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CONTENTS

PRESIDENTIAL ADDRESS

Indian Academy of Pediatrics National Conference (CIAP-PEDICON), 5th February, 2021, Mumbai—PIYUSH GUPTA 113

RESEARCH PAPERS

Dexmedetomidine vs Midazolam for Sedation in Mechanically Ventilated Children: A Randomized Controlled Trial—KRISHNA MOHAN GULLA, JHUMA SANKAR, KANA RAM JAT, SUSHIL KUMAR KABRA AND RAKESH LODHA 117

Duration of Viral Clearance in Children With SARS-CoV-2 Infection in Rajasthan, India—MANOHAR LAL GUPTA, SUNIL GOTHWAL, RAJ KUMAR GUPTA, RAM BABU SHARMA, JEETAM SINGH MEENA, PAWAN KUMAR SULANIYA, DEVESHWAR DEV AND DEEPAK KUMAR GUPTA 123

Clinical Spectrum of COVID-19 in a Mexican Pediatric Population—EDGAR BUSTOS-CORDOVA, DANIELA CASTILLO-GARCIA, MAGDALENA CERON-RODRIGUEZ AND NADIA SOLER-QUINONES 126

Congenital Lung Malformations: Experience From a Tertiary Care Center in India—KRISHNA MOHAN GULLA, MAN SINGH PARIHAR, KANA RAM JAT, SANDEEP AGARWALA, RAKESH LODHA AND SK KABRA 129

Clinico-Etiological Profile of Pediatric Syncope: A Single Center Experience—SWETA MOHANTY, C P RAVI KUMAR AND SOWMYASHREE MAYUR KAKU 134

Mumps Antibody Titer in MMR-Vaccinated and Vaccine Naïve Children at a Public Hospital in Delhi—BHOOMIKA SAXENA, VG RAMACHANDRAN, RUMPA SAHA AND DHEERAJ SHAH 137

Restrictive Threshold for the Management of Patent Ductus Arteriosus in Very Low Birth Weight Neonates—MANOJ MODI, SATISH SALUJA, ARUN SONI AND ANUP THAKUR 140

Extended-Spectrum β -Lactamase-Producing Enterobacteriaceae Causing Community-Acquired Urinary Tract Infections in Children in Colombia—JHON CAMACHO-CRUZ, JAVIER MUNOZ MARTINEZ, JULIO MAHECHA CUFINO, GERMAN CAMACHO MORENO, CAROLINA RIVERA MURILLO, MARIA ALEJANDRA SUAREZ FUENTES AND CARLOS ALBERTO CASTRO 144

Predictive Value of IAP 2015, IAP 2007 and WHO Growth Charts in Identifying Pathological Short Stature—RIDDHI PATEL, CHETANKUMAR DAVE, NEHA AGARWAL, HEMANGKUMAR MENDPARA, RISHI SHUKLA AND ANURAG BAJPAI 149

CONTENTS (*contd.*)

RECOMMENDATIONS

- Indian Academy of Pediatrics Guidelines for Pediatric Skin Care**—R MADHU, VIJAYABHASKAR CHANDRAN, V ANANDAN, K NEDUNCHELIAN, S THANGAVELU, SANTOSH T SOANS, DIGANT D SHASTRI, BAKUL JAYANT PAREKH, R REMESH KUMAR AND GV BASAVARAJA 153

SYSTEMATIC REVIEW

- Comparative Efficacy and Safety of Non-Steroidal Anti-Inflammatory Drugs in Patients With Juvenile Idiopathic Arthritis: A Systematic Review and Network Meta-analysis**
—CHUN-LIAN SHI, YU ZHANG, ZHI-YONG ZHANG, JUAN ZHOU AND XUE-MEI TANG 162

CLINICOPATHOLOGICAL CONFERENCE

- X-Linked Agammaglobulinemia With Chronic Meningoencephalitis: A Diagnostic Challenge**
—ARUSHI GAHLOT SAINI, BISHAN DASS RADOTRA, DHARMAGAT BHATTARAI, AMIT RAWAT AND VIKAS BHATIA 169

