen for >1 hour/day, and 209 (56.5%) for >2 hours/day. Median (IQR) duration of screen exposure was 120 (80, 180) minutes/day. TV viewing and smartphone screen viewing contributed to median (IQR) of 60 (60, 120) and 45 (35, 90) minutes/day, respectively. Most screen viewing for toddlers was supervised by parents (275, 74.3%). In most families (214, 65.2%), dinner time was associated with screen viewing.

Assessment of parental concern regarding screen exposure showed 266 (72%) parents responding as 'not concerned', 71 (19%) 'a little concerned', and 19 (5%) 'quite a bit concerned'. Only 10 (2.7%) were 'very much' concerned with excess screen time of their child. Only 73 (20%) parents were 'very much' concerned and another 15 (4%) were 'quite a bit' concerned for their own screen time, while 153 (41.4%) were 'not at all' concerned. Except two parents, none had any knowledge of recommendations on screen time in infants. More than half of the parents (196, 53%) opined screen activities were beneficial for the toddler as it helps in stimulating learning behavior and helps parents manage their chores while the child plays, 116 (31%) felt it has no benefits, and 57 (15.5 %) were not aware of any benefits. When asked to report any harmful effects of screen exposure, 257 (69%) parents considered screen exposure causes harm mainly in form of effect on vision and tendency of child to be involved in play rather than academic activities. The most common reason to handover screen-based device to toddlers was to engage them in play activities while the caretaker was busy and/or to console the child (366, 95%).

Table I Household Availability of Electronic Gadgets With Screen (*N*=370)

Number of gadgets	*Television*	*Smartphone*	*Others**
None	40 (10.8)	9 (2.4)	327 (88.4)
1	255 (68.9)	139 (37.6)	43 (11.6)
2	60 (16.3)	103 (27.9)	0
>2	15 (4.1)	119 (32.2)	0

*Values in n (%); *computer/laptop/tablet/video game etc.*

DISCUSSION

We found that exposure to screen was almost universal in this group of urban Indian children by the age of 15-18 months, starting as early as 2 months. Television and smartphone were the main screen-based media devices with nearly 90% viewing the screen for more than an hour a day.

Table II Characteristics of Screen Exposure in Children Aged 15-18 Months (*N*=370)

Screen exposure in children	*Television*	*Smartphone*	*Others**
Exposed to screen	328 (88.6)	354 (95.7)	8 (2.2)
Age (mo) at first screen exposure, median (IQR)	10 (8-12)	12 (8-12)	12 (8.5-14)
Daily screen exposure	302 (81.6)	312 (84.3)	-
Screen time >1 h/d[#]	266 (71.9)	175 (47.3)	-

*Values in no. (%) or as stated; *Computer/laptop/tablet/video game etc; [#]No. of children with screen time >1 h/d was 328.*

WHAT THIS STUDY ADDS?

- Exposure to screen-based media is almost universal in urban Indian toddlers 15-18 months of age, starting as early as by 2 months of age.
- Majority of the parents were not concerned about the screen time of their children.

These findings corroborate those reported in studies from high-income countries like Australia, where 40% of children below 18 months of age had a screen time greater than 2 hours daily [6]. In a study from UK, 75% of children younger than 1 year had screen exposure, which increased rapidly at 1 year of age to >1 hour/day at 14 months and >2 hour/day by 30 months [5]. In India, an earlier study reported screen time in preschoolers (2 to 6 years) to be mean (SD) of 2.7 (1.7) hours, with average (SD) daily TV screen time of 1.6 (1.1) hours [10]. Similar to our findings, television and smartphone were major contributors to screen time in this study [10].

Among low socioeconomic strata population of Europe, around 50% toddlers had screen time of 0.5 hour and 1.5 hour in <11 months and 12-23 months, respectively [4]. The proportion of toddlers meeting the AAP recommendations ranged from 2.3% to 83% and average screentime ranged from 36.6 to 330.9 min/day in a US population [11]. Two-thirds (68%) of Canadian children <3 years were reported to use screen media [12]; whereas, another review estimated only 25% adherence to AAP guidelines by toddlers in Canada [13]. A study from Japan reported 29.4% children at 18 months, and 24.5% at 30 months are engaged in TV viewing for >4 hours/day [14]. In a study from China, average TV viewing was reported to be 67.4 minutes/day in those younger than two years, and >2 hours/day in children older than 2 years [8]. A Korean study reported that children at 2 years of age spend 1.2 hours/day viewing TV, and about 44.1% children spend 1-2 hours [3].

Digital boom in India has led to the availability of portable smartphone devices in large number of households. This socio-environmental *milieu* has changed the type of screen exposure in toddlers, as 96% were exposed to smartphones as compared to 86% to traditional media. Mobile touch screen devices can be easily used by infants as they require lower fine motor coordination. These devices are now most favored tools for providing source of entertainment and educational applications, replacing traditional toys to a great extent.

Limitations of this study include descriptive nature and recall-based data collection, which did not allow us to analyze factors responsible for increased screen viewing. Published literature has implicated maternal education, occupation, number of siblings, and day care attendance affecting the screen time [15]. Further, we did not collect information on the content being viewed, and analyze possible adverse influence it might have had on young children.

There is an urgent need to guide parents regarding the screen exposure practices of their children. In view of high proportion of young children having screen exposure for substantial duration, guidelines specific to Indian context need to be framed and disseminated.

Ethics clearance: Institutional ethics committee of University College of Medical Sciences; No. IEC-HR/2019/38/2 dated March 21, 2019.
Contributors: PG: conceptualized the study; PG, DS, PM: devised the methodology and wrote the protocol; PM: collected data and reviewed the literature. PG, PM: analyzed the data. Final manuscript was edited by PG and DS. All authors have approved the final manuscript.
Funding: None; *Competing interest*: None stated.

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RESEARCH PAPER

Genotype-Phenotype Characteristics of Turkish Children With *Glucokinase* Mutations Associated Maturity-Onset Diabetes of the Young

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Objective: To investigate phenotype-genotype correlations in Turkish children with *glucokinase* gene mutations leading to Maturity-onset diabetes in young (GCK-MODY). **Methods:** Retrospective analysis of 40 patients (16 girls) aged under 18 with GCK-MODY. **Results:** Mean (SD) serum fasting blood glucose level was 6.79 (0.59) mmol/L and the mean (SD) HbA1c level at diagnosis was 6.3% (0.5). Sixteen different variations were detected in the *GCK* genes of the 40 cases; 33 missense mutations, 6 deletions, and one nonsense mutation. The birthweight of infants with deletion mutation was significantly lower than that of infants with other mutations [2460 (353.66) g *vs* 2944.11 (502.08) g]. **Conclusion**: GCK-MODY patients with deletion mutation inherited from mothers had lower birthweight and higher fasting blood glucose than those with other inherited mutations but similar HbA1c values.

Keywords: Gestational diabetes mellitus, Next generation sequencing.

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Maturity-onset diabetes of the young (MODY) is a rare form of diabetes inherited in an autosomal dominant manner and developing secondary to beta cell dysfunction. MODY accounts for 1.1-4.2% of diabetic children and has a reported prevalence of 2.4-4.6 per 100,000 [1,2]. GCK-MODY (MODY2) and HNF1A-MODY (MODY3) constitute 90% of all MODY cases [3,4]. Heterozygous, inactivating mutations in the *glucokinase (GCK)* gene cause GCK-MODY, while homozygous or combined heterozygous mutations lead to permanent neonatal diabetes mellitus [5]. GCK mutations are commonly encountered in countries such as Spain, France, and Italy, where blood glucose screening is routinely performed, it is also reported as the leading cause of MODY in the Turkish population [4]. The purpose of this study was to investigate the genotype-phenotype correlations of patients with GCK-MODY followed-up in three different centers in Turkey.

METHODS

Data was retrieved from hospital records for 40 MODY patients with GCK mutations (16 girls) aged under 18 years, who had presented to the department of pediatric endocrinology between 2013 and 2018. All selected cases were variant carriers in the *GCK* gene. Parents with no history of diabetes mellitus were tested for fasting plasma glucose and glycosylated hemoglobin (HbA1c). *GCK* gene mutation analysis was also performed on the parents of children with GCK-MODY. Demographic features, laboratory findings and treatments received were retrieved from hospital.

DNA was isolated from samples as per standard technique. The *GCK* gene was sequenced using the Next generation sequencing (MISEQ-Illumina) method. The pathogenicity of the detected variants in the GCK gene was determined by combined evaluation of bioinformatics, in-silico analysis of the detected variants with segregation studies, and the laboratory and clinical findings. The study was approved by the local ethics committee.

Statistical analyses: All statistical analyses were performed on IBM SPSS Statistics for Windows software, version 23.0 (IBM Corp., Armonk, NY, USA). Relations between the GCK gene variants and both clinical and laboratory parameters were evaluated using the chi-square test. P values <0.05 were considered statistically significant.

RESULTS

The mean (SD) age at diagnosis was 8.6 (4.25) years. The mean (SD) fasting blood glucose level was 6.79 (0.59) mmol/L. The mean (SD) fasting C-peptide level was 1.3

(1.4) ng/mL, the mean (SD) insulin level was 7.44 (4.95) µU/mL, and the mean (SD) HbA1c level at diagnosis was 6.34 (0.56)%. Thirty patients presented with fasting hyperglycemia, while 10 patients were admitted with symptoms of hyperglycemia. The mean (SD) HbA1c value was 6.48 (0.41)% at the last follow-up, and the mean (SD) length of follow-up was 2.14 (1.72) years.

Sixteen different variants were detected in the *GCK* gene of the 40 cases; 33 were missense mutations, six were deletions, and one was a nonsense mutation. The most common mutations were p.Met393Thr (15/40) and p.Ile189Val (6/40). Three of the cases were homozygous, and 37 were heterozygous. We detected a new variant that had not been previously described, named c.537delG / p.Asn180ThrfsTer25 in exon 5 of the *GCK* gene. GCK-MODY was present in the mother or father in 32 of the 40 cases in this study, while the parents in the other eight cases had no GCK-MODY diagnosis. Deletion mutation was determined in six of the fathers with GCK-MODY and missense mutation in 13. Fourteen of the mothers had a missense mutation in the *GCK* gene, and five had deletion. Nine infants (9/40) were small for gestational age. The infants with deletion mutation had statistically significantly lower birthweight than infants with other mutations (***Table* I**).

The mean (SD) insulin requirement in the final trimester of pregnancy among mothers with deletion mutation (0.48 (0.13) U/kg) was higher than that of mothers with other mutations (0.20 (0.13) U/kg) (P=0.07). Permanent neonatal diabetes was diagnosed in one case with homozygous deletion mutation, and glycemic control was achieved with insulin pump treatment. GCK-MODY was diagnosed in two cases with homozygous missense mutation, and medical treatment was not required in these.

Table I Characteristics of Children With GCK-MODY (N=40)

Characteristics	*Deletion mutation (n=6)*	*Other mutation (n=34)*
Age (y)	8 (5.76)	10.5 (4.90)
Age diagnosis (y)	4.4 (4.7)	9.3 (3.77)
Birthweight, g[#]	2460 (353.66)	2944.1 (502.1)
[*]FBG (mmol/L)[‡]	7.4 (0.40)	6.68 (0.56)
[*]HbA1c (%)	6.13 (0.98)	6.38 (0.46)
C-peptide, ng/mL	2.44 (3.76)	1.24 (0.85)
Insulin, µU/mL	9.16 (7.57)	7.27 (4.79)
HDL, mmol/L	1.05 (0.27)	1.29 (0.26)
LDL, mmol/L	1.90 (0.63)	2.09 (0.62)
Cholesterol, mmol/L	3.60 (0.44)	3.74 (0.77)
Triglyceride, mmol/L	1.20 (0.67)	0.85 (0.37)

All values in mean (SD); [*]values at diagnosis; [#]P=0.016, [‡]P=0.007; HDL: High density lipoprotein, LDL: Low density lipoprotein.

DISCUSSION

Patients with GCK-MODY are mostly asymptomatic. The fasting blood glucose level and HbA1c level at first admission in the present study was consistent with the literature [6]. Pharmacological therapy is not recommended in GCK-MODY, except during pregnancy, because of the low effect of blood glucose lowering therapy and the absence of complications in diabetics with this mutation [8].

Most GCK-MODY mutations consist of missense (65%), nonsense, frameshift or splice site mutations [2]. Rare causes include GCK pancreatic islet promoter mutations [9] and partial or complete gene deletions [10]. Consistent with the previous literature, the most common GCK mutation in the present study was missense mutation. High blood glucose is reported to induce glucokinase through post-translation mechanisms, and the clinical phenotype is therefore similar in cases with GCK-MODY irrespective of the severity of the mutations [11]. However, recent studies have demonstrated that the phenotype may significantly differ in patients with GCK-MODY depending on the type of the mutation [12]. Fasting blood sugar in our deletion mutation group was significantly higher than in patients with other mutations, a finding consistent with previous studies revealing a relationship between genotype and phenotype. Velho, *et al*. [13] reported that missense mutations exhibit varying effects on glucokinase activity, and that glucose affinity can be affected, ranging from a small change to complete inactivity. In contrast, we found that children with heterozygous missense mutation GCK-MODY exhibited similar phenotype characteristics to those of children with GCK-MODY with other mutations, and that they presented with mild fasting hyperglycemia. Although homozygous mutations in the *GCK* gene are known to cause permanent neonatal diabetes, few cases with this mutation are diagnosed with mild fasting hyperglycemia, and protein instability has been implicated in this difference in phenotypes [14].

Maternal hyperglycemia during pregnancy is the primary risk factor for fetal macrosomia caused by fetal hyperinsulinism [15]. However, if the fetus inherits the *GCK* mutation from the mother, aggressive insulin treatment directed toward maternal euglycemia may cause fetal growth retardation [16]. In our study, the mean birthweight of the patients with deletion mutation inherited from the mothers was significantly lower than that of patients with nonsense and missense mutations

WHAT THIS STUDY ADDS?

Patients with *glucokinase* gene mutation associated maturity-onset diabetes in young (MODY) who inherited the deletion mutation from their mothers, had lower birthweight and higher fasting blood glucose than those with other mutations.

inherited from mothers. The need for blood glucose-lowering treatment in pregnant women with GCK-MODY with gene deletion may explain the lower birth weight in the infants with the same mutation.

In conclusion, our study shows that patients with deletion mutation inherited from mothers had lower birth weight and higher fasting blood glucose, but similar HbA1c values, compared to patients with other inherited mutations, and that homozygous gene mutations in the *GCK* gene result in phenotypic characteristics ranging from neonatal diabetes to GCK-MODY.

Ethical clearance: Institutional ethics committee of Malatya Clinical Research Institute; No. 23536505-604.02, dated March 13, 2019.
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Indian Academy of Pediatrics Position Paper on Kawasaki Disease

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Objective: To formulate practice guidelines on diagnosis and management of Kawasaki disease (KD) for Indian children. **Justification:** KD is a systemic vasculitis that predominantly affects infants and children less than 5 years of age. Coronary artery abnormalities (CAA) develop in around 15-25% of untreated children with KD. Coronary artery involvement can lead to long-term cardiovascular implications such as development of premature coronary artery disease. Diagnosis of KD is essentially clinical based on recognition of a constellation of characteristic symptoms and signs. Timely diagnosis and initiation of intravenous immunoglobulin (IVIG) therapy is known to produce five-fold reduction in the incidence of CAA. As there is no confirmatory laboratory test for KD, the diagnosis may be missed if one is not familiar with the nuances of clinical diagnosis. **Process:** A committee was formed under the auspices of Indian Academy of Pediatrics in early 2018 for preparing guidelines on KD in Indian children. A meeting of the consultative committee was held in Mumbai, and a draft protocol was devised. All members scrutinized the recent publications on the subject and an attempt was made to arrive at a broad consensus. Published guidelines on the subject were also reviewed. **Recommendations:** The diagnosis is clinical and is aided by laboratory and 2D echocardiography. First line of therapy is IVIG, and should be started expeditiously once the diagnosis is made.

Keywords: *Coronary artery abnormalities, Diagnosis, Intravenous Immunoglobulin, Infliximab, Management.*

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Kawasaki Disease (KD) is an acute febrile illness that commonly affects children below 5 years of age. Classified under predominantly medium vasculitides, it has a predilection to involve coronary arteries. Ever since the first report by Dr. Tomisaku Kawasaki from Japan in 1967 [1], the disease has been increasingly reported world-wide. KD has become one of the leading causes of acquired heart disease among children in many developed countries.

Incidence of KD has been increasing significantly over the last decade, even in India, possibly due to a combination of an actual increase in incidence and also due to heightened awareness amongst the pediatricians [2]. A high index of suspicion supported with relevant laboratory tests and imaging (2D echocardiogram) is often needed in establishing the diagnosis. Though various consensus guidelines are available for diagnosis and management of KD, a nation-wide consensus for a resource constrained setting like ours is the need of the hour.

PROCESS

A National Consultative Group was constituted under the auspices of Indian Academy of Pediatrics (IAP) in March, 2018 for preparing the guidelines on KD in Indian children. This group of experts consisted of pediatricians, pediatric rheumatologists and pediatric cardiologists known for their expertise and experience in treating KD across the country. A meeting of the consultative committee was held in Mumbai in March, 2018 to discuss the scientific contents. The members reviewed the available literature and discussed various aspects of forming the guidelines and a draft protocol was devised. This was reviewed by all the members and a final draft recommendation was formed through a virtual meeting. The draft recommendations formulated by the group were circulated among the members and a consensus document was finalized.

DIAGNOSIS

We have two established criteria that could be used as a guide for diagnosis of KD – The American Heart

Association (AHA) criteria [1] and the Japanese criteria [7]. AHA criteria have been discussed in this document and are detailed in ***Box* I**.

Clinical Features

Thorough history and assessment of clinical findings play a major role in the diagnosis, as there are no specific tests.

Principal Clinical Findings

Diagnosis of KD is usually made on the basis of fever for ≥5 days along with the history/presence of ≥4 out of the 5 key clinical features. Diagnosis is made as per features given in ***Box* I** but the presence of classic clinical presentation or coronary artery abnormality, the diagnosis of KD can be made in less than 5 days.

Fever: The most common manifestation is fever, which is often high grade and remittent type. If untreated, fever continues for 1-3 weeks and resolves spontaneously by 3 to 4 weeks, mean duration of fever being 11 days.

Conjunctival injection: Bilateral, painless and non-exudative conjunctival injection with peri-limbal sparing usually begins in first few days after fever onset, seen in 80-90% cases. Slit lamp examination might reveal anterior uveitis during the first week of fever. Purulent conjunctivitis should suggest alternate diagnosis.

Oral changes: Bleeding, crusting, dryness, erythema and fissuring of lips are common mucosal changes noted in KD patients. Oral mucosal and pharyngeal erythema can also be seen. Erythema of tongue along with the presence of prominent papillae results in a strawberry tongue appearance.

Box I Classical Diagnostic Clinical Criteria of Kawasaki Disease by the American Heart Association [1]

Fever persisting >/=5 days

History/Presence of >/=4 principal features

- Changes in extremities (pedal edema in acute phase, periungual peeling in sub acute phase
- Polymorphous rash
- Bilateral bulbar conjunctival injection without exudates
- Changes in lips and oral cavity
- Cervical lymphadenopathy (>1.5 cms diameter)

Exclusion of other diseases with similar findings.

All manifestations may not be present at the same time in a given child, as they are often transient. However, a thorough history is likely to elicit findings which maybe presently absent.

Cervical lymphadenopathy: Cervical adenopathy is usually non-specific and the least common clinical finding. Unilateral enlargement of a cervical node >1.5 cm diameter in the anterior triangle of neck may be noted. Occasionally the lymph node mimics suppurative lymphadenitis and may be associated with retropharyngeal/parapharyngeal edema (phlegmon) mimicking a retropharyngeal abscess on MRI. But presence of associated clinical features of KD helps in clinching the diagnosis.

Rash: A maculopapular erythematous rash that begins in trunk, later extending to extremities and face, is usually seen by 5 days of onset of the illness. Sometimes it resembles a scarlatiniform, erythroderma, erythema multiforme, or urticaria like rash. Bullous, vesicular or petechial rashes are usually not seen and suggests an alternate diagnosis.

Extremity changes: During the acute phase, erythema of palms and soles along with edema and induration of hands and feet may be seen. Desquamation of fingers and toes usually occurs 10-20 days after the onset of fever and typically starts in the periungual region. It may extend to involve the entire palm and sole.

Other Clinical Findings

Perianal or perineal desquamation is typically seen during the acute phase of KD, as early as day 6 of fever and is a useful clinical pointer.

Reactivation of BCG scar: Erythema and induration can occur at the site of BCG scar. Though noted in a small proportion of children with KD, it is virtually pathognomonic when other findings are missing [1].

Nervous system: Irritability is a common finding especially marked in infants. It is usually out of proportion to the degree of fever and thought to be a manifestation of aseptic meningitis. Profound sensorineural hearing loss may be present. Facial palsy, though rare, has been well documented. Prolonged unexplained fever with extreme irritability may be the only clinical manifestation in many infants below 6 months of age without any of the principal clinical signs of KD.

Gastrointestinal system: Diarrhea, vomiting, pain abdomen, hepatitis, pancreatitis and gallbladder hydrops can be present.

Genitourinary system: Urethritis/meatitis is a common feature in the acute phase presenting as sterile pyuria. Less common features are hydrocele and phimosis.

Musculoskeletal system: Pain and swelling of inter-phalangeal joints may occur during the acute phase. Arthritis of large joints (knees and ankles) usually occur during the convalescent phase and is seen in 10-15% of cases.

Respiratory system: Tachypnea, dyspnea, and cough may rarely be seen. Chest radiograph may reveal peri-bronchial or interstitial infiltrates.

Cardiovascular: Pericarditis, myocarditis, valvular dysfunction, congestive heart failure, and peripheral gang-rene are the cardiovascular manifestations of KD.

About 5% of children may present with cardio-vascular collapse and shock that may be difficult to differentiate from toxic shock [8,9]. High index of suspicion and presence of accessory clinical features helps in clinching the diagnosis. KD shock is readily responsive to IVIg which helps in differentiating from a viral myocarditis.

Beau lines: Transverse grooves in the nails can be noted 1-2 months after the onset of illness indicating a catabolic process in the preceding weeks.

Definitions used in KD diagnosis are provided in ***Box* II**, and approach to a child with suspected incomplete KD is shown in ***Fig*. 1**.

Box II Definitions Used in Diagnosis of Kawasaki Disease

Complete KD: Patients with fever of at least 5-day duration with presence/history of 4 or more of the 5 principal clinical findings are labelled as typical or classic KD.

Incomplete KD: Presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings suggest incomplete KD. Often seen in infants <6 months and children >6 years of age, the incomplete clinical picture often delays the diagnosis. Approach to a child with suspected incomplete KD is shown (***Fig.* 1**).

Atypical KD: Patients who along with the usual clinical features of KD also have few unusual clinical manifestations like pulmonary involvement, renal impairment are diagnosed to have atypical KD.

The terms atypical KD and incomplete KD are interchangeably used, but recent consensus is to use atypical KD in patients who have unusual clinical features and complications of KD.

Laboratory Tests

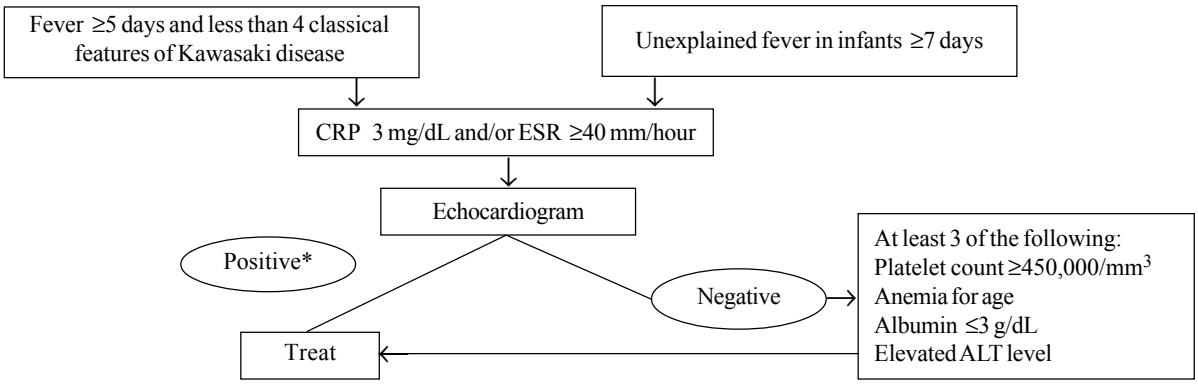
Diagnosis of KD is about pattern recognition with impetus being on a good history and detailed physical examination. Laboratory tests are non-specific and are only supportive and laboratory findings vary with the course of illness.