RESEARCH LETTERS

- Type 2 Diabetes Mellitus in Adolescents From Southern India – A Single Center Experience**
—UMAMAHESWARI GURUNATHAN, HEMCHAND KRISHNA PRASAD, SHERLIN WHITE, THANGAVELU SANGALALINGAM AND NEDUNCHELIAN KRISHNAMOORTHY 176

- Outcome of COVID-19 Positive Newborns Presenting to a Tertiary Care Hospital**
—BHAVYA SHAH, VAIDEHI DANDE, SUDHA RAO, SANJAY PRABHU AND MINNIE BODHANWALA 177

- Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Immunity**
—GEETA M GONVINDARAJ, U RAMYA, TP ASHRAF, REVATHI RAJ AND VINOD SCARIA 179

CLINICAL CASE LETTERS 181

CORRESPONDENCE 190

NEWS IN BRIEF 197

REVIEWERS FOR 2020 198

IMAGE 201

BOOK REVIEW 201

CLIPPINGS 133,143

ADVERTISEMENTS 106-108,111-12,116,151-52,168,190,202-206

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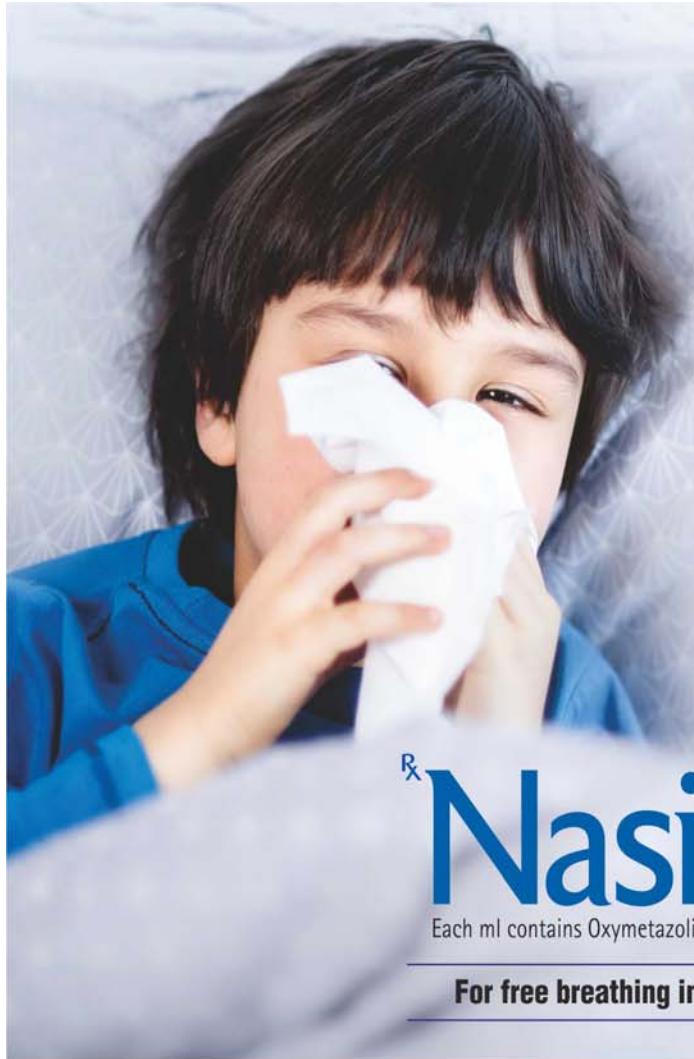
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PRESIDENTIAL ADDRESS

Indian Academy of Pediatrics National Conference (CIAP-PEDICON), 5th February, 2021, Mumbai

PIYUSH GUPTA

National President, Indian Academy of Pediatrics 2021
president@iapindia.org

Think of where we were a hundred years ago. Just out of the throes of a pandemic that infected one third of the world's population. There were no antibiotics, no ventilators, no RNA vaccines, no RT-PCR, no genome sequencing; 500 million infected and a 50 million dead in 2 years [1]. Now think of where we are today a century later. In the middle of another pandemic; 2 million dead, 100 million infected. Yet, we are not as helpless as we used to be. Mankind has produced multiple working vaccines in record time. We have industrial output to match demand of facemasks and other personal protective equipment in hundreds of million. It's been difficult and trying time for society at large. However, there is no doubt that this experience will leave us better prepared to fight the next battle. It will transform the challenges in front of and augment us as medical practitioners and custodians of the health and wellbeing of the next generation.

The pandemic taught us that it's imperative to recognize and acknowledge the problem before we can mobilize to tackle it. Until there was consensus on the unprecedented nature of Covid-19 and its imminent threat of turning into a full-blown pandemic, it was impossible to come to a global effort to contain and minimize it. Travel bans, mandatory masking, home isolation, quarantines etc were put in place only when the disease was already spreading, to be able to make a major difference.

COVID is here to stay and so are we; but as the time passes, we are gaining an edge over the virus. Indian Academy of Pediatrics salutes those pediatricians who have laid down their lives fighting it or have struggled the illness with all their might to conquer the disease. **Mission Co-Win Uday** under the action plan of the Indian Academy of Pediatrics is a small tribute to all these warriors. Initiating with a training of trainers, the sensitization module for pediatricians covers various facets of coronavirus disease among pediatricians and children, COVID-19 vaccines, and its psychosocial impact. Mission Co-Win Uday symbolizes the rising of the pediatrician and is an effort to gear them for a win in this war. More than

100 trainers are being trained in this Pedicon to start a cascade of imparting knowledge and skills on COVID-related issues nationwide, in the coming year.

PARENTS AND THE INDIAN ACADEMY OF PEDIATRICS

So when we focus on the coming, evolved era of child healthcare, we must recognize that it's a landscape we are unfamiliar with, one with increasingly complex and interdependent challenges. We must be ready for a paradigm shift from being mere healers- to feelers, friends, philosophers and guides to children as well as their parents.

Unfortunately, there is a communication gap between the Indian Academy of Pediatrics (the custodian of child health) and the parents (actual caregivers to the children). To fill this gap, Indian Academy of Pediatrics has started constructing bridges to connect the Academy and the Parents. We have been working on a unique project for developing 101 Guidelines for parents for last 6 months. I am happy to announce that the first of these Guidelines was launched on 11 January 2021. As promised, we will be releasing at least one guideline every week throughout the year. These Guidelines will be available to all on www.iapindia.org [2] and later in the form of a book. We encourage you, fellow pediatricians, to share and disseminate them widely to all your colleagues, friends, and laypersons, to reach the parents. By the end of year, we hope to have each of these 101 guidelines available in at least 15 languages of India. Every year, 50 million new parents are added to the parent cohort of India and the Indian Academy of Pediatrics has the potential to transform the lives of their children by connecting directly to them, and that is what we will strive for.

NURTURING CARE FOR EARLY CHILDHOOD DEVELOPMENT

There is a new pandemic at large eating away at us. Something that no vaccination and immunization can control- the pandemic of non-communicable diseases - diabetes, heart attack, stress, and obesity. These problems are already present in the society, now

exacerbated by the Covid-19 pandemic and the resulting lifestyle changes [3]. Keeping these in mind, the paradigm shift I mentioned, should be from cure to prevention. Instead of being there after the act, we should aim to be community leaders, anticipating these problems, and spearheading mass programs aimed at prevention, through awareness and policy making. We pediatricians must take a leaf out of our soldiers' playbook. A soldier remains active whether it is peacetime or wartime. In the latter, he fights and in the former, he builds-bunkers, barracks, deterrent capabilities, reconnaissance data- so that the enemy thinks twice about starting the war. Our mentality, with respect to the welfare of our children, should be the same. Our fight must not be limited to actual disease but prolonging and building on good health as well. For that, doctor visits for presumingly healthy children (well child visits) must increase. Pediatrician-parent interactions must go beyond illness and immunization. Well child visit concept need to be adapted and utilized for talking to parents about the junk food, screen time, sleeping hygiene, toys and plays, peer interaction, safety, security, abuse and much more.