Hemoglobin: Mild to moderate normocytic, normo-chromic anemia is common.

Leucocyte count: Leukocytosis is usually seen in acute phase of illness with neutrophilic predominance.

Platelet count: Thrombocytosis is one of the significant lab findings in KD. Platelet count starts rising after first week, reaching a peak in the third week and normalizing by 4-6 weeks. Thrombocytopenia is uncommon but can occur in first week. Thrombocytopenia is a risk factor for development of CAA and may be a marker of incipient macrophage activation syndrome [10,11].

Acute phase reactants like Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are almost always elevated in KD. IVIG therapy by itself can cause an elevation in ESR leading to doubts in the mind of the treating physician. Hence, CRP is more useful to assess response to treatment with IVIG. Macrophage activation syndrome which can rarely complicate KD should be suspected in patients with severe clinical disease



*(*Positive echocardiogram: refer to the section on echocardiography; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; ALT: alanine transaminase; WBC: White blood cell count).*

Fig. 1 *Evaluation of suspected incomplete Kawasaki disease (Source AHA 2017)* [1].

associated with minimally elevated ESR and markedly elevated CRP. It might be prudent to look for an elevated serum ferritin to confirm this suspicion.

Serum transaminases: Mild to moderate elevation is seen in around 50% of patients.

Serum albumin: Hypoalbuminemia is often noted in the acute phase suggesting severe inflammatory process.

Sterile pyuria (>0 cells/high power field with sterile cultures): This is due to urethritis and sometimes be mistaken for urinary tract infection in infants.

Procalcitonin levels are usually normal, but elevated levels are associated with increased risk of IVIg resistance and CAA [12]. Serum Pro-BNP (Pro-brain natriuretic peptide) and N terminal Pro BNP (NT-ProBNP) levels are elevated in KD and can serve as useful biomarkers in distinguishing incomplete KD and closely mimicking febrile illnesses. Serum levels of NT-Pro-BNP > 225 pg/mL can assist in the diagnosis of KD (suggesting myocardial dysfunction) (86.5% sensitivity and 94.8% specificity) [13]. ECG may reveal evidence of myocarditis and conduction disturbances. An ultrasound of the abdomen may show hepatomegaly, hepatosplenomegaly, acalculous cholecystitis (gall bladder hydrops).

Echocardiography

Echocardiography is the imaging modality of choice for diagnosis, risk stratification, treatment planning, prognostication and follow-up of any suspected or confirmed KD. KD is a clinical diagnosis and role of echocardiography is to only confirm/exclude cardiac involvement, especially coronary arteritis. Thus, treatment of KD should not be withheld for local non-availability of pediatric cardiologist. Simultaneously, the pediatrician should refer to the pediatric cardiologist if pyrexia of unknown origin lasts longer than 7 days.

Objectives of Echocardiography in KD

- To confirm the diagnosis in case of suspected incomplete KD, though a normal echocardiogram does not exclude the diagnosis.
- To quantify coronary changes in proven KD.
- To look for other cardiac complications like myocarditis and cardiovascular collapse (5%), valvular regurgitation (*e.g.,* mitral regurgitation), pericardial effusion [1,8,9].
- To assess response to therapy by serial echocardiography (regression, persistence or progression of aneurysm, myocarditis and valvular dysfunction).
- To look for myocardial ischemia secondary to coronary involvement, usually seen in giant/large aneurysms.
- Rarely rupture of aneurysm with cardiac tamponade especially in acute phase with rapid enlargement of aneurysm.
- Prognostication and counselling of family.
- Long term follow-up of KD with persistent CAA.

Echocardiographic Changes in KD

The cardiac involvement in KD can be grouped into (*a*) early changes (*b*) subacute changes (*c*) late changes.

(*a*) *Early changes (1st week of fever)*: Coronary changes are uncommon in the first week. The important clues are myocarditis (prevalence 50-70%), pericarditis, small pericardial effusion and transient mild to moderate mitral regurgitation (23-27%). We recommend use of advanced echo modalities like myocardial performance index and tissue doppler to document myocarditis in addition to standard parameters like ejection fraction (EF) and fractional shortening (FS) [14,15].

7% of children with KD in US present with cardiovascular collapse (KD shock syndrome). The unique features of KD myocarditis are (1) it presents early (2) precedes coronary arteritis, (3) transient and resolves earlier than other causes of myocarditis as inflammation and myocardial edema subside. In doubtful cases, serum NT pro BNP may be used as a surrogate marker, although it is nonspecific and cut off values yet to be clearly defined [13,16,17]. We reiterate that normal coronaries in the first week do not exclude KD.

(*b) Subacute changes (after 1st week of fever)*: The highlight of this phase is detection of coronary involvement and its aftermath.

Some tips and clues for successful echo in KD child are given in ***Box* III**. The coronary involvement as per z score classification is as follows [1]: No involvement: z score always <2; and Dilatation only: 2 to < 2.5. Aneurysms as per size: Small CAA: ≥2.5 to <5 mm; Medium CAA: ≥5 to <10 mm and absolute dimension >8 mm; Large/Giant CAA: ≥10 mm or absolute dimension ≥8 mm. Aneurysms as per shape: saccular or fusiform.

The Heart Beyond the Coronaries

Apart from early phase, echo during the subacute and long term phases should focus also on:

- Aortic root dilatation and aortopathy
- *Cardiac valves*: Late onset regurgitation is attributed to fixed damage to valve apparatus by the inflammatory mechanism.

Box III Tips for Successful Echocardiography in a Child With Suspected Kawasaki Disease

- Sedation should be used, as these children (especially infantile KD) are extremely irritable and toxic.
- To accurately identify coronary arteries, we recommend use of highest frequency echo transducers (10-12 Hz).
- The main coronary segments to be visualized are: left main coronary artery (LMCA) bifurcating into left anterior descending artery (LAD) and circumflex (Cx), right coronary artery (origin, mid and distal segments).
- The luminal diameter from inner edge to edge is taken in zoomed mode. Please note all measurements are to be compared with the child's body surface area. Weight and especially height are to be considered while interpreting coronary sizes. Z Scores are then calculated as per BSA.

- *Myocardial function*: Both global and regional wall motion abnormalities (RWMA) perfused by particular coronary territories are to be reported. Abnormal RWMA is a clue of myocardial ischemia and prompts further analysis by CT or direct coronary angiography.

How Frequently Should One Repeat Echo in a Child with KD?

- At diagnosis.
- Uncomplicated patients**:** 1-2 weeks and also 4-6 weeks after treatment. This is because dilatation is unusual beyond 6 weeks. Normal coronaries may be discharged from cardiology care after 12 months but the medical records should permanently mention the diagnosis of KD.
- For significant and evolving coronary abnormalities: At least twice per week till luminal dimensions stabilize and we should look specifically for thrombus. After that at 2 weeks, 4-6 weeks, 3 months and then every 6-12 months till parameters normalize.
- To detect coronary artery thrombosis it may be reasonable to perform echocardiography for patients with thrombus at diagnosis, expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset, as failure to escalate thromboprophylaxis is a primary cause of morbidity and mortality.

Long Term Cardiac Assessment in KD

Long-term status is when the patient is stable after the acute illness and the coronary artery luminal dimensions are not increasing or progressing (usually within 15 to 45 days).

- 5% of acute coronary syndrome in US has been attributed to missed KD in childhood [18,19].
- Normal coronaries at initial presentation usually have no long term sequelae.
- Small or moderate aneurysms usually demonstrate normalization of luminal dimensions, infrequently stenosis may happen. Development of late aneurysms especially with coexistent stenosis is also reported especially with repeat KD or suboptimal initial treatment.
- Coronary artery events (thrombosis, stenosis, intervention, MI, death) occurred in 1% of those with an aneurysm Z score <10 and an absolute dimension <8 mm, in 29% of those with a Z score ≥10 but an absolute dimension <8 mm, and in 48% of those with both a Z score ≥10 and an absolute dimension ≥8 mm [20, 21].
- Subclinical functional impairment (fibrofatty changes, necrotic core and calcification) of these coronaries have been observed with advent of intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Interestingly wall thickening was found more in those coronaries where aneurysms normalized on longitudinal follow up. PET scan shows increased uptake in these areas [22-24]. Clinically these translate to impaired myocardial flow and reduced response to traditional coronary vasodilators like nitroglycerin. This poses a risk to myocardial infarction in KD survivors.

Limitations of echocardiography: Despite its primary position as a diagnostic modality for KD, echocardiography has some limitation:

- Abnormal coronaries are seen in only 20- 25% of KD. Hence, a normal echo does not preclude KD [1].
- Coronary artery aneurysms usually appear after 1st week. It must be repeated in all KD patients after 2 and 6 weeks [1].
- Cardiac sequelae in classical and incomplete KD are same. So, cardiologist has to be more meticulous while imaging suspected atypical KD because diagnosis rests on 2 D echo and laboratory findings.

Role of Other Cardiovascular Imaging Modalities

Acute phase: Echocardiography is the best modality.

Medium and long term phase: As the child grows, transthoracic echocardiography may not be able to visualize especially the distal coronary segments. Apparent normalization of coronary diameters may also be due to intimal calcification and fibrofatty changes. So, use of CT coronary angiography, PET scanning, cardiac MRI and documenting inducible myocardial ischemia (Dobutamine stress echocardio-graphy, stress thallium scan, PET) to assess myocar-dial function and ischemia in older children, adolescents and adult survivors is recommended. Exercise TMT alone is not sufficient to detect these changes. If any of these are positive, direct coronary angiography as a planner for subsequent angioplasty or bypass surgery is to be done.

Differential Diagnosis

Infections: Bacterial (streptococcal, leptospirosis, rickettsia), Viral (measles, adenovirus, Epstein Barr virus).

Toxin related: Staphylococcal scalded skin syndrome, toxic epidermal necrolysis.

Inflammatory: Systemic juvenile idiopathic arthritis.

Drug hypersensitivity: Steven-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), mercury hypersensitivity.

Gastrointestinal features like paralytic ileus, gall bladder hydrops, greenish diarrhea, jaundice and raised transaminases may mimic other gastrointestinal infections or surgical conditions. Sterile pyuria and CSF pleocytosis can masquerade as urinary tract infection or aseptic meningitis.

A fever that does not appear to respond to antimicrobials should always raise the consideration of alternate pathologies like inflammatory or vasculitic illness like KD.

TREATMENT

Acute Kawasaki Disease

The goal of treatment is to control the acute inflammation and prevent long term coronary sequelae. IVIG and high-dose aspirin are the cornerstones in the management of KD, although the role of high-dose aspirin in the acute stages is debatable. Treatment should be initiated promptly and must not be delayed awaiting echocardiography, when the clinical features are suggestive of KD.

Single dose of IVIG 2g/kg administered over 12-24 hours should be given within 10 days of illness, preferably in the first 7 days [1]. Timely administration of IVIG reduces the development of CAAs from 15-25 to 3-5%, and the risk of giant aneurysms to 1% [1].

IVIG should be considered even in patients with >10 days of illness with persistent fever, systemic inflammation evidenced by elevated ESR or CRP (>3.0 mg/L), or presence of CAAs. IVIG may not be needed in patients who had

Table I Differential Diagnoses of Kawasaki Disease (KD) and Differentiating Features

	KD	*Scarlet fever*	*Measles*	*SJS*	*TSS*	*SJIA*
Strawberry tongue	Present	Present	Absent	Absent	Absent	Absent
Red eyes	Present (non-exudative)	Absent	Exudative conjunctivitis	Absent	Exudative conjunctivitis	Absent
Red lips	Present	Absent	Absent	Absent	Absent	Absent
Response to antibiotics	Does not respond	Brisk response in 48 h	NR	NR	NR	NR
Peeling	Perineal and periungual	Generalized	NR	NR	Generalized	NR
Follicular tonsillitis	Usually absent	May be present	NR	NR	NR	NR
Edema of extremities	Present	Absent	Absent	Absent	Absent	Absent
Koplik spots	Absent	NR	Present	NR	NR	NR
Oral ulcers	Absent	NR	NR	Present	NR	NR
Hepatosplenomegaly	Absent	Absent	NR	NR	NR	Present
Hypotension /renal impairment	Absent	NR	NR	NR	Present	NR
Leukocyte counts	Elevated	May be elevated	Normal	NR	NR	Elevated
ESR and C-reactive protein	Elevated	May be normal	NR	NR	NR	Elevated

NR: Non-relevant; SJS: Steven Johnson syndrome; TSS: Toxic shock syndrome; SJIA: Systemic onset juvenile idiopathic arthritis; KD: Kawasaki disease; ESR: Erythrocyte sedimentation rate.

resolution of fever with normal inflammatory parameters and normal echocardiography findings [25].

Dose of aspirin used in the acute stages is 30-50 mg/kg/day in 3-4 divided doses, that is continued until the patient is afebrile for 48 hours. The dose of aspirin (ASA) is reduced to 3-5 mg/kg/day and continued for 6-8 weeks and stopped if CAAs are not detected in the 6th week echocardiography. The anti-platelet dose of aspirin is continued in patients who have persistent CAAs until the normalization of coronary artery dimensions. Patients on long-term aspirin need influenza vaccination yearly to reduce the risk of Reye syndrome.

Multiple studies have come up recently, demonstrating the beneficial use of corticosteroids along with IVIG in children predicted to have an increased risk of CAAs and IVIG resistance [3]. Addition of glucocorti-coids (prednisolone) to IVIg has been shown to reduce the risk of CAAs, duration of fever, and inflammation in Japanese children who are at a high risk for resistance to IVIG therapy. A recently published Cochrane database systemic review has even suggested that a long course of steroids along with IVIG should be considered in all children with KD until further evidence are available [26].

Recommended use of steroids in KD: Oral prednisolone (2 mg/kg/day) to be initiated with IVIG and gradually tapered over 15 days after normalization of CRP levels.

In IVIG responsive patients, fever usually subsides by 36-48 hours along with decrease in inflammatory parameters. Patients with recurrent KD, defined as a repeat episode of KD after complete resolution of the first episode, should receive standard therapy with IVIG and ASA.

Anticoagulation in Kawasaki disease is indicated in the following situations: (*a*) Giant aneurysm, multiple or complex aneurysms, presence of thrombus; (*b*) associated stenosis; and (*c*) peripheral gangrene.

It is prudent to initiate with LMW heparin followed by oral warfarin to maintain INR of 2-2.5. However in view of the difficulty of maintaining the target INR in children on oral anticoagulants, one may consider continuing long term thromboprophylaxis with LMW heparin only after proper parental counselling.

For arterial thrombosis/peripheral gangrene-thrombolytic therapy has been tried in addition to anticoagulation.

Treatment of incomplete KD: Incomplete forms should be treated in the same manner as complete KD.

Resistant Kawasaki Disease

Children who have persistence or recurrence of fever 36 hours after the end of IVIG infusion are considered to be IVIG resistant [1]. Around 10 to 20% of patients are IVIG resistant [27]. Prolonged fever and unresponsiveness to the first dose of IVIG are significant risk factors for CAAs.

Risk scores for predicting non response to IVIG: Egami [28], Sano [29] and Kobayashi [30] scoring systems are some of the scoring systems that have been shown to predict IVIG resistance.

There is no established consensus on the pharmacologic treatment of refractory KD. Various therapeutic options available -

IVIG retreatment: Many experts recommend retreatment with second dose of IVIG 2g/kg. Rate of refractoriness to the second dose IVIG is around 22-49% [31].

Corticosteroids: Furukawa, *et al*. [32] compared the effectiveness of second dose IVIG and IV prednisolone in patients with IVIG resistant KD. They found that incidence of CAA and treatment failure were similar between 2 groups; however, the steroid group had a faster defervescence of fever and improvement in inflammatory markers [32]. The AHA recommends that a short duration of high-dose glucocorticoids could be a reasonable treatment option in patients with IVIG resistant KD [1].

Infliximab: Infliximab is a chimeric monoclonal anti TNF-α antibody. Dose is 5 mg/kg given intravenously over 2 hours. Studies have not demonstrated superiority of infliximab over others in IVIG-resistant KD in terms of coronary artery outcomes though fever and other constitutional features resolve well. The AHA recommends the use of infliximab as a substitute for a 2nd dose IVIG or steroids in resistant KD [33,34].

Cyclosporine: Cyclosporine inhibits lymphocyte activation by blocking the NFAT-calcineurin pathway that is thought to influence disease susceptibility and development of CAAs in KD [35]. The AHA recommends the use of cyclosporine as a possible third or fourth-line therapy in patients with KD.

Plasma exchange: Used rarely for children who have active inflammation despite multiple doses of IVIG, corticosteroids, and infliximab.

Cytotoxic agents: Cyclophosphamide is used to treat other severe vasculitides, but the risks of cytotoxic agents limits its use.

Statins: Statins, hydroxymethylglutaryl coenzyme A-reductase inhibitors, have been shown to reduce cholesterol levels as well as improve surrogate markers of atherosclerosis and cardiovascular disease. Huang, *et al*. [36] reported a beneficial effect of short-term (3 months)

statin treatment (simvastatin, 10 mg/day as a single dose at bed time) in KD patients complicated with CAL. Chronic vascular inflammation is also significantly improved, as well as endothelial dysfunction, with no adverse effects. However, long-term and randomized control trials are needed before further conclusions can be made.

It has been recently reported that atorvastatin is able to inhibit critical steps (T cell activation and proliferation, production of the pro-inflammatory cytokine TNF-α, and up-regulation of matrix metalloproteinase-9 and an elastolytic protease) known to be important in the development of coronary aneurysms in an animal model of KD, suggesting that statins may have therapeutic benefits in KD patients [37]. Taken together, statins may be beneficial as an adjuvant therapy in KD patients with CAL.

Management of Cardiovascular Sequelae

Coronary artery aneurysm is a potential serious cardiac complication of KD. With giant coronary artery aneurysm, there is increased risk of thrombosis, stenosis, ischemia, infarction and death [38,39]. The goals of long-term management are to prevent thrombosis and myo-cardial ischemia while maintaining optimal cardiovascular health [39].

Medical therapy for myocardial protection: α- blockers used are carvedilol, metoprolol or bisoprolol. They decrease the risk of myocardial infarction and death by reducing myocardial oxygen demand. ACE inhibitors or ARBs also protect against myocardial infarction and death. Statins in addition to their cholesterol lowering action have other pleiotropic effects in inflammation, endothelial dysfunction, oxidative stress, platelet aggregation, coagulation and fibrinolysis, which make them useful in the management of KD [37].

Thromboprophylaxis: Antiplatelet drugs like aspirin are commonly used in KD. In giant aneurysm or large distal aneurysms, a dual antiplatelet treatment with aspirin and clopidogrel is preferred. Anticoagulation with warfarin to achieve a target INR of 2-3 is used. LMWH is equally effective to warfarin, used in young children in whom dosing with warfarin is difficult [1].

Surgical management: is rarely required in pediatric age group. It includes percutaneous coronary intervention or coronary artery bypass grafting [38].

Macrophage activation syndrome (MAS) is a dreaded complication that may rarely occur characterized by persistent fever, pancytopenia, liver dysfunction, hepato-splenomegaly, hyper-ferritinemia, hypofibrino-genemia, elevated serum lactate dehydrogenase, and hypertriglyceridemia. Prompt treatment with pulse methylprednisolone along with IVIg may result in favorable outcome [1].

KD should be diagnosed and treated by primary care pediatricians. However, involvement of a pediatric rheumatologist is required in some circumstances:

- Incomplete/atypical KD,
- KD in infancy,
- presence of CAL at diagnosis,
- IVIG-resistant KD,
- KD shock syndrome, and
- suspicion of a macrophage activation syndrome.

CONCLUSION

Kawasaki disease is the most common cause of acquired heart disease in children in the developed world. It is being increasingly recognized and treated in various parts of our country. Pediatricians must be aware of the varied manifestations of KD. Early diagnosis and prompt treatment can result in better outcomes.

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Consensus Guidelines for Pediatric Intensive Care Units in India, 2020

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Background: Consensus Guidelines for Pediatric Intensive Care Units (PICUs) were published in Indian Pediatrics in 2002. **Objective**: The current document represents a recent update in the Indian context, regarding unit design, equipment, organization, staffing as well as admission and discharge criteria for different levels of Pediatric Intensive Care and teaching units with PICU training programs, as well as nonteaching units. **Process**: The Pediatric Intensive Care College Council (PICC), an academic wing of the Indian Academy of Pediatrics (IAP) Intensive Care Chapter took the initiative to update the guidelines with members of the PICU guidelines Committee writing group. After a great deal of discussion at conferences and through mailing and feedback with listed members, as well as with the guidance and feedback of senior PICU guidelines advisory committee members, The consensus is now updated. These guidelines are intended to serve as a reference for health Care institutions wishing to establish a new PICU or to modify an existing PICU. As a resource, experience of those members who have worked extensively in western PICUs was also taken into consideration, in addition to published guidelines in the medical literature. PICUs with teaching programs run by the IAP Intensive Care Chapter must follow these criteria for unit accreditation and teaching curricula as applicable. **Recommendations**: Unit design, equipment, organization, staffing as well as admission and discharge criteria for different levels of pediatric intensive care are updated.

Keywords: *Accreditation, Criteria, Critical care, Design, Level of care.*

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Consensus Guidelines for pediatric intensive care units (PICUs) were published in *Indian Pediatrics* in 2002 [1]. The current document represents a recent update in the Indian context, regarding unit design, equipment, organization, staffing as well as admission and discharge criteria for different levels of pediatric intensive care. The Pediatric Intensive Care College Council (PICC), the academic wing of the Indian Academy of Pediatrics (IAP) Intensive Care Chapter, undertook the task of updating the guidelines. These guidelines can serve as a reference for health care institutions wishing to establish a new PICU or to modify an existing PICU.

PROCESS

The PICC, an academic wing of IAP Intensive Care Chapter took the initiative to update the earlier PICU guidelines 2002 [1] by formation of PICU guidelines committee with leadership and members of accreditation committee of PICC, IAP Intensive Care Chapter on 30 June, 2019 at Rainbow Children's Hospital, Hyderabad. A writing group (PICU guidelines advisory committee was also constituted. Advisory committee constituted senior members who have been closely involved with the development of Pediatric Intensive Care Units at both Governmental and Non-Governmental hospitals in India since the inception of the IAP Intensive Care Chapter. During this discussion due consideration was given to adequately develop and adapt the guidelines to be applicable in the Indian context [2]. As a resource, experience of those members who have worked extensively in Western PICUs was also taken into consideration, in addition to incorporating information from published guidelines in the medical literature [2-8]. After a great deal of discussion and through mailings and feedback with listed members, the consensus was achieved on 24th July, 2019. The consensus achieved was then taken up by guidelines writing group, which prepared these guidelines.

RECOMMENDATIONS

Unit Design

The PICU should be dedicated for infants and children, separate from the neonatal and adult ICU [3]. The Unit should be preferably located near the lift, with easy access to the emergency department, operation theatre, laboratory and radiology departments.

The doctors' duty room as well as consultant intensivist's office and counselling room should be close to the PICU, with intercom facility. Other facilities nearby should include a staff area with locker cabinets, a family waiting area to provide for at least one (preferably two) person per admitted patient with bathroom, shower and telephone facility, as feasible.

Size of PICU

Six to twelve beds is desirable. PICUs with less than 4 beds risk inefficiency and PICUs with greater than 16 beds may be difficult to manage, if not properly divided [3]. For the total Pediatric ward beds up to 25, a PICU of six to eight beds is ideal (4:1). Additional beds and separate units may be required if specialized surgery such as heart surgery, multi organ transplant surgery, neurosurgery and trauma surgery cases are routinely expected. In addition an oncology and bone marrow transplant unit may also be required at tertiary care centers to account for total numbers of ICU beds.

Room Layout and Bed Area

Ideally layout should allow actual visualization of all patients from central station; however, a central monitoring station is essential even if direct visualization of the patient from central station is not feasible in order to have a wholesome and close monitoring

Patient area in open PICU should be 100-150 sqft. In a cubicle, the minimum area should be 125 to 200 sqft. with at least one wash basin facility for two beds. Ideally, one for each bed is preferred. At least one, preferably two rooms should have an isolation capability with an area of 250 square feet with an ante room (separate area at least 20 square feet for hand washing and wearing mask and gown) and to provide true airborne isolation capability with negative pressure ventilation.

The area around the bed should allow enough space for performing routine ICU procedures such as central lines, chest tube placement, as well as for easy access for portable *X*-ray machine, portable ultrasound, electro-cardiograph and portable electroencephalograph machine. An easy access to head end of the patient for emergency airway management is a must on all beds. Removable head board should be available in PICU beds for easy access to airway intervention. Wall and ceilings should be constructed of materials with high sound absorption capabilities. Walls, ceilings and the floor should be smooth, non-porous and easy to clean. All edges must be coved to minimize accumulation of dust. Wall oxygen outlets (two), air outlet (two), two suction outlets, and at least ten electrical outlets per bed are recommended for various equipment [3,4]. In rooms, windows are preferable to prevent a sense of isolation. Adequate lighting, child friendly wall papering or paintings with soothing colors on walls/ceiling and soothing color on curtains are desirable.

Power Supply and Temperature Control

Unit should preferably be centrally air conditioned and should have central heating for temperature control. Air conditioning should be designed so that air flow is always from a clean to dirty area. In case of lack of central heating system, overhead warmers should be available. Unit should have an uninterrupted power supply by means of backup power sources such as invertors and generators in accordance with load requirement of various equipment.

Beds

Beds should have ability to manoeuvre head end and foot end as well as availability of two or more air/water mattresses to prevent bed sores. All beds must have a railing to prevent accidental fall of the child. Each bed should have an emergency alarm button for the nurse or intensivist to activate code system [4] for emergencies. An intercom at each bed is desirable. A cart with closet drawer at the bedside is important to hold personal belongings and required patient items.

Crash Cart and Work Area

A crash cart with all standard emergency drugs and portable monitor/defibrillator should be readily accessible. Zones should be provided for medication preparation and cabinets should be available for the storage of medications and supplies.

A PICU receptionist area is ideal to control visitation so that all visitors must go *via* this area before entering then ICU. This area should be monitored by security personnel.

Central Station [5]

A central station should provide visibility to all patient areas [5]. It should have ample area to have capacity for all necessary staff functions. Patient records should be easily available. Adequate space for computers, printers and central monitor is essential. Ample space for staff to write on patient files, and space for unit secretarial staff is

Table I PICU Levels of Care: Design, Equipment, and Support Services

Design	*Level 3*	*Level 2*
Rooms	Conference/duty room mandatory. Clean and dirty utility rooms mandatory. Library desirable.Toilet for patients mandatory	Conference/duty room mandatory. Toilet for patients mandatory
Spacing	Ward type beds: min. 100 sq.ft/ bed (150 sq. ft desirable; cubicle: min. 125 sq. ft/ bed (200 sq. ft desirable)	Not specified
Equipment and monitoring		
Monitoring	ECG, RR, SpO_2, NIBP for all beds. Invasive BP monitoring : at least 50% of beds	ECG, RR, SpO_2, NIBP for at least 50% beds; SpO_2 for all other beds
Ventilator	Compulsory: Invasive ventilators, NIV and high flow nasal cannula (HFNC); Desirable: High frequency oscillatory ventilation (HFOV)	Compulsory: Invasive ventilator; Desirable: N on Invasive Ventilation (NIV)/HFNC
Equipment	Mandatory: Infusion pumps, Warmers, Neonatal open care systems, EEG facility, Defibrillator	Mandatory: Infusion pumps, Warmers, Defibrillator
Crash cart	Appropriately stocked crash cart mandatory	Appropriately stocked crash cart mandatory
Ancillary services		
Lab facility	In house and 24 hour for CBC, RFT, LFT, Coagulation studies, ABG and lactate. Other Investigations can be outsourced	In house and 24 hour for CBC, RFT, ABG.
Support services	24 hours access to blood bank, Pharmacy, Neurosurgery, Pediatric surgery and ENT surgical facilities	24 hours access to blood bank, pharmacy and Pediatric surgery
Quality improvement (QI)	Regular audit of key QI data including Catheter associated urinary tract infection (CAUTI), Central line associated blood stream infection (CLABSI), Ventilator associated pneumonia (VAP) rates, medication errors, readmission, and re-intubation rates; Must use a severity of illness scoring (PRISM or PIM)	Desirable: Regular audit of key QI data including CAUTI, CLABSI, VAP rate, medication error, readmission, and re-intubation

essential. At least two telephone lines should be available. A cordless telephone instrument is desirable for the nurse in-charge and for the PICU doctor on duty. If possible, a telephone line may be dedicated to incoming calls only to facilitate critical care transport requests or other urgent calls.

Imaging Film Viewing Area

A distinct area in PICU should be chosen for viewing and storage of imaging films. An illuminated viewing box should allow viewing of several images as well as for comparison.

Storage

Storage for vital supplies should be located within or closely adjoining to PICU. A refrigerator is essential for some pharmaceutical products. An area must be provided for storage of large patient care equipment items not in active use. An area must be provided for stretchers and wheel chairs.

Clean and Dirty Utility Room

Clean and dirty utility rooms must be separate. The clean utility room should be used for the storage of clean linen. Dirty utility room must contain a separate sink. Covered bins must be provided for soiled linen and waste materials. An area for emptying and cleaning bed pans and urine bottles is also necessary. The dirty utility area and toilets should have independent exhausts that cannot be switched off. Exhaust function should have visible indicators (flutter strips).

Waste Disposal

Mechanism of disposal of contaminated waste (segregation of garbage and contaminated medical waste) and adequate disposal of needles and sharp objects needs to be as per standard applicable pollution control guidelines [6].

Conference Room and Library

A room for intensivist and staff for education, discussion of difficult cases and other necessary meetings related to quality improvement is desirable. This room should have a small library facility with ready access to topical scientific literature. It should also have a computer with reliable internet access to facilitate access to various online resources, and/or to point of care management tool.

Counselling Room

A room for intensivist and parents for regular counselling sessions regarding progress of patient condition and plan of treatment is important. Audio-video recording facility to record the counselling is highly recommended, with prior disclosure and discussion with family. Counselling session clips should be preserved for minimum of 5 years.

Urgent Laboratory

A laboratory (*stat* Laboratory) with quick turnaround time (less than one hour) for urgent investigations such as arterial blood gas, electrolyte, blood sugar, urea, creatinine, prothrombin time, partial thromboplastin time, complete blood count and urine examination with Gram stain should be available. Point of care portable equipment such as i-Stat is also acceptable (if available). Twenty four hour availability of on site or in hospital arterial blood gas is essential.

Equipment

The selection of equipment should be based on: cost benefit analysis; accuracy and adaptability for pediatric population; ease of use for care givers; troubleshooting requirements; proven use on pediatric patients; maintenance requirements; availability of biomedical support in the hospital. It is important to obtain user list before buying new equipment first for after sale service and to identify problem with equipment if any. The list of recommended equipment for a tertiary level PICU is provided at the society's website (*www.PICCIndia.org*). Emergency (crash) cart should be regularly checked with documentation of date, time and person who checked and setting up of a process immediate and ongoing replacement of used item or drugs on a regular basis.

ORGANIZATION AND STAFFING

Medical Director/Intensivist Incharge [5]

The medical director/intensivist incharge should be a Pediatrician fully qualified and trained with experience in delivery of comprehensive critical care of children with the following responsibilities:

- Establishing policies and protocols with the help of a group of experts including but not limited to pediatric consultants and subspecialists, nursing director, administration, laboratory and blood bank representatives as per prevalent norms, as well as using information from existing published guidelines; for example guidelines from the CDC (Centers for Disease Control) for infection control or international surviving sepsis guidelines.
- Smooth functioning of PICU with implementation of policies and protocols including admission and discharge criteria.
- Quality assurance and continuous quality improvement (CQI) (committee membership).
- Advice hospital administration regarding equipment needs.
- Establishing teaching and training system of medical, nursing and ancillary staff.
- Maintaining PICU statistics for mortality and morbidity.
- Active membership of hospital infection control committee (HICC).
- To conduct regular quality improvement meeting including mortality and morbidity meetings to especially analyse infection control and outcome data.

Staffing Requirements

Medical staff: The medical staff should consist of round the clock coverage by post graduate level pediatrician in the PICU with good airway and pediatric basic (BLS) and advanced life support (ALS) skills and active currently valid ALS certification (PALS/IAP-ALS).

Nursing staff: A qualified experienced nursing manager is essential. Adequate nursing staff with all shifts fully covered, is an essential requirement for good quality patient care. All ventilated patients need one Pediatric ICU trained nurse by the bed side (1:1). A very unstable patient (hypotensive/hypoxemic patient despite moderate support) may require two nurses by the bed side (2:1) or more. Other unventilated/relatively stable patients (such as post-operative patients and ones admitted for overnight observation) may require only one nurse per 2-3 patients (1:2-3).

Ancillary support services

Ancillary Staff

All PICUs must be regularly staffed by physiotherapists, dieticians and respiratory technicians for enhancing patient care. In addition, technicians, radiographers, and biomedical engineers should be available on a 24 hours (in hospital) basis for emergencies/problems that require immediate attention such as power failure, central gas supply problems, malfunctioning equipment, or need for urgent *X*-ray of chest in a patient with suspected pneumothorax or CT-scan of head spine, thorax or abdomen, as the case may be. Secretarial/clerical staff is essential to carry out communication as well as paper work necessary for smooth functioning of the Unit. It is

also essential to have cleaning staff that is efficient and sensitive to urgent patient care needs, in addition to regular cleaning and mopping the floor. Presence of social service personnel is desirable to help support families emotionally as well as financially in stressful circumstances.

Levels of PICU Care

Two levels of PICU care are identified, level 3 and level 2. Level 3 (tertiary) PICU can be organized with a level 2 (step down/high dependency) service in nearby but separate area. In small private setups, level 3 and level 2 care can be provided in one unit if facilities and equipment as well as personnel as described below are available. These criteria for level 2 units are given in ***Web Table* I**.

Level 3 Care (Tertiary level PICU) Requirements

(*a*) Defined admission, discharge policies;

(*b*) Four to six ventilator beds;

(*c*) More than 200 admissions per annum;

(*d*) Pediatric intensivist heading the unit;

(*e*) One pediatrician with post graduate training and experience in critical care present in PICU at all times;

(*f*) Minimum one on one nursing on ventilated patients;

(*g*) High level of monitoring capability in all patients;

(*h*) 24 hour access to blood bank, pharmacy, pathology, operating theatre, and tertiary level imaging services;

(*i*) Educational and research activities; and

(*j*) Quality review/audit process in place.

Quaternary Facility/Specialized PICU Level of Care [7]

A quaternary PICU facility is defined as one that is commonly found in university or children's hospitals that provide regional care and serve large populations or have a large catchment area in Western countries. The center would provide comprehensive care to all complex patients, including but not limited to those with significant cardiovascular disease, end-stage pulmonary disease, complex neurologic/neurosurgical issues, transplantation services (both bone marrow transplant and solid organ), ECMO (extra corporeal membrane oxygenation), multisystem trauma, and burns greater than 10% total body surface area. A specialized PICU provides diagnosis-specific care for select patient populations. Examples of this might include a cardiac ICU or a burn unit that provide pediatric critical care. These ICUs have specialized equipment and supplies as well as medical, nursing, and other members of the patient care team with specific skills dedicated to a certain discipline. Such units are few in number but slowly coming up in various parts of our country. Currently our guidelines do not distinguish quaternary level from tertiary care level 3 units.

Box I Admission Criteria to level 3 Care PICU

All patients requiring mechanical ventilation

Patients with impending respiratory failure

- Upper airway obstruction
- Lower airway obstruction
- Alveolar disease
- Unstable airway

All pediatric patients after successful resuscitation

Comatose patients

- Meningitis, encephalitis
- Hepatic encephalopathy
- Cerebral malaria
- Head injury
- Poisonings
- Status epilepticus

All types of shock/hemodynamic instability

- Septic shock
- Hypovolemic shock
- Bleeding emergencies such as gastrointestinal (GI) bleeding, bleeding diathesis, Disseminated Intravascular Coagulation (DIC)
- Cardiogenic shock - myocarditis, cardiomyopathy, congenital heart disease
- Neurogenic shock
- Multiple trauma

Cardiac arrhythmias

- Hypertensive emergencies
- Severe acid base disorders
- Severe electrolyte abnormalities

Acute renal failure

- Patients requiring acute hemodialysis
- Hemofiltration-peritoneal dialysis

Post-operative patients

- Requiring ventilation
- Unstable patients
- Post-operative patients after open heart surgery, neurosurgery, thoracic surgery and other patients after major general surgery with potential for respiratory/ hemodynamic instability (may go to dedicated unit if available)

Patients requiring ECMO (Extra corporeal membrane oxygenation), Nitric Oxide therapy

Malignant hyperpyrexia

Acute hepatic failure

All post-transplant patients (if applicable)

Admission and Discharge Criteria [8]

The suggested admission criteria to level 3 care PICU are

Box II Admission Criteria to Level 2 Care (Step Down Unit /High Dependency Unit)

All ward patients requiring close monitoring due to potentially unstable conditions;
Croup (laryngotracheobronchitis) requiring oxygen;
Asthma requiring hourly nebulization/getting tired with increasing oxygen requirement/mental status change;
All patients requiring more than 50% oxygen to maintain saturations;
Closed head injury/skull fracture admitted for observation;
Diabetes ketoacidosis with pH <7.2;
Patients with episodes of apnea;
Patients with significant abdominal trauma with suspected renal/splenic/hepatic injury;
Severe dehydration with mental status change;
Post-operative patients after major surgery with significant post-operative pain/blood loss/stress;
Patients recovering from critical illness (level 3 Care), but requiring close monitoring

shown in ***Box* I** and in ***Box* II** for Level 2 care (Step down unit /High-dependency unit).

List of Recommended Drugs to be Available

***Web Annexure* I** shows a list of drugs that should be available in the PICU. The list may vary depending on the availability; however, essential emergency drugs must be available round the clock. Crash cart medications should be replaced immediately and crash cart should be maintained on a regular basis with respect to equipment, oxygen cylinder, laryngoscope, lights, battery, defibrillator and other essential material.

CONCLUSIONS

All recommendations concerning pediatric intensive care units in India, including unit design, equipment, organization, staffing as well as admission and discharge criteria for different levels of pediatric intensive care are revised and updated as of year 2020.

Disclaimer: These recommendations are to be considered as guidelines in the strict sense and by no means an established standard of care for all PICUs in India.

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Annexure I

PICU Guidelines Advisory Committee Members

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Web Table I PICU Levels of Care

	Level 3	*Level 2*
General		
Type of unit	Independent (not part of adult ICU or NICU)	Independent (not part of adult ICU or NICU)
Unit head	Qualified Pediatric Intensivist who has at least 1 Year experience in the field of Pediatric Critical Care post qualification OR an Accredited 'Teacher'	Qualified Pediatric Intensivist /Accredited Teacher/ Pediatrician with at least 5 yearsexperience in caring for critically ill children
Unit staff	Qualified Allopathic doctors: Pediatricians/Pediatric critical Care trainees / Pediatric postgraduate students/ Anaesthetist with Pediatric Critical Care training	Qualified Pediatricians (MD/DCH, DNB, any Other PG qualification recognized by MCI) / Anaesthetist
Type of hospital	Part of Multispecialty Hospital of > 150 beds OR Standalone Pediatric Hospital > 50 beds	Part of Multispecialty Hospital of >100 beds ORStandalone Pediatric Hospital > 50 beds
Facilities	Portable X-Ray, Neuroimaging (CT), ECG, Echocardiography, Ultrasound, RRT (PD, HD mandatory, CVVH optional)	Portable X-Ray and ECG mandatory; Access to CT and Blood bank
PICU beds Admissions* Invasive ventilations*	Minimum 8 Minimum 200 Minimum 50	Minimum 6 Minimum 150 Minimum 25
Nursing		
Staffed by	1 dedicated nursing manager/supervisor[#]	Nurses dedicated to PICU desirable; nursing incharge to be ALS trained
Nursing ratio	Desirable to have 1:1 for ventilated children and 2:1 for non-ventilated children.	Desirable for Nurses to be IAP-BLS or ALS certified Nursing Ratio: Not specified
Other staffing	Mandatory: Access to Physiotherapist. Desirable: Access to dietician, clinical pharmacist and biomedical engineer	Desirable: Access to physiotherapist and Biomedical engineer

*[#]who has PICU experience to take care of administrative issues; *per year; ICU: intensive care unit; CT: computed tomography; RRT: Renal replacement therapy; PD: Peritoneal dialysis; HD: Hemodialysis; CVVH: continuous veno-venous hemofilteration; NICU: neonatal ICU; BLS: Basic life support; ALS: Advanced life support.*

Web Annexure I Drugs recommended to be stored in PICU

Acyclovir	Dopamine	Normal saline	Acyclovir	Dopamine	Normal saline
Adenosine	Droperidol	Pancuronium	Cefotaxime	Ketorolac	Sodium nitroprusside
Adrenaline	Fentanyl	Penicillin	Ceftazidine	Labetalol	Streptokinase
Albumin 5%, 10%, 20%	Fluconazole	Pethidine	Ceftriaxone	Magnesium sulphate	Succinyl choline
Amiodarone	Flumazenil	Phenergan	Chlorpheniramine	Magnesium trisilicate	Sucralfate
Amphotericin	Phenobarbitone	Phenytoin	Ciprofloxacin	Milrinone	Thiopentone
Ampicillin	Hemaccel	Potassium chloride	Cloxacillin	Mannitol	Teicoplanin
Atracurium	Heparin	Propofol	Desmopressin	Metronidazole	THAM (Tris
Atropine	Hydralazine	Propranolol			hydroxy amino
Amoxicillin clavulanate	Hydrocortisone	Ranitidine			methane)
Calcium chloride	Insulin	Ringers lactate	Dexamethasone	Midazolam	Trinitroglycerine
Calcium gluconate	Isolyte p	Rocuroniun	Dextran	Morphine	Vancomycin
Captopril	Kayexelate	Saline 3%	Dextrose (5, 0, 50%)	Naloxone Vasopressin	Cefoperazone-
Sulbactam	Ketamine	Sodium bicarbonate	Dextrose saline	Neostigmine	Vecuronium
Diazepam	Nifedipine	Vitamin K	Dobutamine	Noradrenaline	Xylocaine

Expert Opinion on Restoration of Pediatric Pulmonology Services During the SARS-CoV-2 Pandemic

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has had an unprecedented impact on public health and healthcare services delivery worldwide. There are many challenges in resuming non-coronavirus disease (COVID-19) services like pediatric pulmonology services. These include, among others, difficulties in restoration of resources diverted for COVID-19 care, risk of overwhelming of the services due to backlog, and apprehension among the health care workers of acquiring the disease.

In the absence of evidence-based guidelines on restarting pediatric pulmonology services in a pandemic situation, this consensus statement has been designed to provide guidance to healthcare professionals and/or institutions for restoration of pediatric pulmonology services during the SARS-CoV-2 pandemic and post-pandemic phase.

PROCESS

A group of specialists with expertise and experience in pediatric pulmonology, across India was identified and a catalogue of services/procedures to be restarted was listed. The list included clinical care of children with respiratory problems in various settings, therapeutic procedures, and diagnostic procedures (***Table* I**). The group was subdivided to prepare a position statement on various services and procedures based on available literature. This was collated together by the coordinator for review by another set of experts. The internal peer review was shared with the contributors for preparing the revised version which was again subjected to the internal peer review followed by a circulation to the whole group to arrive at the final recommendations.

The target audience for this consensus statement includes healthcare professionals who have been dealing with pediatric respiratory services prior to the COVID-19 pandemic. This consensus statement is not intended to be used for the care of children with confirmed COVID-19, even if asymptomatic.

RECOMMENDATIONS

The position statement suggests following general measures to prevent the transmission of SARS-CoV-2 [1,2].

Reduce hospital visits: The hospital visits should be prioritized for those with unresolved diagnostic or therapeutic issues of urgent or semi-urgent nature. The triaging of needs can be done by using tele-health consultations for all cases (follow-up as well as new) [3]. Routine visits for follow-up in stable patients should be deferred and staggered or preferably replaced by a tele-health consultation. The visits for collection of medicines should be staggered too by making administrative arrangement so that the caregiver can directly collect the

Table I List of Services Along with Risk of Infection, Timing of Resumption, and Required Personal Protection

Service/ procedure	*Risk**	*Timing of resumption#*	*PPE level^*
Clinical care			
Evaluation in out-patient setting	1	I	Standard
In-patient care	2	I	Standard
Emergency care	3	I	Full
Care of children with stable chronic respiratory diseases	1	I	Standard
Therapeutic procedures			
Use of nebulizer (any type)	3	I	Full
Use of metered dose inhaler with spacer	1	I	Standard
Use of heated humidified high flow nasal cannula	3	I	Full
Use of ventilator	3	I	Full
Airway clearance techniques	3	I	Full
Diagnostic Procedures			
Gastric aspirate and induced sputum	3	II	Full
Throat/nasal swab, nasopharyngeal aspirate	3	III‡	Full
Pulmonary function test	2	II	Standard
Flexible bronchoscopy	3	II	Full
Nasal NO/FeNO	2	II	Standard
High speed video microscopy and electron microscopy	3	II	Full
Sweat testing and aquagenic wrinkling	1	I	Standard
Imaging procedures	1	I	Standard
Exercise testing	2	III	Standard
Infant PFT	2	III	Standard
Tuberculin skin test and skin prick test	1	TST: I, SPT: III	Standard

**1-Services with no additional risk of transmission of infection, 2-services with mild to moderate risk and 3-services with high risk of transmission; #As per pandemic phase unless urgent/life-saving/needed for important clinical decision making: I-ongoing pandemic, II-post-peak (flattening of curve/ slowing down), III post-pandemic (controlled phase); ^PPE personal protective equipment (PPE) levels; Standard PPE-N95 mask, gown, face-shield, gloves; Full PPE- N95 mask, full cover water proof gown, face-shield, cap/head cover, shoe cover, double gloves. ‡unless for suspected COVID.*

drugs from the pharmacy without needing to visit the doctor. For those identified to need a direct contact during a tele-consultation, should be given appointment, and preparatory advice about safety and precautions to be followed during the visit. The outcome of the visits can be maximised by advising the basic investigations to be done locally before visit and planning the specialized tests or procedures anticipated on the day of visit as far as feasible.

Reduce chances of cross-infection during visit: Reduce crowding and time spent in health care facility by pre-visit tele consultation, staggered appointments, and by restricting the number of accompanying attendant(s) with children. Screening all cases for active influenza like illness (ILI) on the day of visit at hospital entry, and segregating those with active symptoms to separate designated areas for COVID suspects is important. Advise patients and attendants to wear mask correctly, maintain social distancing, follow the cough/sneezing etiquette, and hand sanitization. Frequent sanitization/ disinfection of patient care area; and use of appropriate personal protective equipment (PPE) by health care workers should be ensured.

In the outpatient area**,** restrict the consult to one patient entering at a time and perform hand hygiene and sanitation of equipment (stethoscope, pen, etc.) before, after and between consultations.

Precautions while admitting children with respiratory problems: Prioritize in-patient care of children for those with a definitive need *e.g.* prophylactic IVIG may be prioritized as there is no alternative therapy while the admissions for pulse steroids could be restricted by using oral steroids instead till the pandemic shows flattening of curve. Similarly, less severe exacerbation of suppurative lung diseases may be advised oral antibiotics at home or injectables at nearby health facility.

In the inpatient area, adequate spacing should be maintained between beds. In the absence of negative pressure rooms, exhaust fans could be used in rooms along with air-conditioning and if required, windows/ doors can be left open for better air exchange. Single use/ disposable/ dedicated equipment should be used and when this is not feasible, thorough cleaning and disinfection of equipment should be ensured before using on any other child. Reduce time of physical rounds by discussing details beforehand. Try to reduce hospital stay of patients to the minimum.