Lancet in 2017 reported that at least 45% children under five years of age in low- and middle-income countries do not reach their optimal developmental potential [4]. For India it translates into more than 50 million children every year [5]. Most important reason is ignorance of the parents to the components of 'Nurturing Care,' especially during the first 1000 days of life i.e., from conception to 2 years, the period most crucial for neuronal connections to proliferate, activate, and mature. Any intervention during childhood extending upto 3 years of age is likely to have far reaching consequences. However, before parents, we, the community of pediatricians, need to understand the concept of **Early Childhood Development** and factors that protect the developing brain. We need to realize the importance of not only good health and good nutrition but equally important are the issues related to safety and security of the child, responsive parenting, and learning opportunities in the formative years of life. Only when we understand their importance, we can inculcate the concept of **Nurturing Care** [6] in parents.

The theme of this conference 'Nurturing care- for Early Childhood Development' will be our flagship program in 2021 and continue for next year as well. We aim to train more than 8000 pediatricians across the length and breadth of the country in spearheading the movement with a budgetary allocation of more than 4 crores. The Academy is thankful to WHO and UNICEF for co-partnership in this project and for financial aid from other donors to execute this noble cause.

CHILD AT SCHOOL

A child spends almost a third of his day in school or travelling to and from it. What they do, learn, hear, or eat there, has an immense impact on their overall development. Acknowledging the importance of school and children's behavior in it, the school has to form a big part of the pediatricians' peacetime approach to child health.

Have we not seen bus-loads of kids on the roads, walking with school bags half their body weight on their backs, their spines bent over. What purpose does it serve, other than physically tire the student before even entering the school, and psychologically make him/her associate school with a tedious, unproductive chore? In the coming year, the IAP will mount a campaign to get rid of the school bag. It will be a logistical nightmare to pull off, and it may take longer than a year to do it, but if we do, I think we will sleep better knowing that we have helped lift some unnecessary burden from our children's backs.

Another factor causing children anxiety, stress and depression is the practice of giving copious amount of homework. It is so deeply ingrained into the workloads of teachers, the routine of the student, that it seems almost impossible to think of school without homework. Yet, that need not be the case. Homework tends to elevate a 30-40 hour working week (for children, presuming 6 hours of schooling every day) into a fifty, even a 60-hour work week. Compare it with some Scandinavian countries, where the average working time for an adult is anywhere around 30-40 hours a week. It is necessary that IAP members call upon their extensive experience of research, and conduct studies to accurately assess what this excessive workload does to children's psychological health, and if it proves beneficial at all after a point. Outside the protection of labor laws, it's upto us to fight to limit the working hours thrust upon a child throughout his school life.

The school boards must also be encouraged to relook at their curriculum in order to reduce workload on students. It must leave time for them to develop extracurricular interests, and the time to pursue them. One of the most important functions of the school is to let children socialize. Time must be allotted for activities that help them work in teams and develop other social skills. The safety of children encompasses three distinct places- the home, the school, the road – and each must be dealt with differently. We are open to discussion and feedback, which is why a dedicated communication channel must be opened between IAP and the education policy makers.

Rising of the members of the Academy for health of children in this year is the focus of another flagship program launched as **Mission School Uday**. More than 100 pediatricians are being designated and trained to be the trainers for dissemination and sensitization of school children, their teachers and parents across the country to the three most important elements contributing to the epidemic of lifestyle disease in the coming generation, i.e., junk foods, screen time, and mental health issues. Canteens in most Indian schools cater towards kids with no parental supervision, where they are likely to buy and consume junk or ultra-processed foods. Canteens need to offer healthy, nutritional food in the middle of an active working day instead. We will also utilize this opportunity for interaction with school authorities and how to carry with the precautions after reopening the schools, as per IAP Guidelines released last year.

The ability to push through these reforms in schooling will be an unprecedented challenge for IAP, which is why we will need to be proactive, not waiting for government or other support. The IAP needs to make a school accreditation guideline – checklist consisting of the best school practices for children – and accredit schools based on it. Adoption of the accreditation system can be done through outreach to premier schools, convincing them that it is in the children's best interest, and making parents aware via advertisements and informative bite-sized videos.