Pre-testing for COVID: In case the facilities and capacities exist, particularly in non-urgent situations, testing for SARS-CoV-2 using RT-PCR or CBNAAT can be done before hospitalization and before all aerosol generating procedures like gastric aspirate, induced sputum, and flexible bronchoscopy. While in case of an emergency situation, management should take precedence with all standard infection control measures as for COVID-19 suspected cases.

Safety of the health care workers: Before starting a service or test, ensure the availability of staff, space, and PPEs. All efforts should be made to segregate and stagger the services in these areas to avoid overcrowding. ***Table* I** summarizes risk of infection with different services/procedures, when these can be resumed, and required level of PPE. Healthcare workers should inform hospital authorities in case they develop ILI symptoms for appropriate action and avoid going to patient care facilities.

Care of Chronic Respiratory Diseases

Asthma [4]: All patients should continue inhaled steroids as before. A short course of prednisolone may be advised early for asthma exacerbation to prevent hospital visit. Avoid nebulization as far as possible, using metered dose inhaler (MDI) with spacer instead. Treatment for allergic rhinitis may be continued as before.

Tuberculosis (TB) [5,6]: Continue anti-tubercular treatment as before. Modify regimen for multi-drug resistant tuberculosis to all oral drugs to reduce hospital visit. If a child with tuberculosis develops COVID-19, continue TB treatment.

Cystic fibrosis [7,8]: Continue usual care as before. Minimize the use of nebulizer. Recognize and treat CF exacerbations promptly and aggressively with oral or, if required, parenteral therapy at home. Hospitalize only for severe exacerbations.

Interstitial lung disease (ILD): Continue treatment for follow-up cases of ILD. For new cases, start immunosuppressive therapy only if absolutely necessary. Repeat blood test and imaging only if it is required to adjust the therapy.

Suppurative lung diseases: Continue usual treatment as before. Treat the exacerbation early and aggressively, preferably at home.

Diagnostic and Therapeutic Procedures

Diagnostic Procedures

Pulmonary function tests (PFTs) [9]: PFTs should be performed only in situations where the available information is not adequate to make certain diagnostic or therapeutic decisions and PFT can resolve these. These should be timed with other essential visits of the patient. Use disposables as much as possible and use viral filter for PFTs. Disinfect the equipment as per advice of manufacturer.

Chest imaging: There is a need to optimize imaging procedures after a detailed discussion, and routine imaging should be avoided. Prior discussion with radiologist can help to keep the procedure focused, essential, and finish in minimum possible time. A digital copy of the imaging procedure can decrease the need for visits to collect and show the reports.

Gastric aspirate and induced sputum: Restricting the testing to those with clinical or radiological chest findings will optimize the yield as well as lessen the risk by avoiding unnecessary cases. Where possible, gastric aspirate may be preferred over induced sputum. During induced sputum procedure, premedication with salbutamol may be done with MDI and spacer, and thus restricting nebulization only for hypertonic saline medication.

Flexible bronchoscopy [10,11]: It should be performed only when alternate diagnostic modalities have failed to reach a diagnosis and when bronchoscopy findings will offer an immediate management. There should be minimum staff in bronchoscopy suite and child should be well sedated during procedure to avoid excessive crying or coughing.

Tuberculin skin test (TST) and skin prick test (SPT): TST can be administered by staff taking all precautions (including PPE) and should be combined with essential visits to decrease the visits to the hospital. SPT has limited role in management of asthma and may be deferred till control of pandemic.

High speed video microscopy (HSVM) and electron microscopy (EM): These tests can be considered with flattening of curve as there is no definite treatment for primary ciliary dyskinesia and supportive therapy may be started based on clinical diagnosis. If test is done during

ongoing pandemic, consider pre-procedure SARS-CoV-2 testing of the patient.

Sweat test and aquagenic wrinkling skin test: These tests should be resumed as delay in diagnosis of cystic fibrosis may increase morbidity. These are not aerosol-generating procedures, though crying of child during procedure may be a potential risk factor for disease transmission.

Therapeutic Procedures

Inhalation therapy: There must be a balance between risk of transmission of disease and the negative effect of not delivering inhalation therapy. Nebulization should be used only, if there is no alternative or in case of life-threatening asthma. Use breath actuated nebulizers, mouth piece interface instead of face mask, and filters or one way valves whenever feasible. In pediatric intensive care unit (PICU), use mesh nebulizers (if available) and filters in expiratory limb of ventilator. Wherever possible, use MDI with spacers.

Airway clearance technique (ACT) services: ACT services should be resumed to prevent progression of chronic suppurative lung diseases. Patients already on ACTs can share videos with healthcare providers for assessment and corrective actions [12]. ACTs to newly diagnosed patients should be taught with all general measures with the help of videos of ACTs. At home, ACTs should be performed in separate well-ventilated room and nebulizer and ACT devices should be cleaned/ disinfected thoroughly after each session of ACT. ACTs in acute care setting should be those not requiring disconnection from ventilator and it should be followed by closed suction [13].

Emergency Care

Some milder emergency visits may be obviated by using tele-consultation. Divide pediatric emergency department (ED) into clinical triage zone (for quick assessment for sickness level, ILI, and SARI), quarantine zone (to keep suspected COVID-19 till report available) [14]. Ensure rapid turn-over of COVID testing to segregate and channelize cases rapidly from ED (positive cases to COVID wards or home isolation for mild cases, and negative ones to wards/PICU).

Use minimal possible flow for high flow nasal canula (HFNC) and preferably use mask over canula. For non-invasive ventilation, use NIV with non-vented masks and use a viral filter in expiratory limb of the circuit. If using a vented mask, may try to apply a 3-ply surgical mask in front of NIV mask. If intubation is required, use rapid sequence technique, keep minimum number of persons, and intubation should be performed using cuffed tube, by the most experienced person. Personnel involved in CPR should be kept to minimum necessary.

In acute severe asthma management, use nebulization minimally, mainly for life threatening acute asthma; medications should preferably be given using MDI and spacers, where possible [15].

CONCLUSIONS

The ongoing SARS-CoV-2 pandemic is hampering non-COVID services including pediatric pulmonology. As the pandemic is unlikely to go away in near future, we need

Box I Gaps in Knowledge and Research Needs

- The literature/evidence is limited regarding viability of SARS-CoV-2 on different objects/surfaces, and risk of transmission of disease by using different type of oxygen providing devices and by various aerosol generating procedures. It is also unclear how much transmission risk exists when infants cry.
- There is a need for a study to assess the risk of transmission among HCWs in different clinical areas like OPD, in-patient, ED, and pediatric intensive care units, different ACTs, during various PFTs in children, during flexible bronchoscopy, and for a particular radiological procedure.
- Long term impact of COVID-19 on lung health in normal children and children with chronic respiratory diseases need to be evaluated.
- Drug interactions of drugs for TB and COVID-19 need to assessed. Effect of COVID in children with TB is not clearly known.
- Remote testing including mobile based 6-minute walk test with oximetry monitoring, one-minute sit to stand test and 40 steps test and assessing physiological parameters and attempting pulmonary rehabilitation using telemedicine may be explored for exercise testing.
- There is lack of study documenting presence or absence of SARS-CoV-2 in sweat in adults or children and risk of transmission by sweat.
- There is lack of studies regarding remote reading of TST.

to resume non-COVID services. It is a consensus statement to guide health care professionals to restart the pediatric pulmonology services. We recommend general measures to reduce hospital visits, to reduce cross infections etc. There is need to adapt specific measures for various clinical, diagnostic and therapeutic services. Safety of health care workers is of paramount importance. There are still may gaps in knowledge regarding COVID-19 and need further research.

Disclaimer: The group recognizes the fact that the understanding of COVID-19 is evolving as it is a new disease and the pandemic is a dynamic process. This consensus statement, therefore, may become outdated, changed or redundant over time as more evidence is generated. Hence, it is recommended to that the guidance are followed in line with the directives and other statutory guidelines adopted by local authorities and the medical societies. It is an executive summary of the position statement. The full position statement is available at *http://pedspulmcar.aiims.edu/Login/Login.aspx*

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Developing Humanistic Competencies Within the Competency-Based Curriculum

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We herein, describe the rationale, content, methodology and evaluation of a health humanities module in the new competency-based curriculum, and share our experience of the same. Providing training in health humanities to the healthcare trainees will definitely go a long way in having a professional and responsive Indian medical graduate, who is able to provide empathetic and holistic healthcare to all sections of the society.

Keywords: *Cultural diversity, Disability studies, Medicine in the Arts, Narrative medicine, Patient advocacy, Professionalism.*

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The humanities being incorporated in medical education is a relatively newer concept in our country. There are various reasons that prompted the authorities to consider using the humanities in medical teaching: student burnout, mental health issues, and suicides; faculty and provider burnout; student anecdotes about faculty teaching by humiliation; provider-patient encounters resulting in miscommunication; missing empathy and poor communication skills; violence perpetrated by patients' relatives; and public displays by providers showing unprofessionalism and unethical behavior [1-4]. Clearly, conventional medical education methods were lacking a critical humanitarian element [5]. These observations confirm the intuitive rationale for the inclusion of the humanities in health professions education (HPE) – "*to educate for sensitivity so that we do not produce [providers] who place cases and smart diagnoses before persons and feelings*" [6].

THE EVOLUTION OF MEDICAL HUMANITIES

The Flexner report revolutionized medical education in the US in 1910, but 15 years later, Abraham Flexner was appalled that students had no grounding in the humanities before they arrived for medical training [6]. Historian George Sarton coined the term 'medical humanities' in the US in 1947. The first department of humanities was established in 1967 at Pennsylvania State University's College of Medicine, and the first Institute for the Medical Humanities at the University of Texas Medical branch in Galveston a few years later [6]. The UK joined the movement by organising the first UK medical humanities conference in 1998 [6].

In India, University College of Medical Sciences was the first medical college to document introduction of humanities to medical students, faculty and non-teaching staff through the creation of a Medical Humanities Group (now called Health Humanities Group) in the year 2009. Other Indian institutions that followed this lead in the initial years were Jorhat Medical College, Assam; Seth GS Medical College, Mumbai; and St John's Research Institute, Bangalore. The medical humanities movement also received exposure because of journals that dedicated themselves to the cause. It started with the *Journal of Medical Humanities* in the US in 1979. *Research and Humanities in Medical Education (RHiME)*, an open access peer-reviewed online-only journal, the only medical humanities journal in Asia, was started in 2014. Interestingly, the journal also encourages submissions in Indian vernacular languages, particularly Hindi.

Medical Humanities or Health Humanities

This topic has generated a great deal of debate. While it all began as the medical humanities, some feel that adding the 'medical' to the humanities creates an unfortunate and restrictive association that compels one to examine the humanities from the perspective of medicine and not in their own right [5]. Others find that the term seems to preclude 'health', which has a broader reach than that of medicine. In their view, in a kind of tubular vision, this term focuses on the patient-provider relationship, while 'health' as a construct includes the socio-cultural aspects and historical biases of the cultures [7]. Additionally, the term 'medical' seems to exclude other providers of healthcare, like nurses, pharmacists, and technicians, and

the receivers of healthcare, like the patients and their caregivers. This differentiation between the two, and the debate around whether they are completely diverse or if one (health humanities) should replace the other (medical humanities), is a continuing debate [7]. When we began our experimentations with the humanities, we envisaged our medical humanities practice as being inclusive of cultural diversity, of disability, of social justice, and of everything – medical or artistic or humanities-based – that could benefit the provider-patient-caregiver circle in the long run [4]. For that reason, we find the distinction to be a matter of semantics and we embrace the term Health Humanities in deference to all "healthcare providers, patients and family caregivers" [8]. The special interest group under the aegis of Academy of Health Professions Educators is also named Health Humanities [9].

HUMANISTIC COMPETENCIES

"Medicine is the most humane of sciences, the most empiric of arts, and the most scientific of humanities" - Edmund Pellegrino

Around a decade back, we developed experiential workshops that employed different tools from the humanities. The workshops, designed to engage faculty and students from other medical institutions in the humanities, led us to develop an integrated, inter-disciplinary humanities approach to the development of appropriate analytical Attitude, ethical and professional Behaviour, effective Communication, respect for Diversity, and Empathy (the ABCDE paradigm) [4,10-12].

We, herein, broaden the theoretical framework of Peterkin [13] and apply it to the ABCDE attributes [4] - these, then, directly translate into five competencies that we believe all health professions learners should seek to acquire. These five 'humanistic competencies' are narrative competence, critical reflexivity, visual literacy, advocacy, and structural humility. In India, of all health professions educators (HPE) regulatory bodies, only the Medical Council of India (MCI) has updated the medical curriculum and has aligned it to a competency-based system [14]; therefore, we use that to exemplify how the five humanistic competencies are complementary to the five roles of an Indian Medical Graduate (IMG) as prescribed by the MCI (***Table* I**). At the time of writing, the Nursing Council of India (NCI) has also uploaded a draft document [15], and we also refer to the draft competencies from that document. This may serve the purpose for other health professions' educators who wish to include humanistic competencies in their own curricula.

Narrative Competence

The first expected role of an IMG is to be a clinician who compassionately promotes health, and prevents, cures, and manages illness in a holistic way [14]. Clinicians must consider the patient as a whole; likewise, they must engage with their patients with more than just their intellects, involving also their hearts and their emotions in the interactions. Such engagement can happen only when clinicians are able to absorb, interpret and respond to the patient-provider stories unfolding in front of them. The

Table I Suggested Tools to Develop Humanistic Competencies

*Roles of IMG**	*Nursing competencies*[#]	*ABCDE paradigm*	*Humanistic competency*	*Suggested tools*
Clinician	Patient-centered care; Evidence-based practice; Safety	Analytical attitude	Narrative competence	Stories, Narrative medicine (illness narratives, life writings, metaphors, close reading, connotation, denotation), Medical history, Poetry, Literature, Theology, Philosophy
Professional	Professionalism	Professional behavior	Critical reflexivity	Bioethics, Theatre of the Oppressed, Reflections, Critical thinking, Professional identity formation
Communicator	Communication	Effective communication	Visual literacy	Visual arts, Reading films, Graphic medicine (Comics), Image theatre, Performance (Street theatre), Creative writing
Leader	Leadership; System-based practice; Teamwork and collaboration	Respect for diversity	Advocacy	Mentoring, Postmodernism, Social Justice studies (disability studies, feminism, gender studies, age studies, *dalit* rights)
Lifelong learner	Health informatics and technology; Quality improvement	Empathy	Structural humility	Forum theatre, Patients as educators, Identity, Wellness, Music, Dance, Digital humanities

*IMG-Indian Medical Graduate; *As per Medical Council of India [14]; [#]As per Indian Nursing Council [15]; ABCDE: Attitude, behavior, communication, diversity and empathy* [4].

analytical attitude required to witness the patient's story has been termed as narrative competence, which enables a clinician to practice medicine with empathy, reflection, professionalism, and trustworthiness [16].

Critical Reflexivity

The MCI expects an IMG to be a professional, one who demonstrates a commitment to the profession, who ethically responds to patient needs, and is accountable to them and to the community [14]. The patient-physician relationship in India is still largely paternalistic. This attitude, unfortunately on display in the 'hidden' curriculum, impacts future learners.

Critical reflexivity refers to the understanding of one's own limitations and of the social realities (beliefs, values, social structures) of others [17]. Through it one can examine the assumptions underlying clinical practice and understand how such dimensions influence professional behavior. This competency is inherently creative and we have extensively used Augusto Boal's theatre of the oppressed (TO) to encourage learners to reflect and to understand professionalism [4,10-11].

Visual Literacy

The next role of an IMG is that of a communicator who has to connect with peers, with patients, their families, and the community [14]. Effective communication involves all of our senses. Visual literacy is the ability to see, to understand and, ultimately, to communicate visually. Visual communication is a process of noticing, not merely the sickness, but the whole person who is often neglected and even hidden from the provider. A visually literate IMG will be able to *'* see' the anguished looks and the frowns, the tears and the smiles beyond just the disease.

Advocacy

The MCI expects an IMG to be a 'Leader' of the healthcare team and a member of the healthcare system [14]. This involves self-awareness of social accountability which is the capacity to respond to society's health disparities and to address such needs through interprofessional collaboration [18]. This necessitates advocacy which is the process of people participating in decision-making processes affecting their own lives, and society in general. An important component of this is giving voice to the most vulnerable. Health humanities is, in essence, a form of advocacy - a means of addressing problems of under-representation as in feminism, disability justice, and transgender rights.

Educators have highlighted how the new CBME curriculum lacks emphasis on respect for diversity [19]. By recognizing the lived experiences of doctors with disabilities and in response to the global disability rights movement's motto of *'Nothing about us, without us,'* we framed disability competencies for health professions education [12]. Going a step further, we were also able to bring about policy change and curricular reform through advocating for its inclusion into the new curriculum [12].

Structural Humility

The coronavirus pandemic has highlighted an important role of an IMG – that of a 'lifelong learner' who is obligated to improve skills and knowledge over time [14]. The pandemic has taught us to face the fear of managing uncertainties, and to recognize the complexity of the structural constraints that patients and doctors operate under. Structural oppressions within the community and the healthcare system tend to preserve rather than mitigate social inequities and health disparities.

Cultural competency is a term used to signify the identification of our own biases in order to improve patient-provider relationships. It came into existence when it was recognized that physician beliefs were also culturally determined; however, it soon transformed into a list of traits/stereotypes about various cultural groups that learners would memorize, and it led to stereotypical reactions. This generated a paradigm shift towards cultural humility to emphasize ongoing humility, reflection and lifelong learning [20]. However, as the corona virus disease 19 (COVID-19) pandemic has shown, there are additional structures which constantly affect health outcomes. Policies (lack of accessible material for the deaf), economic systems (migrants stuck in inhospitable habitats during the nation-wide lockdown), and social hierarchies (flagrant racism against a particular community or lifestyle) interplay with inequalities and leads to a deepening of health disparities.

An IMG should recognize such structural barriers as patients may not be able to identify them. Structural competency is perhaps a better way of looking at things as it builds upon the sociocultural conditions that produce inequalities in health in the first place [20]. Acknowledging our biases and looking at the underlying structural oppression that contributes to it is perhaps structural humility. Structural humility is looking beyond one's own experience (as well as admitting ignorance) and approaching the experiences of others without judgment and without our own biases. It is a lifelong commitment to the development of self-critique, reflection, and a capacity for empathy at both intrapersonal and interpersonal levels [21].

In our experience, empathy decline replaces the initial enthusiasm and humanity that students present with at the beginning of the medical course. When confronted with clinical reality, there is a decline in empathy over the clinical phase of training [22]. Empathy is the hallmark of the provider-patient communication and plays a vital role in achieving patient-centeredness. The empathy decline we are witness to is of serious concern and must be addressed.

What begins from the pre- and para-clinical departments with an emphasis on dissection and vivisection continues into the clinics with a paternalistic approach to decision-making. This leads to a bias towards curative rather than caring medicine. In a country as diverse as India with respect to culture, language and inequities, it is challenging for a medical student to imagine the experiences of a culturally different patient. This is where the cultural competency model fails as it might invoke unintentional tubular vision into cultures. We experienced this in the COVID-19 pandemic, where cultural and culinary practices were wrongly linked with the contagion. This is where identifying the structural oppression and stepping back from being an 'expert' is required. Structural humility seeks to bridge the divide between structural competence and cultural humility.

INCORPORATING HUMANITIES IN HPE

The Tools

The connection between the roles of an IMG, the desired ABCDE attributes, and the humanistic competencies is shown in ***Table* I**. It also suggests humanities tools that could help in achieving the humanistic competencies. These tools are equally applicable to virtual environments, for as humanists, we need to pay attention to 'webside' manners also.

The Facilitators

Any faculty member, resident, or groups of students with a special interest in any of these diverse tools may be encouraged to employ a humanities approach in their teaching-learning activities. An interdisciplinary approach assures that a number of teachers, with diverse skills, are available at any given time. Understandably, depending on local interest and inclinations, different institutions will focus on different tools. In addition, a trans-disciplinary approach may be employed where faculty from the humanities disciplines, and experts from outside academia may be invited to contribute to learning. An eclectic mix of people may be more meaningful in understanding the nuances of interpersonal relationships and real-life communication [23,24].

The Timetable

The gazette notification of MCI of 6 November, 2019 heralding the CBME mentions humanities as a new teaching element in the preclinical phase of medical education [14]. In addition, cultural competence and disability competencies (after our judicial advocacy) have been made part of the month-long foundation course [12]. The highlight of the CBME undoubtedly is the inclusion of the Attitude, Ethics and Communication (AETCOM) module longitudinally throughout the curriculum. In addition, two optional electives of one month each are scheduled after the end of third MBBS (Part I). Electives are ideal to implement a complete health humanities module. Its optional nature will encourage small groups and critical thinking, although with our large overall class sizes, achieving a realistic small group may not be possible. At our institution, we used the health humanities to introduce the first-year medical students to disability competencies during the foundation course in 2019.

The draft of the revised Nursing Curriculum by the Indian Nursing Council (INC) categorically states that *"Nursing as a profession and a discipline utilizes knowledge derived from arts, sciences, humanities and human experience"* [15]. Humanities may be applied directly during semester III (professionalism, professional values and ethics including bioethics), IV (nursing education), V (mental health nursing and Indian laws), and also as an elective in semester III and IV (human values; palliative care), and VII and VIII (soft skills).

Whether we incorporate humanities during the foundation course, phase I, or during electives, it is important not to compartmentalize the experience but to use it in a creative and flexible way [25]. We suggest using humanities as a tool to teach AETCOM and to utilize the self-directed learning hours towards building the five humanistic competencies described above. Informal opportunities may present themselves and should be exploited for initiatives to teach health humanities. We suggest the near-peer mentoring network, student cultural societies, lunch break, and Saturday afternoons to be used in a productive way to hone humanistic competencies [1-3,23,24]. In addition, together with students, faculty may explore how humanities may be used during early clinical exposure and self-directed learning hours. In fact, every interaction presents an opportunity, and it need not be limited to the classroom, to a field visit, or to a clinic.

Assessment

Competency based assessment (be it formative or summative) is challenging in the humanities as the latter, by design, is meant to be disruptive. In the classroom,

limiting student learning by defining specific learning objectives is deemed to be anti-educational in the context of something as versatile as the health humanities. Moreover, many humanistic competencies are not easily amenable to reliable assessment. However, if one is to assess the learning that accrues from the health humanities, then the outcome can be made quite meaningful by assessing multiple times and in different contexts.

Theatre of the oppressed, being a performance-based intervention, already lends itself well to a formative assessment in the form of observations recorded by facilitators (non-jokers) in the games and exercises which form an important component [10,11]. In that sense, it answers the call of competency-based assessment and feedback. Its more nuanced form, forum theatre, in terms of Miller pyramid, falls under the topmost 'does' category, where learners, by becoming spect-actors, allow direct observation of the skills displayed during the intervention, which can then generate authentic feedback [26].

Assessment during humanities electives may be directed towards a portfolio comprising a mix of written reflections, essays, narratives, poems, and a humanities research project. For longitudinal programs like AETCOM, Objective Structured Clinical Examination, bedside discussion, Workplace-based assessment, Stan-dardized patients and Multi-source feedback may be used.

Evaluation

For program evaluation, we suggest a mixed methods approach utilizing both quantitative (standardized surveys, in-house program evaluation instruments) and qualitative methods (semi-structured interviews, focus groups, observation notes). Qualitative methods in particular can be used to explore students' experiences and needs, and processes of the humanities program so that it can be improved and replicated in other institutions. In our study on developing disability competencies, we relied on focus group discussions to give a voice to historically neglected stakeholders (doctors with disabilities) [12]. Focus group discussions are particularly helpful in that they capture laughter and expressions of sadness which might not be gauged by quantitative studies.

Challenges Within the Competency-based Curriculum

One of the biggest challenges will be where to fit the health humanities in the curriculum. The MCI gazette mentions humanities as a new teaching element in phase-I but it does not schedule teaching hours (*Table IV*, pg 69 of gazette) which makes it unclear where it will be clubbed [14]. The elective nature of the humanities module in the curriculum may not attract the students who really need an exposure to creativity - like those who are stressed more than usual, who are isolated, are experiencing a decline in empathy, have non-conventional learning styles, or have poor communication skills. Perhaps, teachers could identify students in need and nudge them towards a humanities elective. As passionate humanists we would love to see all HPE students being exposed to humanities. However, this wish list is more of a burden considering the student batch size in HPE courses in India. The mandatory approach might work (if handled with discernment) for a session with less than 100 students, but might be counter-productive for a batch of 250-plus.

The other problem may result from an inadequate or ill-prepared faculty. As mentioned earlier, interested faculty should be recruited; however, they may still need to be oriented to the program and trained in the humanistic competencies. Though it looks like a daunting task initially, we imagine that the effort will snowball as more and more faculty get trained. This effect is already in evidence in the country with every National Conference on Health Professions Education including the humanities in one way or the other in the program schedule. Senior residents could fill the gap; however, they are not entitled to attend MCI-mandated revised basic courses. Senior resident training on education principles (STEP) or similar workshops could be conducted in other institutions [27].

Another problem we foresee is that, though there is an 8-hour module of 'Music and Healing' mentioned in the Curriculum Implementation Support Program (CISP) booklet of the CBME under the humanities section, the instructional modality outlined there as well as in the AETCOM module is largely case studies based - a "problem-solving" model. This model is largely criticized by humanists as a threat to critical thinking [25]. Having an inflexible humanities curriculum, with the same cases presented across the country in a non-contextual way, could jeopardize innovation and creati-vity, and is anathema to the very idea of humanities edu-cation. Assessment of acquisition of humanistic competencies is likely to be another challenge. As teachers, we may not necessarily be able to grade the quality of submissions made by learners in response to humanities initiatives. That they must be evaluated goes without saying in view of the paradigm that assessment drives learning. Fortunately, it is possible to make objective assessments using prepared rubrics like Narrative Reflection Assessment Rubric (NARRA) and Reflection Evaluation for Learners' Enhanced Competencies Tool (REFLECT) [28,29]. Some training in the use of these rubrics may be required.

Future Directions

The All India Institute of Medical Sciences (AIIMS), Delhi is revising its curriculum to make it competency based. Naturally, the new AIIMS like institutions will adopt the same. This opportunity should not be missed, and areas not addressed in the MCI curriculum should be incorporated in this curriculum. The Dental Council of India should also make similar efforts.

The draft nursing curriculum of INC makes only a superficial pitch to humanities. Its further insistence on soft skills gives the message that these competencies are optional. Unlike MCI, they invited stakeholder feedback early this year and we hope that they will act on them to make it a truly inclusive curriculum.

The pharmacy practice curriculum has not received much attention in India, even though experts stress that *"pharmacy is a profession that has at its core a human relationship"* [30]. Thus, the regulatory body must consider upgrading the pharmacy curriculum.

CONCLUSION

The potential for the humanities in health professions education is increasingly being recognized and accepted in the Indian context. Of the many tools available, teachers and learners may choose those that are supported by local interest groups or by expertise in their specific setting. Scheduling the sessions is dependent on local facilities and should not be restricted to traditional settings or the formal curriculum. Assessment is likely to be challenging but can find a place in the newer modalities being rolled out in the new competency-based curriculum. Evaluation of health humanities modules are desirable and educators who are spearheading such movements must share experiences, resources and expertise. The framework we suggest may be used by Councils/Institutions currently modifying their curriculum, and we encourage them to hone and develop it in innovative ways to make it as robust as possible. Flexibility is the key to the health humanities and creativity is its oxygen.

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Compliance to Prescription of Routine Vitamin D Supplementation in Infants

We assessed compliance to routine vitamin D supplementation in 330 infants (age 6 wk to 9 mo), who were prescribed supplemen-tation at birth. 137 (41.5%) had received vitamin D supplemen-tation at some point of time till enrolment. Median (IQR) compliance to routine vitamin D supplementation was 66.7% (50%, 83.3%) in those who ever received supple-mentation. Only 29 (8.8%) were receiving appropriate routine vitamin D supple-mentation in terms of dose, frequency and duration. There was low level of reinforcement (35%) from healthcare workers and low parental awareness (34%) of the need of supplementation.

Keywords: *Adherence, Guidelines, Prevention, Rickets.*

Routine daily vitamin D supplementation in infants is recommended by the Global consensus on rickets prevention, American Academy of Pediatrics and the Indian Academy of Pediatrics [1-3]. However parental adherence is key to its success, which has been shown to be sub-optional worldwide, resulting in poor outcome of the supplementation [4-8]. There is no relevant Indian data. We conducted this survey to estimate the proportion of infants adhering to prescription of routine vitamin D supplementation between birth and 9 months of age.

This cross-sectional study was conducted in the department of pediatrics of a public medical college-affiliated hospital in Delhi. An approval from the institutional ethics committee was obtained. Considering parental adherence of 68.9% [4], with alpha error of 5%, absolute precision of 5%, and confidence level of 95%, 330 mother-infant pairs were required to be enrolled. Healthy infants between 6 weeks to 9 months of age, who were prescribed vitamin D at birth, were recruited from the immuni-zation clinic, after obtaining written informed consent from the mother. We included only those infants who were born in a health facility and having documents showing prescription of vitamin D at birth. The hospital policy is to prescribe routine vitamin D supplementation at the time of discharge from the health facility at birth. Term and preterm infants are prescribed 400 IU and 800 IU vitamin D, to be given daily till 12 months of age, irrespective of mode of feeding. No specific measures for reinforcement of supplementation are in place on follow-up.

Baseline socio-demographic information was recorded. Mothers were asked whether they are still providing routine vitamin D supplementation to their infant. If not, whether they administered vitamin D to their child at any time and if yes, for how long along with the dose. Compliance was the duration for which supplementation was given as a proportion of the duration of prescription till enrolment. We also ascertained the proportion of infants who had received oral vitamin D supplementation (400 IU) in last 7 days and in previous month, to minimize recall bias.

Parental understanding of the prescription was also assessed for their knowledge regarding total duration for which they needed to give the supplement. Parents were asked whether they were explained verbally by the healthcare worker about routine vitamin D supplementation, the reason for its requirement and method to give it; and whether they received reinforcement for same in their subsequent health visits, if any. They were asked whether they received vitamin D from the health facility, or it incurred out of pocket expenditure. In case of non-compliance of the prescription, the parents were asked for the reason. After the interview, mothers were advised to follow routine supplementation of vitamin D, if they were not giving it earlier. The practices of routine vitamin D supple-mentation were compared between groups using chi square test. Compliance was compared between groups using the indepen-dent samples Mann-Whitney U test. A P value of <0.05 was considered statistically significant.

We interviewed 330 mothers between March and August, 2019. The median (IQR) age of their infants was 3.5 (2.5, 6) months, 190 (57.6%) were <6 months of age, and 180 were boys. Majority of mothers were literate (288, 87.3%) and home-makers (307, 95.5%). Most families (233, 70.6%) belonged to lower socioeconomic strata; 85 (25.8%) were from middle socioeconomic group. Most (300, 91%) infants were born at term, 117 (35.5%) were low birthweight and 36 (10.9%) had required admission in neonatal intensive care unit (NICU) at birth. The study population did not have any infant with active rickets.

Overall, 137/330 (41.5%) infants received vitamin D supplementation at some point of time till enrolment; median (IQR) duration of vitamin D supplementation in 137 infants was 60 (30, 105) days. Only 52 (15.8%) children were receiving vitamin D continuously for 7 days in the last week. Thirty-six (26.3%) of those practicing routine supplementation (n=137) did not receive vitamin D in last 7 days, and 25 (18.3%) did not receive it anytime over last one month. Median (IQR) compliance to routine vitamin D supplementation in these 137 infants was 66.7% (50%, 83.3%). Only 29 (8.8%) infants were receiving appropriate routine vitamin D supplementation in terms of dose, frequency and duration. A significantly higher proportion of preterm infants and NICU graduates received vitamin D supplementation (ever, within 7 days and within 4 weeks) as compared to term and those not requiring NICU care, respectively (***Table* I**). The compliance was also significantly higher in preterm and NICU graduates. There were no significant differences in supplementation practices or compliance according to gender or feeding status.

Table I Adherence to Routine Vitamin D Supplementation in Infants (*n*=330)

Category	*Ever received vitamin D*	*Received vitamin D in last 7 days*	*Received vitamin D in last 4 weeks*	*Compliance (%) Median (IQR)*
Gender				
Male (*n*=180)	71 (39.4)	50 (27.8)	57 (31.7)	66.7% (60.0%, 77.5%)
Female (*n*=150)	66 (44.0)	51 (34.4)	55 (36.7)	66.7% (66.7%, 81.5%)
P value	0.47	0.27	0.34	0.71
Gestation				
Preterm (*n*=30)	25 (83.3)	20 (66.7)	19 (63.3)	83.3% (66.7%, 85.7%)
Term (*n*=300)	112 (37.3)	81 (27.0)	94 (31.3)	66.7% (50%, 82.2%)
P value	<0.001	<0.001	<0.001	0.026
Admission history				
NICU (*n*=36)	31 (86.1)	26 (72.2)	27 (75.0)	80% (66.7%, 86.6%)
Non-NICU (*n*=294)	106 (36.1)	75 (25.5)	86 (29.3)	66.7% (50%, 83%)
P value	<0.001	<0.001	<0.001	0.020
Mode of feeding				
*Exclusively breastfed (*n*=190)	94 (49.5)	72 (37.9)	83 (43.7)	66.7% (50%, 85%)
Mixed fed (*n*=65)	24 (36.9)	20 (30.8)	20 (30.8)	66.7% (65.7%, 84.4%)
P value	0.08	0.30	0.07	0.43

*Values in no (%) except where stated otherwise; Compliance is calculated for infants who have ever received vitamin D supplementation (n=137). *Mode of feeding is depicted for infants <6 months age; compliance in this category is calculated for infants <6 months who ever received vitamin D supplementation (n=118).*

Of the 137 mothers who administered vitamin D to their infants, only 67 (49%) had understanding of correct duration of supplementation requirement. Verbal explanation regarding routine vitamin D supplementation at initial discharge after institutional delivery was reported by 115 (35%) mothers. Reinforcement during previous follow-up healthcare visits was reported by 74 (22.4%) mothers. Overall, 111 (33.6%) mothers were aware about routine supplementation. Most parents (98%) incurred out-of-pocket expenditure for supplementation.

Perrine, *et al*. [5] reported that even the educated parents from USA fared poorly in adherence, which was 10.5% in exclusively breastfed and 8.5% in mixed-fed younger infants. In another study from USA, only 15.9% of breastfed infants received routine supplementation [6]. Overall, 27.1% of US infants in 2009-2016 met vitamin D intake guidelines and there was no increase in proportion of infants who meet the guidelines over 5 years [7]. In 2011, a study in Poland showed 82.1% and 60.2% of infants aged 6 and 12 months, respectively, received daily vitamin D supplementation [8]. In 2017, a study in 29 European countries collectively reported good (≥80% of infants), and low adherence (<50%) by 59% and 10% (3/29) countries, respectively [9].

It is important to identify factors contributing to non-compliance. It appears that providing the drug and information, and monitoring adherence at surveillance visits could be important factors. Previous studies have suggested to reinforce parental education regarding supplementation and methods for reducing forgetfulness in mother; and identification of risk factors for poor compliance in the subsequent health visits to improve the outcome of routine supplementation [4,9]. It is possible that better supplementation practices and better compliance in infants born preterm and NICU graduates in our study were the result of reinforcements they received through more frequent follow-up in dedicated high-risk neonatal clinics.

This had limitation of being a single center study, with probability of recall bias. Further research on identifying the factors and finding remedies thereof are needed to improve adherence to routine daily supplementation of vitamin D to infants. It is important to note that this low compliance may offset the projected gains, based on 70% prescription rate by the pediatricians in the same setup [10]. Results from different regions, and preferably cohort studies, will provide more robust date to guide practice and policy.

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Olanzapine for the Treatment of Breakthrough Vomiting in Children Receiving Moderate and High Emetogenic Chemotherapy

The efficacy of olanzapine (mean dose 0.09 mg/kg/dose) was evaluated in 31 children 2-18 years of age, for chemotherapy induced breakthrough vomiting. Among 42 chemotherapy blocks with emesis, complete and partial responses were observed in 34 (80.9%) and 6 (14.3%) blocks, respectively, while 1/31(2.4%) patient had refractory vomiting. Mild sedation and transient transaminitis were the observed side effects.

Keywords: *Anti-emetic, Emesis, Malignancy, Vomiting.*

Chemotherapy induced vomiting (CIV) has been shown to have a detrimental influence on quality of life and treatment compliance of patients [1]. Despite the use of novel anti-emetics, breakthrough CIV can occur in 30-40% of children receiving moderate or highly emetogenic chemotherapy (MEC/HEC) [2,3]. There is paucity of data regarding choice of optimum agent and management of breakthrough CIV in children [3]. The present study was planned to demonstrate efficacy and safety of olanzapine in the treatment of breakthrough vomiting in children receiving MEC or HEC.

This observational study was conducted over a period of 6 months in children aged 2-18 years, receiving MEC or HEC who developed breakthrough emesis on protocol-defined prophylaxis, as described previously [4]. Institutional ethics committee approval and written informed consent from parents were obtained. The dose of oral olanzapine was 0.05-0.1 mg/kg/dose (maximum 5 mg/dose) once in every 24-hour period for 3 days, regardless of duration of chemotherapy block or subsequent response. The dose was rounded off to the closest half or full tablet of commercially available preparations of 2.5 mg and 5 mg strengths. Laboratory investigations included complete blood count, liver and kidney function at screening and before each cycle. Each episode of vomiting and treatment related adverse events like sedation and transaminitis were recorded as per the Common terminology criteria for adverse events ver 4.03, for atleast 5 days [5].

The primary outcome was an assessment of response for 5 days from the first dose of olanzapine. Complete response (CR) was defined as no emetic episode and use of no other rescue medications. Partial response (PR) was if patient had 1-2 emetic episodes with no use of rescue medications, and failure (refractory) if patient had more than 2 emetic episodes and/or use of rescue medications. Rescue drugs were permitted as per physician's discretion (commonly metoclopramide). Data were analyzed using IBM SPSS version 23.0, using standard physician's statistical methods.

During the study period, 108 (median age 9.2 years) pediatric cancer patients received 412 blocks of MEC and HEC. A total of 31 (31.8%) patients and 42 (10.1%) chemotherapy blocks were associated with breakthrough emesis. Eleven patients had breakthrough emesis in more than one block. Demographic data of patients is shown in ***Table* I**. The mean (range) olanzapine dose was 0.09 (0.04-0.15) mg/kg/dose.

Complete and partial responses were observed in 34 (80.9%) and 6 (14.3%) chemotherapy blocks, while 1 (2.4%) patient had refractory vomiting. One patient did not receive the

Table I Demographic Characteristics of the study Population (*N*=31)

Characteristic	(%)
Male	21 (68)
Age <10 years	18 (58)
Type of malignancy	
Hematological	17 (54)
Solid Tumor	14 (45)
Disease status	
Standard risk/Non metastatic	19 (61)
High risk/metastatic	12 (39)
Emetogenic potential	
Moderate	14 (45)
High	17 (54)
Cisplatin regimes	5 (16)
Dexamethasone	29 (93)
Intrathecal drug	14 (45)
Chemotherapy schedule	
Single day	05 (16)
Multiple day	26 (84)

drug after first dose and was not included in response assessment. The mean (SD) dose of olanzapine in patients with CR was 0.09 (0.02) mg/kg/dose and in PR was 0.08 (0.02) mg/kg/dose, *P*=0.68. There was no statistical difference in CR rates based on age (<10/>10 years, *P*=0.23), gender (*P*=0.68), emetogenic regimen (MEC/HEC, *P*=1.0) or single/multiple-day chemotherapy (*P*=0.2). The most commonly reported adverse events were grade I-II sedation in 9 patients (11 chemotherapy blocks) and increased serum transaminase levels in 3 patients (3 chemotherapy blocks). Olanzapine was discontinued in one patient due to orthostatic hypotension. The mean (SD) olanzapine dose in patients who had and did not have sedation was 0.11 (0.022) and 0.08 (0.001) mg/kg/dose, respectively; odds ratio 1.17, (95% CI: 1.08-1.27, *P*=0.0001). It is recommended to use an antiemetic with a different mechanism of action, for the treatment of breakthrough vomiting, than that used for prophylaxis [6]. A CR rate of 57% with an overall response of 86% has been reported earlier in a retrospective study on 20 subjects [7]. Our study was prospective in nature with pre-defined anti-emetic prophylactic protocols and indications for olanzapine use. We believe, this led to a more accurate and early use of olanzapine, resulting in better control of CIV and higher CR rates. Two studies in adult patients report similar results, CR, 70% and 61% respectively [8,9].

The most common side effects reported are sedation, transaminitis and weight gain [7-9]. Significant weight gain was not expected as the duration of treatment with olanzapine for refractory CIV is short. Flank, *et al*., reported sedation in 7%, and it was significantly associated with higher olanzapine dose, as also observed in our study [7].

The results of this study, despite small sample and lack of controls, suggest olanzapine as an effective anti-emetic drug for breakthrough CIV. Its low cost, oral formulation and safety profile are of added value in cost-constraint settings.

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Effect of Tactile-Kinesthetic Stimulation on Weight in Preterm Neonates in Neonatal Intensive Care Unit

This study evaluated the efficacy of tactile kinesthetic stimulation on the weight of 40 preterm (28 weeks to <37 weeks) infants. Experimental group received two sessions per day of tactile-kinesthetic stimulation, for 10 consecutive days along with routine hospital care (RHC) and control group received only RHC. Increase in mean (SD) weight gain was significantly higher in the experimental group as compared to control group [10.79 (0.62) g *vs* 4.03 (0.89) g; *P*< 0.001].

Keywords: *Developmental care, Exercise, Growth, Massage.*

Premature infants are exposed to a stressful environment, high intensity noise, and bright light continuously. They are deprived of mechanosensory stimulation which they receive in utero [1], constant tactile stimulus of amniotic fluid, and are also exposed to various touch stimulus during routine care [2]. Massage therapy may help in facilitating weight-gain process. We studied the efficacy of tactile- kinesthetic stimulation on the weight of infants in a neonatal intensive care unit (NICU).

This study was conducted in a level III neonatal unit from May, 2019 to August, 2019, after ethical clearance from the institutional ethics committee. All infants born between 28 weeks to <37 weeks gestational age, and birthweight of 1000 g - 2500 g and admitted in the NICU within the first 48 hours were enrolled. Additional inclusion criteria were: Apgar score >7 at 1 and 5 minute with no resuscitation required at birth, and medically stable with medical conditions primarily related to immaturity (such as elevated bilirubin, mild hypoglycemia and hypocalcemia). Those with genetic anomalies, congenital anomalies, any infections, and any evidence of intraventricular hemorrhage were excluded. Enrolled infants were randomized by using computer-generated random numbers to receive tactile-kinesthetic stimulation and routine hospital care (RHC) after 48 hours of their birth. Experimental group infants received two sessions of tactile-kinesthetic stimulation for 10 minutes each day, for ten consecutive days along with RHC, whereas the infants in the control group received only RHC.

The stimulation protocol was taken from field study in 1986 [4]. For the tactile stimulation, the infant was placed in a prone position. The researcher used the palms of the scrubbed and warmed hands on the infant's body while the baby was in the incubator. The following five regions of the infant's body were then gently stroked for five seconds, 12 times consecutively (totalling one minute). From the top of the neonate's forehead down the side of the face to the neck and back to the forehead; from back of the neck across the shoulders and back to the neck; from the upper back down to the waist and back up; from the thighs down to the ankles and back to the thighs; and from the shoulders to the wrists and back to the shoulders. For the kinesthetic and proprioceptive stimulation, the infant was placed in supine position. This stimulation was given for five minutes with five one–minute intervals. It included six passive flexion and extension movements in the right and left arm, the right and left leg and the two legs together.

The weight of the babies from both the groups were measured daily by digital electronic weighing scale by the same nursing assistant who was blinded about the allocation of groups. The outcome of this study was the weight of infants in the two groups after 10 days of intervention.

A total of 46 preterm babies were enrolled and forty infants completed the study. Both the groups did not differ on the matched variables of gestational age, birthweight, weight on day one of the study, and 1 and 5 minute Apgar scores **(*Table* I)**. The mean (SD) fluid and calorie intake in the infants of the two groups was also similar. The mean (SD) weight gain after 10 days was higher in the experimental group as compared to control group [10.79 (0.62) g *vs* 4.03 (0.89) g; *P*<0.001] **(*Table* I)**.

The present study assessed the effect of tactile-kinesthetic stimulation on weight of preterm infants and found a significant positive effect on weight gain in the experimental group. Small sample size due to time constraints, recruitment from a single centre, and exclusion of the factors which influence the energy expenditure of the infants, were the major limitations of this study.

White-Traut RC, *et al.* [5] and Mathai, *et al.* [6] had demonstrated the same benefit, when massage was combined with kinesthetic stimulation or physical activity. Along with weight gain, vagal tone and gastric motility [7], and bone mineralization and skeletal growth are also reported to improve [8-10]. Our findings provide further evidence that tactile kinesthetic stimulation improves weight gain in stable preterm infants.

In conclusion, tactile- kinesthetic stimulation for preterm infants between 28 to <37 weeks of gestational age had significant effect on weight gain. Further clinical studies with larger sample size to confirm the result obtained in our study and to standardize the protocol are the need of the hour.

Table I Baseline Characteristics and Outcomes in Preterm Neonates Enrolled on the Study (*N*=40)

V*ariables*	*Experimental group (n=20)*	*Control group (n=20)*
Gestational age, wk	33.8 (1.8)	33.4 (1.5)
Birthweight, g	1848.7 (226.3)	1830.8 (234.1)
1-minute Apgar score	7 (0)	7 (0)
5-minute Apgar score	8 (0)	8 (0.5)
Baseline weight, g	1809.5 (208.1)	1779.1 (142.6)
Weight gain day 1-5, g	77.9 (35.09)	79.6 (49.1)
*Weight gain day 6-11, g	53.9 (3.9)	20.1 (4.5)
*Daily weight gain, g	10.8 (0.6)	4.03 (0.9)

*All values in median (IQR) except weight gain in mean (SD); *P<0.001.*

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Lipid Profile in Children With Thalassemia: A Prospective Observational Study From Eastern India

This was a prospective observational study to evaluate abnormalities in lipid profile in 50 children with transfusion dependent thalassemia. Dyslipidemia characterized by high triglycerides, low high density lipoprotein (HDL), and high total cholesterol: HDL ratio was noted. These pro atherogenic risk factors may be lead to significant cardiovascular morbidity in these patients.

Keywords: *Atherosclerosis, Co-morbidity, E beta thalassemia, Outcome*.

Life expectancy and quality of life of beta-thalassemia patients have improved in recent years. However, non-siderotic complications are known to cause significant morbidity in these patients with beta-thalassemia. In recent years, many studies have shown risk of developing subclinical atherosclerosis in beta-thalassemia patients. Strong association of abnormal serum lipid levels [low total cholesterol (TC) and (high density lipoprotein) HDL-cholesterol, high triglycerides (TG) and TC: HDL ratio) with premature atherosclerosis have been noted in children with beta thalassemia [2-5]. Low HDL - cholesterol and high TC:HDL ratio are pro-atherogenic factors, which help in cardiac risk stratification and prognostication [6,7]. Pediatric data regarding lipid profile in thalassemia is limited. Our primary objective was to evaluate abnormalities in lipid profile in children with thalassemia.

A prospective observational study was performed at Institute of Child Health, Kolkata between July, 2016 and June, 2017. Children with transfusion- dependent thalassemia, under regular follow up in our thalassemia clinic, were included for this study. The patients had been diagnosed following appropriate clinical history, physical examination, complete blood count and high performance liquid chromatography (HPLC) and were on regular transfusion and chelation therapy. Children having family history of dyslipidemia were excluded. None of the patients had previous history of cardiovascular illness. Fifty age- and sex-matched healthy children were taken as control. Ethical clearance was obtained from the institution ethics committee and written consent was obtained from care givers.