EDUCATION, PUBLICATION AND RESEARCH

Capacity building of the pediatricians in the specialty areas has been a major focus of the IAP that is being achieved through its subspecialty chapters. Several fellowship programs are being run under the aegis of these chapters. Indian College of Pediatrics, a dream, instituted during the Golden Jubilee Year 2013, is now becoming a reality. Other than formalizing and accrediting all IAP fellowships and bringing them under a single umbrella, a hurricane of educational activities will be thrust through a Digital Center of Excellence (DCOE), under which e-lectures, e-modules, e-courses on all topics will be available not only for UG, PG, and fellowship students but for the practicing pediatricians as well.

Considering that more than 70% of the child patients are treated by private practitioners, this offer a huge opportunity for research in office practice. We hope to have a functional ethics committee this year to facilitate research in office practice. We are also going to launch a course on bioethics for the practitioners, to help them deal with the day-to-day ethical issues faced in office practice.

To foster an environment of research and publication in the Academy, we will be conducting workshops on

research methods (for practitioners), thesis writing (for PG students and supervisors), and paper writing (for younger faculty), in all the regions of the country.

A few other things that are on cards where the work has been going on for past few months include the much awaited IAP Guidelines on media use and screen time, and prevention and treatment of rickets and vitamin D deficiency.

To encourage practitioners, postgraduates, and fresh faculty, we have launched a new Journal that will be exclusively publishing case-reports. It is the first of its kind of journal from any professional society in India. *Indian Pediatrics* has taken up this additional responsibility and I am proud to release the first issue today of *Indian Pediatrics Case Reports*, very aptly shortened as **IP CaRes**. Because the Journal cares for you, the Indian Academy of Pediatrics cares for you!

TO CONCLUDE ...

Dreams are never-ending, so are our deeds, but our actions are limited by the time. To over-ride that, kick-start the process, you will always find a set of people that will carry your dream. In this speech/write-up, I have just been able to give a glimpse of what I have thought has been translated into action. With you more than 30,000 pediatricians with me, I promise that I will keep on dreaming because I know that they are ultimately going to be realized with your collective efforts and wisdom, even when I am not at the helm of affairs. The torch will continue to light the lives of millions of children for whom I dream; for whom, you dream...

Jai Hind! Jai IAP!

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**Institute of Maternal and Child Health
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Department of Pediatrics at Government Medical College, Kozhikode has been conducting the prestigious **Intensive Clinical Training Programme** for exam-going postgraduate students for the past 17 years. It has been an unprecedented success, and students from all over India attend it, and relish the academic feast. Our Department is a recognized center for DNB examinations.

This year due to the special circumstances prevailing due to COVID-19 we will be conducting the clinical case presentation and discussion on an online platform. The case discussion will be conducted from 8/3/2021 to 13/3/2021, evening 6pm to 9 pm. Two cases will be discussed every day (1.5 hours for each case). The exam oriented case discussion will be done by renowned MD/DNB examiners. The **OSCE** will be conducted as an online examination on **14/03/2021** similar to the original DNB examination. A detailed discussion on the questions will be done on the same day. Attractive cash prizes await the top scoring candidates.

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Dexmedetomidine vs Midazolam for Sedation in Mechanically Ventilated Children: A Randomized Controlled Trial

KRISHNA MOHAN GULLA, JHUMA SANKAR, KANA RAM JAT, SUSHIL KUMAR KABRA AND RAKESH LODHA

From Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr Rakesh Lodha, Professor, Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. rakesh_lodha@hotmail.com

Received: April 24, 2020; Initial review: May 15, 2020; Accepted: November 05, 2020

Background: There is a paucity of data on use of dexmedetomidine as a sedative agent in mechanically ventilated children.

Objectives: To compare the efficacy of dexmedetomidine and midazolam for sedation in mechanically ventilated children aged 1 month - 15 years. Secondary objectives were to compare the need for top-up doses of fentanyl and paralytic agents, duration of mechanical ventilation, ICU stay and hospital stay, and adverse events.

Design: Open label, non-inferiority, randomized controlled trial.

Setting: PICU of a tertiary care teaching hospital in India.

Patients: Consecutive children aged 1 month to 15 years who were mechanically ventilated.

Intervention: Children were randomized to either dexmedetomidine or midazolam and the doses were titrated to maintain target sedation score of 4 or 5 as measured by Penn State Children Hospital Sedation algorithm.