Blood samples for serum fasting lipid profile and ferritin were taken after a 12 hour overnight fast. Spectrophotometry was used for assessing fasting lipid profile. Statistical analyses were carried out using GraphPad Prism, version 5.0. Continuous, non-parametric data were compared using the Mann-Whitney U test, while categorical data were compared by chi square test. $P<0.05$ was considered as statistically significant.

Out of a total of 53 eligible children, 3 were excluded for having family history of hyperlipidemia. Thus, 50 children

Table I Comparison of Fasting Lipid Profile between Children with Beta Thalassemia Patients and Control Group

Parameters	*Children with thalassemia (n=50)*	*Control group (n=50)*
Total cholesterol	95.5 (78.75, 111.3)	156.5 (143.5, 184.8)
HDL-cholesterol	23 (19, 32)	48.5 (39.8, 54.3)
Triglycerides	258 (142, 415)	118 (78, 199.3)
*TC:HDL ratio	4.79 (3.79, 6.94)	3.00 (2.73, 4.08)

All values in median (IQR) except total:high density lipoprotein cholesterol ratio (TC:HDL). All P<0.001.

(62% males) with a median age of 2 years 5 month (range 0-18 years) were enrolled. All patients had low HDL-Cholesterol, 74% had high TG levels, 84% had a high TC: HDL ratio and 60% had low total cholesterol (***Table* I**). Out of the 37 patients with elevated triglyceride levels, 28 had hyperferritinemia. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were in normal range. Patients with thalassemia had lower HDL cholesterol and higher triglycerides and elevated TC: HDL ratio compared to the controls (***Table* I**). Children with E beta thalassemia had lower TC than children with beta thalassemia major (***Table* II**). TC: HDL ratio was increased and HDL-cholesterol was decreased irrespective of age and gender.

Iron overload and oxidative stress are postulated mechanisms for causing dyslipidemia in patients with thalassemia [4,8,9]. Similar to our results, hypocholesterolemia in patients with thalassemia has been demonstrated in earlier studies [8]. Iron overload contributes to liver injury contributing to decrease in production of cholesterol. Increased consumption of cholesterol due to enhanced erythropoiesis and increased uptake by the histiocytes are other factors [9]. Elevated triglyceride levels, possibly because of decreased lipolytic enzyme activity, have also been reported previously [2,4,9,10]. Unlike our study, females were found to have elevated TG in previous studies. The low HDL-cholesterol levels in our patients weres presumably due to excessive clearing of HDL by the activated macrophages [4].

Table II Comparison of Fasting Lipid Profile between Children with Beta Thalassemia Major and E-beta thalassemia

Parameters	*β-thalassemia major (n=29)*	*E β-thalassemia (n=21)*
Total cholesterol[#]	109 (96,147)	76 (69, 86.5)
HDL cholesterol	23.5 (19.75, 29.75)	23 (17.25, 33)
Triglycerides^	176.5 (137.8, 352.5)	334.5 (254.3 -457)
*TC:HDL ratio	4.32 (3.79 – 6.29)	4.9 (3.86 – 7.13)

*All values in median (IQR). Units for all values in mg/dL; *TC: Total cholesterol. [#]P<0.0001; ^P=0.02*

The limitation of our study was a small sample size. Larger studies with follow up echocardiography and cardiac MRI will provide further insight and information regarding the cardiovascular complications in children with thalassemia having deranged lipid profile. This may also help in framing guidelines for monitoring lipid profile in these children, in order to reduce long term morbidity and mortality.

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Deficiency of Adenosine Deaminase 2 (DADA2) – A New Autoinflammatory Disease with Multisystem Features

A male child born to a non-consanguineous couple had been extensively investigated for recurrent, prolonged febrile episodes from 2005 to 2011. The fever episodes were accompanied by multisystem manifestations consisting of myalgia, arthralgia, rashes, recurrent and episodic severe abdominal pain (one episode leading to an appendicectomy), episcleritis, generalized adenopathy and hepatomegaly [1]. Mutation testing for then known auto-inflammatory diseases including Tumor necrosis factor receptor associated periodic syndrome (TRAPS) was negative. TRAPS was considered as the best fit clinical diagnosis considering that literature had identified subsets of patients with a clinical profile matching TRAPS without mutations in the *TNFRSF1A* gene. The family was advised to start Tumor necrosis factor (TNF) blocker, etanercept at the dose of 0.4 mg/kg subcutaneously twice weekly, after tuberculosis screening. The patient's symptoms including fever, arthralgia, myalgia, and abdominal pain abated rapidly with normalization of his anthropometry over the next 2 years. His complete blood counts, Erythrocyte Sedimentation Rate (ESR) and C Reactive Protein (CRP), also normalized and stayed stable over the next seven years.The cost of etanercept lead to a gradual, progressive self-titration of dose to 0.4 mg/kg every 20-22 days, at which point symptoms would recur.

In January 2019, at age 20 years, he was diagnosed with asymptomatic hypertension (180/120 mmHg) during a pre-employment check. Urinalysis was normal and serum creatinine was 0.91 mg/dL with e-GFR of 114 mL/hr. His 2D-echocardiogram showed mild concentric left ventricular hypertrophy with grade 2 diastolic dysfunction suggesting long-standing hypertension. The ejection fraction was 60%. His kidneys were of normal size. A magnetic resonance angiogram (MRA) showed diffuse narrowing of the right renal artery and scarring of the right kidney (***Fig.* 1**). Positron emission tomography computerized tomography (PET-CT) did not show any vascular inflammation. Whole exome sequencing (WES) in the patient and his asymptomatic parents identified compound heterozygous mutations (p. Gly47Arg (c.139G>C; p.G47R) and a splice mutation c.753+2T>A). His father and mother were carriers of the respective mutations. The patient was started on antihypertensive therapy and etanercept was increased to 0.8 mg/kg once weekly starting April 2019. He is doing well since and is presently additionally receiving metoprolol 50 mg once daily.

DADA2 was described independently by two groups in 2014, and considerable time after our patients first presentation and report [2,3]. Now over 200 patients have been reported globally. Its prevalence is higher in endogamous populations (Middle Eastern countries) or in founder populations (Finnish, Dutch). Our patient hails from the endogamous Agarwal community and we have since diagnosed two other children of the same community with DADA2 homozygous for the p.Gly47Arg (c.139G>C; p.G47R) mutation.

Typically features begin in early childhood or adolescence. Vasculopathy/vasculitis (polyarteritis nodosa, lacunar infarcts) and hematological manifestations remain the cardinal features [4]. Hypertension has been described in 21%, renal artery stenosis in 4% of patients, and cases with large vessel involvement have been reported. Notable in our patient is an episode of acute abdomen for which he underwent appendicectomy. Uncommonly DADA2 can present as a polyarteritis nodosa (PAN)-like disease in adults. Screening such patients for ADA2 activity can radically modify management.

Laboratory findings are non-specific and include elevated acute phase reactants during flares and raised transaminases. Positive lupus anticoagulant autoantibodies have been noted in some. Sharma, *et al*. [5] have reported DADA2 in a 35 year old woman also from the Aggarwal community, who presented as a APLA-like syndrome with recurrent abortions [5]. The G47R pathogenic variant has been described in DADA2 patients from Middle East and South Asia and with an allele frequency higher than in other populations (Caucasian, Latino, African). Functional protein assay on fresh serum or plasma samples, which detects low or absent ADA2 enzymatic activity or measuring ADA2 catalytic activity on dried plasma filter paper spots can provide a rapid confirmatory protein diagnosis.

Despite the increasing availability and reducing costs of genetic testing, challenges of cost, interpretation, and long turn-around times exist. Our patient's samples awaited analysis at National Institutes of Health (NIH) (a global referral center for autoinflammatory diseases) for WES and were fast-tracked after recent developments. It was serendipitous that the child was started on etanercept in 2011. Retrospectively, spacing the

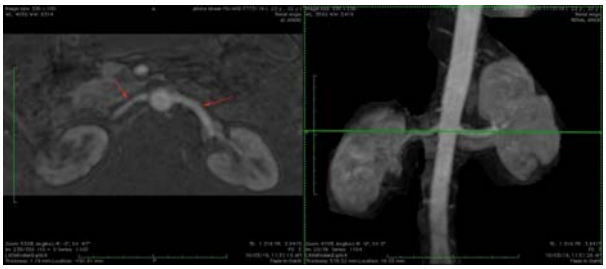

Fig. 1 *MR angiogram showing diffuse narrowing of the right renal artery and scarring of the right kidney.*

doses for cost considerations was not prudent since the child has developed a vasculopathy with renal scarring. Anti-TNF agents prevent and eliminate vasculitis symptoms in DADA2 patients with a remarkable reduction in ischemic stroke risk [6]. They decrease inflammatory burden of the disease, increase growth and development, and improve some hematological manifestations such as anemia and thrombocytopenia. Thalidomide has been reported useful in a large study. Aspirin and anticoagulants are contraindicated since hemorrhage may complicate the stroke. Hematopoietic stem cell transplantation can be curative in patients who present with bone marrow failure or are non-responsive to anti-TNF therapy [4].

In conclusion, pediatricians in India must be aware of this recently discovered entity and its myriad presentations, including PAN, early-onset strokes, arterial obliterations, immunodeficiency, and aplastic anemia. With high rates of consanguinity and endogamy in several parts of India, we believe more patients of hereditary auto-inflammatory diseases would be diagnosed with increasing physician awareness and availability of genetic testing.

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Crisponi/Cold Induced Sweating Syndrome Type 1 With a Private Cytokine Receptor Like Factor 1 (CRLF1) Mutation in an Indian Family

Crisponi/cold induced sweating syndrome type 1 (CS/CISS1; Mendelian Inheritance in Man [MIM] #272430), a rare autosomal recessive disorder, is possibly under-recognised due to its complex phenotype with likely misinterpretation of symptoms. Worldwide, there are fewer than 100 reported cases and we present the second Indian patient with a *CRLF1* genetic mutation [1-4]. A 1½-month-boy presented with intermittent high-grade fever, episodic contractions of facial and neck muscles and feeding difficulties since birth. He was sixth born to a non-consanguineous healthy couple hailing from North India. There was history of two sibling deaths, a male and a female in third week of life. Both the babies were born at term gestation, had normal birth weight but associated with birth asphyxia followed by progressive feeding abnormalities and abnormal posturing. His three elder female siblings were all alive and healthy. There was history of one spontaneous abortion in mother. Antenatal course of the present pregnancy was uneventful; mother received 2 doses of tetanus toxoid. The baby was delivered vaginally at term gestation with a birth weight of 3.25 kg. He was non-vigorous with meconium stained liquor but cried after stimulation. He required NICU stay with oxygen therapy and intravenous antibiotics though all laboratory investigations including sepsis work up were within normal limits. At presentation at 1½ months of life, he had fever (103°F), tachycardia, tachypnea, SpO2 of 98% at room air but clear chest. He was underweight (3.7 Kg) with normal length (60 cm) and head circumference (36.5cm). He had a round expressionless face (***Fig.*****1a**) with bilateral camptodactyly and clinodactyly with adduction of thumbs (***Fig.*****1b**) and overriding of the toes of both feet (***Fig.*****1c**). Neurological examination revealed a weak cry and decreased spontaneous motor activity. There were paroxysms of facial and neck muscle contraction leading to puckering of lips, tight eye closure, neck extension (***Fig.*** **1d**) along with inward rotation of the upper limbs and clenching of the hands lasting a few minutes. These episodes were associated with crying and often precipitated by tactile or painful stimulation with a frequency of 25-30 episodes during daytime. Episodes were absent during rest and sleep. Partial remission was obtained with clonazepam administration. Initially, possibilities of hypoxic ischemic encephalopathy, neonatal sepsis with meningitis, neonatal tetanus, Sandifer syndrome and inborn error of metabolism were considered.

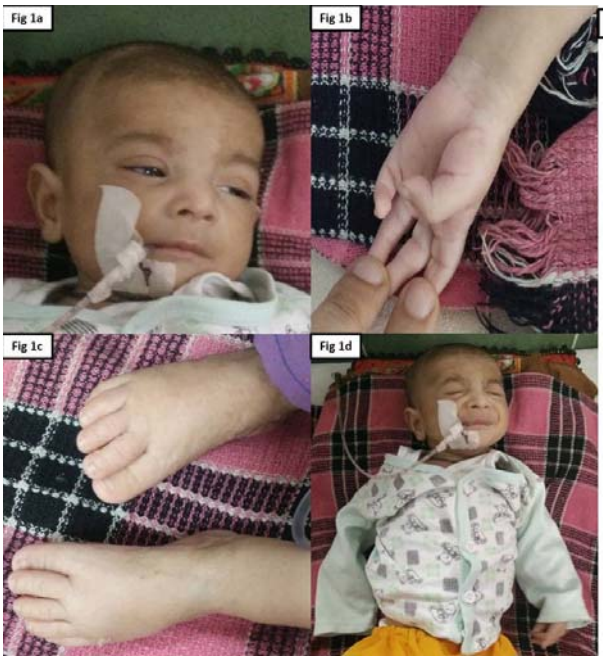

Fig.1 *A 1½-month-boy with 1a- round expressionless face; 1b- bilateral camptodactyly and clinodactyly with adduction of thumbs; 1c–overriding of the toes of both feet and 1d- paroxysms of facial and neck muscle contraction leading to puckering of lips, tight eye closure, neck extension.*

Laboratory investigations showed normal sepsis screen and sterile blood and urine cultures. Urine microscopy, cerebrospinal fluid examination, fundus, electroencephalography, chest *X*-ray, magnetic resonance imaging of brain, skeletal survey and ultrasound abdomen were normal. Metabolic screen (blood sugar, serum ammonia, arterial lactate, blood gas and urine ketones) was negative. ENT evaluation and *X*-ray temporo-mandibular joint (TMJ) ruled out TMJ ankylosis. 24-hour pH monitoring revealed mild gastro-esophageal reflux. Further literature search lead to a possibility of Crisponi/cold-induced sweating syndrome type 1 (CS/CISS1) and genetic analysis for its confirmation was done at the Institute of biomedical and genetic research, National research council, Italy. Molecular analysis carried out for all the nine *Cytokine receptor like factor 1* (CRLF1) [NM_004750.4] coding regions (including the exon-intron junctions) by sequencing analysis of the PCR products showed the presence of a homozygous small deletion [c.120delA;p. (Ala41Leufs*2)] in exon 2. This variant has very strong evidence of pathogenicity according to American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) 2015 guidelines classification (PVS1, PM2, PP4) and multiple algorithms predictions such as SIFT (damaging) and mutation taster (disease causing) [4]. Both parents as well as the two sisters were heterozygous, while the youngest sister was homozygous for the wild type allele, confirming the familial origin of the pathogenic variant. Genetic counselling was done for the family. The child was continued on orogastric (OG) feeds, anti-pyretics, lanzoprazole and clonazepam. He could gradually be weaned of OG feeds by 8 months of life but was subsequently lost to follow up.

CS/CISS1 is characterized by neonatal onset marked facial muscular contractions with trismus and abundant salivation, simulating a tetanic spasm precipitated by tactile stimulation or crying. There is associated intermittent hyperthermia, feeding problems (due to orofacial muscle spasms, poorly developed swallowing reflex, and associated gastroesophageal reflux (GER) and respiratory difficulties. A round face, broad nose with anteverted nostrils, small mouth, micrognathia and bilateral camptodactyly are typical [5]. It is usually lethal in the first few months of life. In rare surviving individuals, hyperthermia and muscle contractions may disappear after infancy while kyphoscoliosis and paradoxical cold induced sweating may develop towards the end of first decade; few may develop a mild psychomotor retardation [5,6]. Important differential diagnoses include neonatal tetanus (differentiated by absence of typical dysmor-phology), Stuve-Wiedemann syndrome (differentiated by lower limb bowing) and Freeman–Sheldon syndrome. CS/CISS1 is caused by variants in the *CRLF1* gene. Thirty-seven disease causing *CRLF1* pathogenic variants in 96 patients have been reported in the medical literature [1,4]. Although genotype/phenotype correlation has been elusive, it has been suggested that the level of the mutant protein may correlate with the phenotypic severity [4]. Treatment of CS/CISS1 is primarily symptomatic. Clonazepam for muscle spasms and moxonidine for cold induced sweating have been tried with variable response. Monitoring is recommended for development of kyphoscoliosis and psychomotor retardation [4,6]. The need for suspicion of CS/CISS1 in cases where the other common differential diagnosis have been ruled out and specially in presence of a suggestive family history is exemplified in the index case. Further, the role of genetic diagnosis for genetic counselling and preventing recurrence of the disease in the family cannot be over emphasized.

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X-linked Lymphoproliferative Disease (XLP1) Presenting as Non-Epstein Barr Virus (EBV) - Related Hemophagocytic Lymphohistiocytosis (HLH)

X-linked lymphoproliferative disease (XLP1) is a rare immunodeficiency disorder with immune dysregulation, caused by *SH2D1A/SAP* gene mutations. Clinical manifestations include fulminant infectious mononucleosis (FIM), hemophagocytic lymphohistiocytosis (HLH), lymphomas and dysgammaglobulinemia [1]. HLH in children can be primary/familial HLH or secondary/reactive HLH [2]. In 80% of familial HLH cases the genetic defect can be identified. To the best of our knowledge this is the first report of XLP1 in an infant with non-Epstein Barr virus (EBV) HLH in India.

An 11 months old male infant, born to third degree consanguineous parents presented with intermittent fever and loose stools for twenty days. There was no history of vomiting, blood in stools, bleeding manifestations, cough/cold, weight loss or past recurrent infections with an unremarkable family history. Child had normal nutritional status, some pallor and massive hepatosplenomegaly. Investigations revealed anemia with hemoglobin of 8.3 g/dL, neutrophilic leucocytosis, absolute neutrophil count of 1704/mm3, low normal platelet count and along with elevated liver enzymes (alanine transaminase: 210 U/dL; aspartate transaminase: 399 U/dL). He was started on antibiotics ceftriaxone and doxycycline. Further investigations including smear for malarial parasite, serology for scrub typhus, cytomegalovirus, EBV and retrovirus was negative. As his fever spikes persisted, ultrasound abdomen, echocardiogram and Immunoglobulin profile were done and found normal. .

Re-evaluation revealed decreasing neutrophil counts (ANC of 624/mm^3), thrombocytopenia (platelet count of 0.49×10^9/L) and coagulopathy (INR of 1.6). Antibiotics were escalated to meropenem and vancomycin because of worsening clinical condition and laboratory parameters though the blood cultures remained sterile. In view of pancytopenia, deranged liver functions, organomegaly and persisting fever spikes, hemophagocytic lymphohistiocytosis (HLH) was considered. Follow up investigations showed elevated serum ferritin (5498 ng/mL), serum triglycerides (278 mg/dL), soluble CD 25 levels, decreased serum fibrinogen (175 mg/dL), bone marrow hemophagocytosis, and cerebrospinal fluid lymphocytic pleocytosis, all consistent with the diagnosis of HLH [2]. He was treated with intravenous immunoglobulin, dexamethasone and etoposide. Workup for primary HLH showed normal perforin protein expression and CD 107a. With the background of consanguinity and male sex, XLP was considered. Next generation sequencing revealed mutation in *SH2D1* characteristic of XLP1. Unfortunately, the child had HLH progression and expired of fulminant hepatic dysfunction and coagulopathy. Parents were counseled regarding antenatal diagnosis of XLP in next pregnancy.

X-linked lymphoproliferative syndrome (XLP) is a rare inherited immunodeficiency affecting approximately one in 1,000,000 males. XLP patients have severe immune dysregulation often after viral infection (typically with Epstein-Barr virus [EBV]) [1]. However, a proportion of boys (approximately 10%) have immunological abnormalities before evidence of EBV infection [3] like in our case.

One of the manifestations of XLP1 is hemophagocytic lymphohistiocytosis (HLH) which is a multisystem inflammatory disorder characterized by cytokine overproduction by activated lymphocytes and macrophages.

XLP arises from 2 different genetic defects in *SH2D1A,* in Xq25 gene (XLP1, the most common) and *BIRC/XIAP* gene (XLP2). *SH2D1A* encodes the cytoplasmic protein *SAP* (*SLAM*-associated protein) which is a key regulator of normal immune function in T cells and naturalkiller cells [4]. Defects in SAP lead to the varied immune defects in XLP1 patients. Our child had a mutation in *SH2D1A* confirming XLP1.

Hematopoietic stem cell transplantation (HSCT) remains the most effective curative treatment for XLP though IVIG and rituximab have been used previously in prevention with questionable benefit [4,5].

Any male child with HLH or FIM should undergo genetic testing for therapeutic implications like bone marrow transplant. Early genetic confirmation of diagnosis also plays a major role in prenatal diagnosis and genetic counselling for the next pregnancy.

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Perianal Abscess With Stellate Lacerations in a 3.5-year-old Previously Healthy Boy

Perianal abscesses are soft tissue infections of the perianal region and are common in infants [1-3]. Most of them are idiopathic, although there may be an association with congenital abnormalities of the crypts of Morgagni or an infection of the cryptoglobular glands [1-3]. They occur mainly in males, which may be due to androgen excess in cases of androgen-estrogen imbalance or to abnormal development of androgen-sensitive glands *in utero* [1]. In older children, the etiology shifts to underlying diseases, such as inflammatory bowel disease, immune deficiency syndromes, trauma, infected mass lesions and other immunodeficiencies [4]. The most common organisms isolated are mixed aerobic and anaerobic bacteria from gastrointestinal tract flora [5]. The appropriate management of perianal abscess is incision, drainage and antimicrobial treatment [3].

A 3.5-year-old boy presented with a three day history of pain, skin irritation and discharge of pus around the anus. Notably, fifteen days prior to admission, he developed an upper respiratory tract infection treated with oral second-generation cephalosprin. Five days later, while on antimicrobial treatment, he complained of pain during defecation and his mother noticed mild redness around the anus. The patient was afebrile. Laboratory investigations revealed severe neutropenia (absolute neutrophil count: 0.14×10^9/L). The patient was treated with topical corticosteroids, but showed no improvement. The child continued to complain of perianal pain and the inflammation worsened with purulent discharge. Three days prior to admission, he received oral metronidazole, without improvement.

Past medical history was unremarkable, and there was no history of constipation before or during the preceding viral illness. Physical examination demonstrated notable swelling, redness and tenderness in the rectum area with concomitant laceration of the anus leading to stool incontinence. His physical examination was otherwise unremarkable. A rectal examination revealed painful inflammation purulent discharge and stellate lacerations of the anal mucosa and skin (***Fig. 1a***).

Laboratory investigation upon admission revealed white blood cell count of 14.9×10^9/L (neutrophils: 35.4%, lymphocytes: 55.8%, monocytes: 8.3%) with normal hemoglobin and increased platelet count. Both C-reactive protein and ESR were mildly raised. Liver and renal function tests were normal. There was a family history of recurrent abscesses in mother and maternal aunt raising the suspicion of immunodeficiency disorder, but all immunological investigation came out to be normal including classes and subclasses of the immunoglobulins, immunophenotyping, dihydrorhodamine (DHR) test and cell adhesion molecules (CAMs). Physical examination findings also raised the possibility of sexual abuse, which was further ruled out after behavioral and psychological assessment of child and his parents. The family was daily reviewed by the pediatric team who found no evidence of child abuse or family conflicts. There was no evidence of any behavioral changes or psychological problems in the child during hospitalization and the follow-up consultation for the next 2 years showed no indication of psychological problems or any other changes in the behavior of the child.

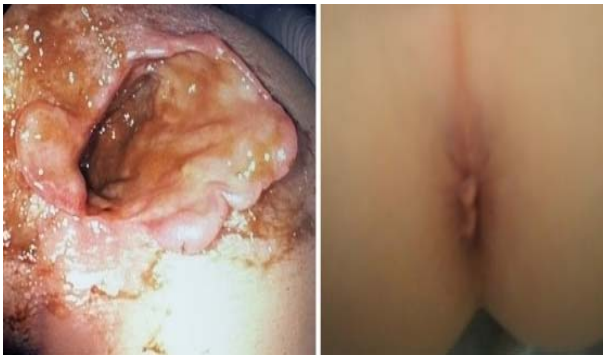

Fig. 1 *Perianal abscess of the 3.5-year-old child (a) on admission and (b) 10 days after treatment.*

Though the stool culture was negative, purulent discharge culture revealed *Klebsiella oxytoca* and *Proteus mirabilis* and the culture of perianal skin revealed *Klebsiella oxytoca, Enterobacter cloacae* and *Escherichia coli*. The patient was seronegative for HSV 1 and 2. Rectosigmoidoscopy was unremarkable and pathology did not reveal any evidence of underlying inflammatory bowel disease; colonic biopsy revealed only moderate alterations suggestive of active focal erosive rectitis. Additional investigations with polymerase chain-reaction in the blood, skin lesion and rectal tissue for Herpes viruses (HSV1, HSV2, VZV, EBV, CMV) were also negative. Empiric antimicrobial treatment with cefotaxime, clindamycin, metronidazole and acyclovir was initiated and continued for 14 days. The clinical course was favorable with complete clinical resolution (***Fig.* 1b**). In the follow-up period for next two years, child continued to remain well with no stool incontinence.

We report this unusual case because of the clinical presentation mimicking lesions associated with sexual abuse, as stellate lacerations were present. We elected to treat with broad spectrum antibiotics and provide antiviral treatment. The complete resolution of his lesions and anal incompetence was remarkable. Since the investigation did not identify any underlying disease, we concluded that the most likely pathogenetic cause was the development of severe neutropenia post viral infection. This highlights the importance of a complete blood count and a peripheral blood smear in the initial evaluation of perianal abscess upon presentation. Moreover, although his family history strongly suggested possible phagocytic dysfunction, the investigation failed to diagnose such an immune deficiency.

Contributors: DD, AD, SF: conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript; DD, AD: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed the manuscript. NZ, VP: conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Early Onset Predominantly Diffuse Lung Disease in an Infant of Combined Methylmalonic Acidemia With Hyperhomocysteinemia Cobalamin C Type

Elevated blood methylmalonic acid (MMA) levels combined with elevated homocysteine is called combined methylmalonic acidemia with hyperhomocysteinemia [1,2]. It is found that MMA may damage the central nervous system, retina, liver, kidneys and blood cells. It also causes macular coloboma, thrombotic microangiopathy [3], and sometimes pulmonary arterial hypertension (PAH) [4,5], but an association between combined methylmalonic acidemia with hyperhomocysteinemia and diffuse lung disease (DLD) has rarely been reported in infants [6].

A 7-month-old boy was admitted with complaints of pallor for 30 days. It was followed by cough 8-10 days later. Personal history showed delayed motor development. The child was hospitalized in a local hospital for respiratory distress. Investigations showed white blood cell count of 9.78 $X10^9$/L, hemoglobin of 6 g/L, platelet count 319$X10^9$/L, and reticulocytes of 9%. High resolution computed tomography (HRCT) scan of the lungs revealed diffuse lesions in both lungs. Cytomegalovirus DNA detection revealed 5.08x10^5 copies/mL in sputum. Injection meropenem, azithromycin, voriconazole and ganciclovir were administered. In spite of the above treatment, child continued to have progressively worsening respiratory difficulty. He was intubated transferred to our hospital.

We added trimethoprim-sulfamethoxazole with a possibility of *Pneumocystis carinii* infection. Further investigations were non-contributory for bacterial, fungal and tuberculosis infection, and liver and renal function tests were

within normal limits. Serum erythropoietin level was >750.0 mIU/mL, vitamin B12 >1000 pg/mL and folic acid >24.0 ng/mL. The morphology of red blood cell of the peripheral blood, and bone marrow aspiration had no abnormalities. Thoracoscopic lung biopsy was performed and pathology showed alveolar septum widened with local atelectasis and pulmonary arteriolar thickening. Further blood tests and tandem mass spectrometry revealed increased homocysteine levels (95.9 µmol/L; normal: 10-40 µmol/L) and highly elevated MMA (0.2598; normal levels: 0.001). We performed a whole exome sequencing and confirmed a compound heterozygosity in *MMACHC* gene, with c.80 A>G (p.Gln27Arg) and c.609 G>A (p.Trp203Term) sequence variants. Therefore, the child was considered to be combined methylmalonic acidemia with hyperhomocysteinemia cobalamin C type (MMACHC). The patient was treated with folic acid 5 mg twice daily orally, vitamin B12 (cyanocobalamin) 1 mg daily intramuscularly, betaine 500 mg three times daily orally, and L-carnitine 100 mg/kg/d intravenously. After two weeks of further treatment, there was some clinical and radiological improvement. Ventilator setting was decreased but the child could not be weaned off completely. Due to poor prognosis and high costs, parents decided to discontinue treatment and left against medical advice. The child subsequently died.

The baby had a brother admitted to our hospital three years ago who was aged 5 months. The chief complaint was paleness for 4 months, repeated cough for 22 days, and diarrhea for 18 days. He was diagnosed with cytomegalovirus pneumonia, severe anemia, brain dysplasia, enterogenous acrodermatitis, and possible metabolic disease. Pulmonary CT suggested diffuse lesions in both lungs along with brain atrophy on CT head. After admission, child was started on antibiotics and supportive treatment but as the patient did not show any improvement, patients discontinued with the treatment.

In this study, we suggest that there may be a relationship between MMACHC and DLD in infants. No other causes of DLD such as connective tissue disease, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, alveolar hemorrhage syndromes, pulmonary vasculitis, hypersensitivity pneumonitis or drug induced interstitial pneumonia were detected in these siblings. Thus, we think that it is possible that DLD was caused by MMACHC in this case. The occurrence of DLD in MMACHC may be related to the abnormal proliferation of vascular smooth muscle cells and pulmonary interstitial cells caused by abnormal accumulation of metabolites [6]. The specific cellular and molecular mechanisms need to be further studied.

Our patient presented with early and progressed rapidly, though literature review shows a history of several months or even years without significant respiratory failure [6]. We propose that one of the reasons that the condition was too severe and it was too late to start treatment, so the pathological changes of the tissues could not be reverted [2]. Early onset disease also suggests a more serious metabolic enzyme deficiency and greater accumulation of metabolic waste adding to a poor prognosis and higher mortality [3]. Treatment with hydroxycobalamin and betaine has been shown to be efficient in MMACHC. Hydroxycobalamin is considered to be the only form of cobalamin to be beneficial in patients with MMACHC [1]. A possible reason of slow improvement could be non-availability of hydroxycobalamin; however, beneficial effect with cyanocobalamin is also reported [6].

MMA patients have been reported to have pulmonary vascular embolism [6]. Our patient also had hematologic abnormalities; however, there was no obvious abnormality in the peripheral blood smear, and no micro-thrombotic change in the lung biopsy. Although the elder brother did not have a definite diagnosis, MMACHC was the most likely candidate considering his medical history and his brother's final diagnosis suggesting that genetic background plays an important role in the age of onset and phenotype of the disease.

In summary, our report suggests that MMACHC should be considered as a potentialcause of DLD. Early recognition, diagnosis and treatment of MMACHC defect are important, especially in early-onset cases.

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Chylous Ascites in Nephrotic Syndrome

Ascites is a common feature in children with nephrotic syndrome, and if not treated early, it may gradually increase. The fluid is a transudate with a very low protein content and few cells. Occurrence of chylous ascitic fluid has been occasionally reported in adult patients with nephrotic syndrome, usually being caused by obstruction to lymphatics [1]. We report the case of a child with steroid resistant nephrotic syndrome (SRNS) who developed massive ascites. Paracentesis revealed the chylous nature of the fluid. Such a feature is rare and not well explained.

A 6-year-old child with SRNS was referred to us for with massive ascites, respiratory distress and oliguria. He was diagnosed 1 year back with SRNS, following no response to the standard treatment with prednisolone (2 mg/kg daily for 6 weeks followed by 1.5 mg/kg on alternate days for 6 weeks). A renal biopsy was advised but declined by the parents seeking alternative treatment. The child developed abdominal distension about 8 months back, which had recently increased significantly to cause difficulty in breathing and decreased urine output. There was no associated history of jaundice or upper gastrointestinal bleeding or any other systemic illness.

Examination showed a severely malnourished child with massive ascites respiratory distress, facial and pedal edema, marked pallor and cold peripheries. Vitals revealed tachycardia, tachypnea and a blood pressure of 80/40 mmHg. On laboratory evaluation the hemoglobin was 6.2 g/dL, serum albumin 1.4 g/dL, globulin 1.4 gm/dL, urea 101mg/dL and creatinine 1.7 mg/dL. The levels of serum electrolytes, bilirubin and liver enzymes were within normal range. Fasting lipid profile including serum cholesterol (138 mg/dL) was normal. Urine showed 4+ protein and no red cells on microscopy. Fluid resuscitation was done with 0.9% saline following which peripheral perfusion improved but oliguria persisted (urine output 100 ml in first 24 hour). He was given 20% albumin infusion and diuretics. Abdominal paracentesis was done to relieve respiratory distress. Paracentesis revealed milky white fluid, which on analysis showed protein content of 1.2 gm/dL and triglycerides of 145 mg/dL. Microscopy showed 110 cells/mm^3, mostly lymphocytes and predominant chylomicrons. The culture of the fluid was sterile.

Ascites was slowly drained over the next 72 hours. He was put on a fat free, MCT based diet. A CT abdomen was done to look for obstruction of lymphatics, but did not reveal any abnormality. The accumulation of fluid gradually abated. In view of the same, lymphangiography or MR scanning was deferred. The subsequent course in the hospital was complicated by the occurrence of cerebral sinus thrombosis, which resolved with anticoagulant therapy and supportive care. Following discharge from the hospital, he was managed by the family doctor.

Chylous accumulation in peritoneal cavity may be caused by intestinal lymphangiectasia which may be congenital or associated with trauma, lymphoma, intestinal malignancy, pancreatitis, liver cirrhosis liver and right-sided heart failure [1]. Chylous ascites is not commonly a feature of idiopathic nephrotic syndrome in children.

A few isolated cases of chylous ascites have been described in adults with nephrotic syndrome with membranous nephropathy [2], focal segmental glomerulosclerosis [3] and renal vein thrombosis [4]. Recently chylous ascites was reported as a presenting feature in a child with systemic lupus [5]. In our patient various secondary causes of nephritic syndrome were excluded. Extensive literature search disclosed only one case of nephrotic syndrome complicated by chylous ascites in a 2-year and 8-month-old girl [6]. Repeated ascitic drainage in this girl was followed by resolution of ascites, whose proteinuria further responded to immunosuppressive drugs. The observations in this case were very similar to those being reported by us.

The mechanism of chylous ascites formation in nephrotic syndrome is not clear. It has been suggested that leakage from the dilated subserosal lymphatics from the edematous bowel mucosa and submucosa may be responsible [6]. Such lymphangiectasia may be caused by a slowing of venous return due to pressure exerted by persistent voluminous ascites. The gradual resolution of ascites with paracentesis and judicious use of diuretics supports the above hypothesis.

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Tuberculosis During Covid-19 Pandemic: Challenges and Opportunities

Both novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and *Mycobacterium tuberculosis* involve the lungs and share symptoms like cough, fever, and respiratory difficulty. The transmission for both agents is through aerosol and close contact, although the incubation period for tuberculosis is relatively longer. There is limited experience of COVID-19 infection in tuberculosis (TB) patients, but it is estimated that there may be a catastrophic impact of COVID-19 on TB [1]. This pandemic of COVID-19 has elicited social stigmata and discriminatory behaviour, coupled with pre-existed TB related stigmata [2,3]. Together, it is likely to increase the burden on the family as well as on limited resources in developing countries.

Currently, GeneXpert is the primary diagnostic tool for TB; however, its equipment is shifted and being used for COVID-19 testing, which is seriously jeopardizingthe testing capacities for TB [4]. Moreover, the protection of health care staff involved in the TB program is a big concern, as sputum production is considered as an aerosol generating procedure [5]. Further-more, access to health care facilities is also hampered due to lockdown.This may lead to interruption of treatment and increase the possibility of drug resistance TB (DR-TB). All stakeholders should ensure that gene expert machines during the COVID-19 pandemic should be used in such a manner that there should be fractional testing for both COVID-19 and TB. Health care workers (HCW) and other personnel involved in TB care should be retrained on the importance of universal safety precautions and infection prevention control. The mechanism of the door to door drug delivery needs to be developed and strengthened in such an extent that the treatment of TB will not be hampered. The universal use of masks in COVID-19 will also help in reducing the incidence of TB, and considering the high TB burden in India, this practice should be continued in the post-COVID era too, especially in crowded areas.

We feel that lessons learned from this pandemic can be fruitfully be used for tuberculosis eradication in future.

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Pediatric Renovascular Hypertension: The Diagnostic Algorithm

Apropos of the recently published review on management of renal artery stenosis in the journal [1]. Diagnostic algorithm in the article shows that diagnosis is to be confirmed by Digital Subtraction Angiogram (DSA) even if findings are suggestive of renal artery stenosis (RAS) on computed tomograhy angiography (CTA) or magnetic resonance angiography (MRA). In this context it is prudent to note that MRA is reported to have a sensitivity of 62.5% for RAS detection with 100% specificity [2], whereas sensitivity for CTA is known to be as high as 84.2% [2]. Authors have rightly pointed out radiation risks associated with CTA and DSA. In pediatric diagnostic imaging modalities, efforts are always made to reduce the radiation exposure by using radiation reduction protocols [3,4]. DSA unarguably remains gold standard for accurate diagnosis of RAS with a sensitivity and specificity of almost 100% [2]. However, it is the most invasive of all tests, requires anesthesia and involves radiation exposure. Thus, if CTA or MRA findings are suggestive of RAS then there should not be any need for DSA for diagnosis.

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AUTHORS' REPLY

Thank you for your interest in our review article [1]. The different imaging modalities were placed in the review to provide a comparison of the various tests and the associated risks. Although an MRA and CTA have been shown to have high sensitivity and specificity alongwith high quality images, renal artery stenosis can still be missed, specifically in patients with intra-renal arterial disease. The sensitivity and specificity of MRA is not as good in small children as it is in adults. This is the reason why DSA was selected for pediatric patients with a high pre-test probability of renovascular hypertension and patients with an associated genetic syndrome (see ***Web Table* 1** [1]). We reiterate that we should suggest DSA to confirm a diagnosis of RAS, given the small vasculature within the pediatric population and its ability to guide potential timely intervention.

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Vitamin D Deficiency: Definition Matters!

We read the recently published articles on vitamin D deficiency in the journal [1,2], and wish to raise certain related issues. We believe that the true burden of vitamin D deficiency/ insufficiency and its associations cannot be estimated unless a standard consensus definition is used. At least, for the studies having important public health implications, the adherence to the "consensus definitions" is desirable, as the prevalence of the problem varies with the definition used. The cut-offs used for defining deficiency/insufficiency by Singh, et al [1] are based on a decade-old study. Almost all the current guidelines state that vitamin D3 level <12 ng/ml should be considered deficient, 12-20 ng/mL as insufficient and >20 ng/mL as sufficient [3,4]. The nutrition-based studies have shown that a level of 20 ng/mL would meet the needs of 97.5% of the population [3,4]. Singh, *et al* [1] used a cutoff of 11-32 ng/mL for defining insufficiency, which includes many babies with sufficient levels [1]. Hence, their conclusions should be interpreted carefully. It would have been helpful if the results were shown as odds ratio (Odds of having neonatal sepsis in presence of vitamin D deficiency), and the dose relationship of vitamin D levels with sepsis could be presented. It will help in better risk-stratification and will have therapeutic implications too.

Conversely, the consensus definition of neonatal sepsis is lacking until now and the definitions that are currently used in various studies vary greatly [5]. This extreme degree of variability makes the interpretation difficult. In this study [1], the criteria used for defining various categories of neonatal sepsis are extremely confusing and differ greatly from the somewhat "agreeable definition" of neonatal sepsis. We acknowledge that this variability may be due to the lack of consensus on the best definition of neonatal sepsis.

Vitamin D deficiency is reported to be quite prevalent in India, and there is a recognized need for prophylactic supplementation during infancy. However, as highlighted by a recent survey [6], the practice of prescribing routine vitamin D supplementation varies greatly. Therefore, there is an urgent need for the researchers to use a single, scientific, and consensus-based definition for defining vitamin D deficiency, so that clear evidence-base is provided for guidelines on routine vitamin D supplementation in infancy.

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AUTHORS' REPLY

We thank the readers for taking interest in our study [1]. As rightly pointed out, levels for vitamin D deficiency have been a source of contention. The International Association of Endocrinology defined a vitamin D level of 21-29 ng/mL as insufficiency and <20 ng/mL as deficiency in adults [2]. However, the levels of vitamin D insufficiency and deficiency are not clearly defined and the discussion about the prevalence of vitamin D deficiency is ongoing [3]. The cut-off levels used in our study were based on a study in neonates [4], as we did not have Indian guidelines in place at that time. IAP consensus statement on vitamin D [5] was published after we completed our study. Indian studies can now be done taking these values as guidelines for our population. Association of dose relationship of severity of vitamin D deficiency with sepsis and odds ratio will definitely provide information on risk stratification, and other researchers are encouraged to address this.

Sepsis in neonates still needs definitions that can be followed practically by neonatal centers. The definition used by us was the most practical in our setting, as it has taken clinical criteria and laboratory investigations as parameters in a scoring system for defining sepsis [6]. Non availability of micro ESR in our setup prevented us from using neonatal sepsis definitions which incorporate it in the scoring system [7].

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Using Whatsapp to Facilitate Inter-institutional Patient Transfer

Social media and messaging services like WhatsApp have found an important place in the medical field and patient care. It has been widely used for intra-institutional referral, patient awareness and medical education [1], and also for telemedicine [1,2]. However, its use in inter-institutional referrals and patient transfer is not widely documented.

Lack of a proper referral system affects patient care as many are referred to tertiary centers due to non-availability of specialized services in local hospitals. In majority of the cases the referrals are not planned, and it is not through institutional mechanisms. Hence, the patients visit the hospital on their own, and may face refusal. This causes significant delay in treatment which contributes directly to morbidity and mortality. We used WhatsApp as a medium to facilitate transfer of pediatric patients, including neonates, from pediatric department of one hospital (which does not have pediatric surgical support) to our tertiary care hospital. The WhatsApp group included the consultants and residents of the concerned department from both the hospitals. Patient details, investigations (biochemistry, hematological and radiological) are initially uploaded on the group. We assess the case on the messenger and coordinate the transfer. The patient is then transferred to us in an ambulance with an accompanying doctor. Our team saves a lot of precious time in investigating these patients as they have already been done as per our requests, and surgery is planned at the earliest based on the indication and patient condition. The total number of cases transferred since the creation of this group (June, 2019) was 182 (140 newborns and 42

older children). Surgical findings and the post-operative course of the patient is also shared with the other team, which results in their learning process. Many patients follow-up at the referring hospitals after the surgical problems have been taken care of.

There are; however, certain minor drawbacks of this system. During the initial days, some children with surgical problem were referred to our hospital and when we took consent for surgery, the parents refused. We improvised by ensuring that the referring hospital took consent for transfer and possible surgical intervention before updating patient details on Whatsapp. Another aspect which needs attention is that sensitive patient data is being shared and retained on this platform. We have devised a two-pronged solution to this problem. Firstly, keeping record of all patients physically (either analog or digital) at the referred hospital and periodically delete all archived data. Lastly, taking consent from parents, regarding sharing of their patient's details by this method for the purpose of transfer. We prefer the latter as the archived data can be used for retrieving patient details later, as was done in this study. The archived data is also a very vital tool to follow-up patients, by either of the two institutions. We suggest use of newer communication methods for ensuring adequate referral and management of patients, particularly in countries which lack an organized infrastructure to support such services.

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Rat Hepatitis E in an Immunocompromised Patient

We recently managed a teenage patient in whom rat hepatitis E virus (HEV) was detected in blood by a real-time RT-PCR assay during investigation of worsening cholestasis. The patient developed cholestasis in the course of a very complicated history of acute myeloid leukemia including relapse after failed hematopoietic system cell transplant, graft versus host disease, cytomegalovirus infection, and staphylococcal septicemia. The pediatricians had no experience in managing this infection. To aid understanding, management and counseling, we performed a PubMed search using the keywords "Rat hepatitis E" and noted only three publications describing rat HEV infection in humans [1,2]. Two of these publications were from Hong Kong and one from Canada. According to the latest epidemiological data from the Hong Kong Center for Health protection, there have been 14 confirmed cases of rat HEV in Hong Kong between the years 2017 and 2020, including the current case. Rat HEV is an under-recognized cause of hepatitis infection, which is missed by commonly performed molecular diagnostic assays for hepatitis E. Serological assays may cross-react between human and rat HEV, but have been known to miss cases of rat HEV, especially in immunocompromised persons [3]. The source of rat HEV infection in our patient is uncertain at the time of writing but screening of archived rodent samples showed that rat HEV circulates in rats in Hong Kong [3].

Viral hepatitis, including HEV is a notifiable disease in Hong Kong. Sanitation is the most important measure in prevention of hepatitis E, consisting of proper treatment and disposal of human waste, higher standards for public water supplies, improved personal hygiene procedures, sanitary food preparation and pest control [4]. Cooking meat at 71°C for five minutes kills the hepatitis E virus.

Zoonotic HEV is also a potential threat to the blood product supply [4,5]. The viral load in blood products required to cause transfusion-transmitted infection is variable. Transfusion transmission of hepatitis E virus can be screened via minipool HEV nucleic acid testing [5]. There have been no large randomized clinical trials of antiviral drugs. Oral ribavirin has been found to be an effective antiviral for chronic HEV infections in immunocompromised people [4]. Immuno-suppressive therapies should be reduced to aid clearance of HEV in these patients [4].

We wish to underscore that sanitation and handwashing are the most important measure in prevention of hepatitis E, as with many other diseases, including the currently circulating coronavirus.

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Medical Education Adjustments Amid COVID-19: UK Medical Students' Views

The coronavirus disease 2019 (COVID-19) pandemic has caused unprecedented disruptions worldwide. Medical educators have had to respond promptly to ensure future physicians' competency and training. Sahi, *et al.* [1] share their thoughts on the pandemic's implications to medical education. As UK medical students, we offer our perspective on adjustments to pre-clinical and clinical education.

Before the COVID-19 pandemic, UK pre-clinical teaching was already being digitalized through online lectures and "flipped classrooms". Indeed, students often opt for e-learning which enables content consumption at individual pace, allowing users to pause and revisit teachings. The universal popularity of Free open access medical education (FOAMed) amongst undergraduates and postgraduates also supports the shift to e-learning [2]. In addition, during the pandemic, students have innovated ways to educate peers remotely through online platforms, such as social media and Zoom [3]. Nevertheless, while remote digital education has become the new norm, we agree with the authors that there are limitations to this transition. We have lost the sense of community and camaraderie between students siting in lecture theatres together, as well as the ability to interact directly with lecturers. Problems with time-management, self-motivation, and dependence on technologies and stable broadband connection are increasing issues. Additionally, we feel that physiology practical sessions and anatomy dissection sessions have not been adequately replaced by virtual learning. Thus, further innovation is required to retain the advantages of face-to-face teaching.

Meanwhile, clinical placements, including community-based medicine for pre-clinical students and hospital placements for clinical students have been suspended in the UK since March. Although simulators, telemedicine and other technologies are possible alternatives, clinical teaching is best achieved in clinical setting [4]. Face-to-face experiential learning from patient interactions is undoubtedly irreplaceable at this point in time. Yet, before resuming clinical placements, it is crucial for educators to balance education, service, and students' safety and wellbeing. In a recent survey, two students have reported concerns for themselves as well as housemates, family members and patients over coronavirus infection and spread [5]. Therefore, whilst aiming to minimize infection risk, educators should communicate frequently with students allowing them to share their concerns, and provide support when needed.

COVID-19 has imposed significant challenges to medical education. Although troublesome, the current crisis presents a unique opportunity to accelerate evolution in medical training. Students, educators and physicians must seize the moment and innovate ways to deliver safe and high-quality care and education.

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The Psychological Effects of COVID-19 Pandemic Related Lockdown in Children

In India, varying degrees of lockdown due to coronavirus disease 2019 (COVID-19) pandemic have been enforced in most states since late March, 2020, which has extended for more than four months now. Schools across India have closed and restrictions on public movement is in effect. Most children are forced to stay indoors because of this lockdown, which has significantly disrupted their routine and reduced social contact.

This prolonged indoor stay is likely to affect their psychological well-being in many ways. Restriction of movement, inability to indulge in physical outdoor sports activities, reduced social contact with peer group, monotonous daily routine and difficulty in being engaged can have a negative bearing on the child. The childhood psychological reactions to COVID-19 pandemic can be broadly classified into internalizing problems like anxiety, depression, withdrawn state and somatic complaints and externalizing problems like irritable states, aggression, disruptive and rule breaking behavioral responses. An Italian study done among children during COVID lockdown reported an increase in externalizing tendencies like irritability, intolerance to rules, whims and excessive demands [1]. A similar Spanish study showed increase in nervousness, worry, feeling of loneliness, boredom and anger which includes both internalizing and externalizing tendencies [2]. Lockdown also impaired the quality of sleep and sleep stabilization in children [3]. Quarantined Indian children were found to experience greater psychological distress like worry, helplessness and fear [4]. On the other hand, reduction in academic pressure and more time spent with family may also contribute to reduction in stress.

Our understanding about the psychological effects of COVID-19 lockdown in children is still evolving. Most of the available data are based on unvalidated, ad hoc questionnaire-based studies with poor external validity and have to be interpreted cautiously. More studies on this aspect are needed in order to understand and prevent psychological problems in children

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Do All Children With Autoimmune Encephalitis Need Aggressive Immunotherapy?

Autoimmune encephalitis is increasingly being recognized in children in India, and the recent review was therefore timely [1]. Many centers have reported that autoimmune encephalitis as a group is more common than encephalitis caused by any single etiogical agent like virus/bacteria [2]. They usually have an acute to subacute poly-symptomatic presentation [3].

Prompt immunotherapy in time gives good neurological outcomes in most of them. As antibody testing results takes few days, many clinico-laboratory criteria have been proposed for diagnosis of early possible/probable and seronegative autoimmune encephalitis so that treatment can be started pending the results [4]. This puts the pediatrician under pressure to start immunomodulation after common infectious causes are ruled out. Which drugs to use for immunomodulation is not clear from the literature. Though many authors and guidelines advocate use of methylprednisolone pulse therapy (MP) with intravenous immunoglobulin (IVIG) as the initial modality of treatment, it is not clear whether they should be used simultaneously or sequentially [3]. If sequentially, after how many days of methylprednisolone therapy should IVIG be used is also not clear. Whether IVIG should be used in all or on the basis of clinical severity or response to MP is also unclear.

Like Guillain-Barre syndrome and many other diseases, there is a spectrum of severity of autoimmune encephalitis and all children may not need aggressive treatment with both MP and IVIG. While milder ones may be self-limiting, the mild to moderately severe ones may need just 2-3 cycles of MP and the severe ones may need more than one agent and chronic immunomodulation for longer duration. Most of the milder forms of autoimmune encephalitis may not reach the tertiary

care centers also and these cases may be missed from the series of tertiary care centers.

While working in a medical college situated in a district place, we have managed six cases of anti-NMDAR autoimmune encephalitis (antibody confirmed) with poly-symptomatic presentation in the last four years. Four of them responded to just 3-6 monthly cycles of MP while only two (presented to us more than 4 weeks after onset) had to be given either IVIG or rituximab after methylprednisolone because of lack of response to MP in one week. Most of them could not afford IVIG/ rituximab, and received only MP. They showed good clinical response. None of the children who received MP have had any relapse (duration of follow-up: 6 month-4 years).

We want to suggest that all children with anti-NMDAR antibody encephalitis do not need aggressive immunomodulation with MP, IVIG and other agents. Many of them may just respond to 3-6 doses of MP alone. However more studies including milder cases from peripheral centers are needed to generate robust evidence on this aspect.

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AUTHORS' REPLY

We thank the readers for their interest in our publication [1]. Several expert recommendations for treatment for autoimmune encephalitis are available but there is no uniform standardized approach to therapy. However, the degree of aggressiveness of therapy needed may often be clinically guided by certain prognostic factors in an individual patient. Additionally, second-line agents such as rituximab or cyclophosphamide are used when first-line agents (steroids, intravenous immunoglobulin or plasmapheresis) fail. In a cohort of 577 patients with anti-NMDAR encephalitis, of whom 211 were children, 94% underwent first-line therapy/tumor removal, and 53% improved within 4 weeks. Most patients improved with immunotherapy, with 81% living independently two years after the diagnosis [2]. In this cohort, predictors of favorable outcome (including in 177 of 211 children) were early initiation of treatment and lack of intensive care unit (ICU) admission. Hence, authorities recommend escalation to second-line therapy if there is lack of significant improvement on first-line therapy in 10-14 days in anti-NMDAR encephalitis, especially among patients admitted to the ICU [3]. However, this brisk escalation may not be warranted for other autoimmune encephalitis and clinicians may wait longer before introducing second-line therapy [4].

While steroids are definitively therapeutic in this condition, there are certain issues with their use. Often, it is difficult to differentiate infectious causes of encephalitis from autoimmune encephalitis, and steroid initiation may be delayed. Additionally, the immunological effects of steroids are much more on T-cells compared to B-cells, and since autoimmune encephalitis is antibody-mediated largely, whether steroids alone would be as effective in all cases of autoimmune encephalitis is uncertain [5].

However, as the authors note, there are no clear guidelines on how frequently to repeat steroid dosing and the dosing interval is usually dictated by severity of the disease and the response of the child to therapy, including relapses. Indeed, all children may not warrant aggressive immunotherapy and it is better to individualize treatment rather than the 'one-size-fits-all' approach.

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Online MD Pediatrics Exit Examination: A Novel Method of End Curriculum Summative Assessment Amidst the Ongoing COVID-19 Pandemic

Due to the situation arising from the ongoing coronavirus disease-19 (COVID-19) pandemic, the erstwhile Medical Council of India (MCI), in its circular of May 22, 2020, relaxed the norms for appointment of external examiners in postgraduate examination and permitted partial online examinations. We recently successfully conducted the MD Pediatrics exit examinations online, and wish to share our experience.

All theory papers, practical/clinical, objective structured clinical examinations (OSCEs), and oral/viva-voce examination were conducted in early-May, 2020 with strict observance of social distancing and other measures to prevent COVID-19 transmission. Although the theory examination (clinical vignettes based) did not pose much challenge, conducting the practical examination in compliance with the norms was an uphill task. Two external examiners were in the examination board to conduct and supervise the practical examination on the online video platform Skype. A mixed approach was followed in which both the internal examiner (physically present in the examination room) and external examiners (online) were involved in assessment by face-to-face, real-time online evaluation. Every possible effort was made to include all essential components from a traditional practical exit examination, including clinical cases, OSCEs, spot cases, and oral/viva voce examination.

Practical examination was conducted over two days under real-time video monitoring, supervision, and active participation by external examiners. Two desktop system having inbuilt camera with high speed LAN connection were setup in pediatric ward and NICU. A Skype group consisting of all examiners was created. Pre-examination meetings on skype involving all examiners were conducted wherein examination components (OSCE, spot cases, short and long cases) and strategy was discussed beforehand. The OSCEs were designed to test all six domains of the Accreditation Council for Graduate Medical Education (ACGME) [1]. On the day of examination, case presentation by examinees was done in the traditional way except that the external examiners were directing the examination process online, in real time and virtually. Assesment sheets and final marks sheet were shared and signed by e-mail. Both the external examiners provided positive feedback on the overall examination process and logistics. The overall expenses were less than one-third of the conventional physical examination method.

Computer-based online testing in a high-stakes examination of the medical curriculum is one of the best ways to test the clinical skills of an outgoing postgraduate, and in the current times of COVID-19 pandemic it seems to be a feasible option in order to meet the timeline of course completion [2]. Dearth of clinical material due to COVID-19 lockdown may be addressed by mock clinical situations, virtual case scenarios and high fidelity mannequins.

Skype, Zoom, Webex meetings, Google Meet, Team Viewer, and various other web conferencing platforms have taken over medical education through webinars and online teaching sessions during the COVID-19 pandemic, as face-to-face classes are suspended in almost all places [3]. Boeve, *et al*. [2] demonstrated a similar score of students in the computer-based examination, as compared to paper-based examination and comparable acceptance by teachers and students in the medical curriculum. The USMLE and MRCPCH examinations are being conducted using online testing methods since long.

Acceptance by examinees and examiners, appreciation of clinical findings by external examiners, need for extra software/ hardware, technical glitches, communication errors and other institutional barriers are challenges to be considered while conducting such an examination. Mock examinations, pre-examination meeting and briefing of examiners conveying case details, and support from the information technology department helped in overcoming these challenges.

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Sepsis Induced Pediatric Acute Respiratory Distress Syndrome (PARDS) – Are Biomarkers the Answer in a Resource Limited Setting?

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection that can have myriad etiologies. Amongst the organ dysfunction caused, sepsis-induced acute respiratory distress syndrome (ARDS) is a common entity that has been associated with poor patient outcomes [1]. The pathogenesis of sepsis-induced ARDS is essentially a pulmonary manifestation of systemic inflammatory response syndrome (SIRS). More than 4% of all hospitalized patients less than 18 years and an approximate 8% of patients admitted to pediatric intensive care units (PICUs) in high- income countries have sepsis [2]. Amongst the organ dysfunctions mentioned, Pediatric acute respiratory distress syndrome (PARDS) accounts for an average mortality rate of 20-30% worldwide [3], and 70% in developing countries [4]. Gupta, *et al*. [5] reported sepsis as the precipitating cause in 37% of their patients with PARDS. Another study on outcomes and predictors of mortality in ARDS [6] highlighted the importance of inflammatory biomarkers at admission to predict patient outcomes.

Owing to significant data extrapolation from adult studies in sepsis and ARDS, there is a need to have dedicated research in this specific area. It is imperative to find a therapeutic answer that may predict the onset of PARDS, thereby alerting the intensivist, and subsequently shall lead to reduced morbidity and better patient outcomes. It therefore becomes quintessential to distinguish between pulmonary and non-pulmonary infection to better understand the epidemiology of sepsis and PARDS.

The enzyme-linked immunosorbent assay (ELISA) is the gold standard for biomarker measurement of plasma proteins [7]. Owing to the heterogeneity of PARDS, literature suggests combination of clinical indices and plasma biomarkers, that include IL-6, IL-8, soluble tumor necrosis factor receptor-1 (sTNFr-1), plasminogen activator inhibitor (PAI-1), angiopoeitin-2 (Ang-2), Soluble receptor for advanced glycation end products (sRAGE) at 6 and 24 hours of diagnosis [7]. Pediatric Acute Lung Injury Consensus Conference (PALICC) guidelines from 2015 [5] advocate serial monitoring of biomarkers to predict patient outcomes, thereby bringing bench to bedside.

PARDS is under-recognized due to lack of a universally accepted definition till now and this has led to under-and over-estimation of its true prevalence. In resource-limited settings, an insight into markers-specific approach towards at risk patient population using combinations of plasma and clinical biomarkers in sepsis induced PARDS is likely to be the cornerstone of precision medicine, and eventually be the answer to the uncertainty that exists today.

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Wearing face masks do no harm

The principal mode of SARS-CoV-2 transmission involves viral entry through the respiratory tract. This generally occurs when an infected individual coughs, sneezes, or speaks, generating aerosols carrying the virus. At the onset of the pandemic, there was rudimentary knowledge about the virus, and policies were developed based on the best available evidence. Thus, guidelines regarding wearing face masks differed among countries and over time. At present, scientists are convinced that masks are paramount in reducing viral spread.

As the pandemic ravages the world relentlessly, there has been a setback in government measures to contain the virus globally. A large number of protestors have taken to the streets against the compulsory use of face masks. They have condemned mandatory mask-wearing as *"an infringement of freedom"*, *"violation of religious rights"*, or a part of a broader conspiracy that *"COVID-19 is a hoax"*. Some have proclaimed that mask-wearing engenders*"more harm than good"* due to rebreathing CO_2, with some even considering that *"masks are lethal."*

Researchers at Florida recruited 15 house-staff physicians without any pulmonary conditions and 15 patients with COPD. They monitored their $EtCO_2$ and SpO_2 throughout the time they were wearing surgical masks, and arterial blood gases before and after a 6-minute walking test with masks on. They found that gas exchange was not significantly affected by the use of masks, even in those with severe lung impairment. They feel that dyspnea experienced by some people wearing masks does not stem from hypercarbia or hypoxemia; rather, it occurs from a restriction of airflow, especially when higher ventilation is needed on exertion.

This research, although small, dispels some misconceptions surrounding the use of face masks in the context of the surging COVID-19 pandemic.
(Annals of the American Thoracic Society 2 October 2020)

Classical music improves epilepsy: The Mozart effect

Epilepsy is a common disorder, affecting approximately 0.64% of the world population, resulting in substantial neurologic, cognitive, psychological, and social consequences. Treatment frequently involves multi-drug therapy, but seizures persist in about 30% of them. Among the non-pharmacological approaches for drug-resistant epilepsy, there is an evolving interest in non-invasive forms of neurostimulation such as music therapy. A recent meta-analysis has shown that listening to Mozart's piano music can reduce the frequency of epilepsy.

The music compositions of Wolfgang Amadeus Mozart date way back to the 18th century. It was in 1993 that Francis Rauscher claimed that listening to Mozart's music improved the spatiotemporal senses of normal subjects. However, clinicians have always treated the 'Mozart Effect' with some scepticism.

More recently, two Italian researchers, Gianluca Sesso and Federico Sicca, systematically reviewed existing research works and found that listening to Mozart led to a remarkable decrease in epileptic seizures (31%–66%) and interictal epileptiform discharges. These effects occurred after a single music session and were sustained after a prolonged treatment duration. Sonatas for two pianos, K448 and K545, had an exceptionally positive effect. The researchers believe that Mozart's sonatas might have distinctive rhythmic structures specifically suited to working on epilepsy.

The highly congruous results of this meta-analysis firmly imply that Mozart's music could be an effective non-invasive method for improving clinical outcomes in epilepsy, especially in difficult-to-treat ones. Nevertheless, the exact mechanisms of the Mozart effect on the brain should be understood to use this method in clinical settings.
(European College of Neuropsychopharmacology Congress September 2020, Clinical Neurophysiology April 2020)

SARS-CoV-2 spike protein allays pain

A group of researchers based at the University of Arizona Health Sciences have reported that SARS-CoV-2 spike protein could relieve pain.

Numerous biological pathways signal the human body to perceive pain, one among which is the vascular endothelial growth factor-A (VEGF-A)/neuropilin signaling pathway. VEGF-A binds to the receptor neuropilin and kicks off a cascade of events causing neuronal hyperexcitability and resulting in pain.

Neuropilin-1 is the second receptor proposed for SARS-CoV-2 in some studies; angiotensin converting enzyme-2 being the first. The research team found that the SARS-CoV-2 spike protein binds to neuropilin at the same location as VEGF-A, thereby hindering VEGF-A from binding to it. In a series of experiments in the laboratory and in rodent models, spike protein reversed VEGF-A induced pain signaling.

This research finding could perhaps explain how SARS-CoV-2 reduces pain in some patients and stays under the radar. According to the U.S. Centers for Disease Control and Prevention, 50% of COVID-19 transmission occurs before symptom onset and 40% of infections are asymptomatic. This research also paves the way to explore a novel class of non-opioid therapeutics for pain targeting the VEGF-A/neuropilin pathway that would reduce opioid abuse.

This finding could have important implications at a time we arewaging a war against the COVID-19 pandemic and the opioid epidemic.
(PAIN 1 October 2020)

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CLIPPINGS

Theme: Infectious Diseases

SARS-CoV-2 Infection among community health workers in India before and after use of face shields (*JAMA. Published online August 17, 2020*)

As the SARS-CoV-2 pandemic progresses relentlessly, it is believed that close proximity with airborne respiratory droplets from infected persons is responsible for disease transmission. This study attempted to look at the difference in transmission if any, before and after the use of face shields.

The study was commenced on May 3, 2020 on the community health care workers of a research network at Chennai, India. They were assigned for counselling of asymptomatic family contacts of patients who had tested positive for SARS-CoV-2 at their residence. They maintained social distancing at all times and wore 3-layered surgical masks, gloves and shoe covers, and used hand rub.

Two workers became symptomatic 2 weeks later. The remaining 60 workers were tested for SARS-CoV-2 by RT-PCR. After this, the workers were provided with face shields of 250 μm thickness made of polyethylene terephthalate which were decontaminated at the end of the day. The workers were screened weekly for symptoms and RT-PCR.

Comparison between the positive test results before and after the introduction of face shields was done. After the introduction of the face shields, 50 previously uninfected workers continued to provide counselling and no worker developed symptomatic or asymptomatic infection. The face shields may have helped to decrease the ocular exposure, contamination of masks or hands and diversion of air movement from around the face. Some limitation of this study include the before- after design. Further investigation of face shields in community settings is warranted.

Height of fever and invasive bacterial infection
(*Arch Dis Child. Published Online August 20, 2020*)

This study aimed at correlating the height of fever with the occurrence of invasive bacterial infection (IBI) in infants below 60 days of age. This case-control study included infants who appeared well. The maximum temperature of these infants was measured either at home or in the ER. The cohort included infants with and without invasive bacterial infection. Interval likelihood ratios for the diagnosis of invasive bacterial infection IBI was computed at intervals of half-degree Celsius. Results showed that temperatures between 39-39.9 pC was associated with a higher likelihood of IBI. However, 30.4% of infants with IBI had lower maximal temperatures at 38.5pC. This study proved that height of temperature alone cannot be used as a risk stratification tool for IBI.

Parents' knowledge and attitudes towards the use of antibiotics in patients within the paediatric age range
(*Pediatr Oncall J. 2020;17*)

Antibiotics play a major role in the medical practice, accounting for an increasing number of prescriptions. Antibiotic resistance is a growing menace that poses a threat to the existing drugs and prompts a need to discover newer molecules. This study has attempted to analyze the knowledge and attitudes of parents towards antibiotic prescription. Respondents were parents of children below age 18 years living in urban as well as rural regions of Lisbon, Portugal (n=294). Approximately 51% understood that antibiotics were specific for treating bacterial infections, 35% thought they needed to be administered for all types of infections. While 81% acknowledged the occurrence of side effects, 31% felt they were not satisfied if antibiotics were not prescribed to them.

This study corroborates the lack of knowledge of parents in relation to the use of antibiotics. Therefore, it is important for health professionals to understand this lacuna and educate the patients, which will help in ensuring compliance of the prescribed treatment. A higher level of education and the promotion of information campaigns by the mass media could result in a greater degree of knowledge regarding antibiotic resistance and adverse effects.

Evolution and expansion of multidrug-resistant malaria in South East Asia: A genomic epidemiology study
(*Lancet. 2019;19:943-51*)

A multidrug-resistant co-lineage of *Plasmodium falciparum* malaria, named KEL1/PLA1 was found in Cambodia between 2008 -2013. This was responsible for a high rate of treatment failure with the frontline combination drugs dihydroartimesinin-piperaquine.

An epidemiology study was undertaken to analyze the whole genome sequence data samples obtained from the Malaria GEN *P. falciparum* Community Project. A large proportion of the samples were collected during the clinical studies, while other unpublished sample data was retrieved from other projects. DNA from dried spot samples were subjected to whole genome amplification before sequencing. The kelch 13 mutation is known to be associated with artemisinin resistance. Sequencing was done to align with the kelch13 amino acid positions 350 and above.

Results were analyzed from a dataset of 2465 whole parasite genome on samples collected. The study showed that the frequency of KEL1/PLA1 increased over the study period and more than half the parasites sampled in the later part of the study were KEL1/PLA1, indicating the expansion of the co-lineage. Before 2009, the KEL1/PLA1 was found only in western Cambodia, but a rapid rise was notable in north eastern Thailand and Vietnam. This study suggests that multiple KEL1/PLA1 subgroups were able to spread rapidly across borders in separate transmission waves, following the acquisition of exclusive mutations.

This is of significance as malaria incidence and mortality has been increasing since 2015, putting the global targets of malaria control at risk. The findings show an evolutionary process in action. KEL1/PLA1 can be viewed as an aggressive cell line, invading new territories and acquiring new genetic properties. Effective longitudinal genetic surveillance is crucial to support timely decisions on first line therapy. and guide elimination efforts against multi-drug resistant *P. falciparum.*

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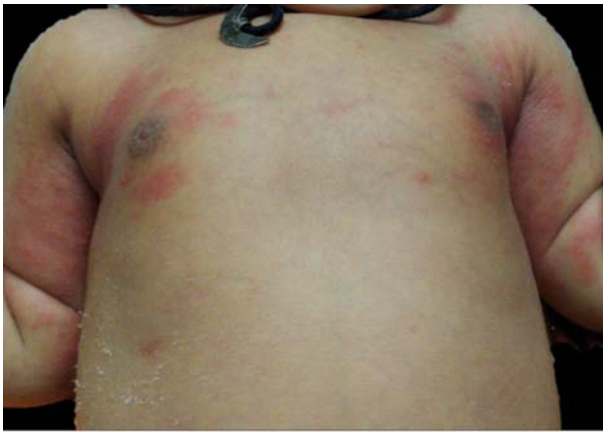
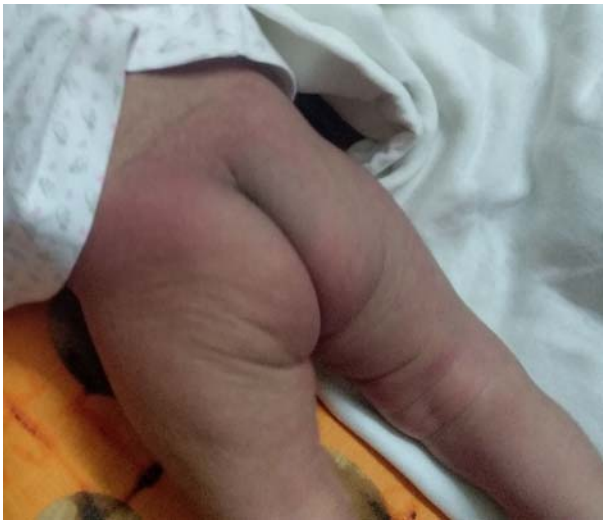
Symmetrical Drug-related Intertriginous and Flexural Exanthema

A 10-day-old neonate, on exclusive breast feeds, had acute dacrocystitis appearing on day 6 of life. The neonate was managed with topical tobramycin drops, injectable cefotaxime and amikacin for two days and then switched to oral syrup amoxicillin-clavulanic acid as the eye condition improved. Two days after starting the oral antibiotic, the neonate developed macular rash involving gluteal region and symmetric maculo-papular rash involving flexures of elbow and axilla as in ***Fig.* 1 (*a* & *b*)**. A diagnosis of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) was made, based on the typical morphology and incriminating drug history. The drug was stopped, and rash improved over the next two days. Naranjo algorithm - adverse drug reaction (ADR) probability scale score was 5, and ADR was labelled as probable.

SDRIFE, also called Baboon syndrome, is a benign, self-limiting symmetrical erythematous rash on the flexures after systemic exposure to a drug, regardless of prior sensitization. It is diagnosed by the following criteria: exposure to a systemically administered drug either for the first time or repeat exposure (excluding contact allergens), sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/peri genital area, involvement of at least one other intertriginous/flexural localization, symmetry of the affected areas and absence of systemic symptoms and signs. Among all the drugs known to cause this condition, the most common is amoxicillin, which our patient received. The other drugs known to cause SDRIFE are pseudoephedrine, codeine, cimetidine, nystatin, fluconazole, monoclonal antibodies, and radio contrast media. The differential diagnosis includes conditions like allergic contact dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), seborrheic dermatitis, intertrigo, inverse psoriasis, granular parakeratosis, Darier disease, Hailey-Hailey disease and acute generalized exanthematous pustulosis (AGEP). Prognosis of SDRIFE is generally good and the rash disappears after discontinuation of the offending drug. SDRIFE is an uncommon rash in neonates but the characteristic morphology clinches the clinical diagnosis.



(*a*)



(*b*)

Fig.1 *(a) Maculopapular rash involving flexures of elbow and axilla; (b) Macular rash in gluteal region.*

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Iron Deficiency Anaemia