Outcome: The percentage of time spent in level 4 or 5 of Penn State Children Hospital sedation algorithm for ventilated children.

Results: 49 children were randomized (24 to 'midazolam group' and 25 to 'dexmedetomidine group'). There was no difference in the percentage of time spent in the targeted sedation between the groups [midazolam 67.3% (18.8) vs. dexmedetomidine 56.3% (28.6); $P=0.12$]. The absolute difference in the percentage of time spent was -10.9% [SE (95% CI) 7.05: (-25.15 to 3.25)]. The lower end of 95% CI for the difference breached the non-inferiority limit of -20%. Number of fentanyl boluses, duration of mechanical ventilation, ICU stay, and hospital stay were similar. Four (17.4%) children in dexmedetomidine group developed persistent bradycardia.

Conclusion: Non-inferiority of dexmedetomidine compared to midazolam for sedation in children on mechanical ventilation could not be established.

Keywords: Alpha-2 adrenoceptor agonist, Benzodiazepines, Intubation, Pediatric intensive care unit.

Trial registration: CTRI/2016/10/007347

Sedatives are required in mechanically ventilated children not only for reducing pain and anxiety, but also to allow synchronized respiratory support, and preventing accidental extubation. Commonly used agents are benzodiazepines (midazolam) and opiates (morphine/fentanyl) [1]. Dexmedetomidine, an alpha-2 adrenoceptor agonist acting on locus ceruleus and spinal cord, with insignificant respiratory depression [2] has been used as a sedative agent in children for day care procedures, non-invasive and invasive ventilation [3-5]. In adults, it has been shown that, compared to midazolam and fentanyl, dexmedetomidine reduces the duration of mechanical ventilation and length of ICU stay [6]. In children, dexmedetomidine has been reported to be an effective sedative agent without much side effects compared to benzodiazepines or opioids with the additional advantage of reducing the dose of conventional sedative agents [4,7-9]. Though use of dexmedetomidine in mechanically ventilated children has increased over last few years, there is wide variation in practice regarding the

dose and duration of the drug [10]. A recent meta-analysis has shown the superiority of dexmedetomidine over midazolam for sedation in children undergoing day care procedures [11]. However, few trials that exist, evaluating the efficacy of dexmedetomidine as a sedative agent in mechanically ventilated children, have several limitations [12-14]. Hence, we conducted this non-inferiority trial with an objective to compare dexmedetomidine with midazolam for adequacy of sedation in mechanically ventilated children.

METHODS

Mechanically ventilated children, 1 month to 15 years old, admitted in a pediatric intensive care unit of a tertiary care referral center between August, 2016 to April, 2018 were eligible. Children with catecholamine resistant shock (shock persisting despite the use of the epinephrine at the rate of >0.3 mcg/kg/min or norepinephrine at the rate of >0.3 mcg/kg/min), children already on sedative drug infusion, bradycardia, atrioventricular conduction block, primary central nervous system involvement at the

time of admission, hepatic impairment, infusion of muscle relaxants, or previous participation in this study, were excluded. Since these stringent criteria resulted in the slow recruitment of subjects, the exclusion criteria were modified after institutional ethics committee approval from December, 2017 onwards, with catecholamine-resistant shock at the time of randomization and children already receiving sedation prior to randomization, being removed from exclusion criteria list. The study was approved by institute's ethics committee and was registered prospectively in Clinical Trial Registry of India.

Based on a study in adults [15], we assumed 5% difference between the two groups with SD of 43.5% for the percentage time spent in the desired sedation level, the estimated sample size was 39 per group to be 80% sure that lower limit of one-sided 95% confidence interval would be above the non-inferiority margin of -20%.

Computer generated, block random sequence was created by a person, not a part of the study. Block size of 4 with the investigator being ignorant of the block size. Random codes were printed on a pieces of paper placed in a serially numbered, opaque sealed envelopes. Envelopes were opened by the investigator after taking informed consent from the parent/legally authorized representative of the child, who was found to be eligible for the study.

Two mL of dexmedetomidine (1 mL=100 mcg) was diluted with 48 mL of 0.9% saline to get a concentration of 4 mcg/mL. Midazolam was diluted to a concentration of 0.1 mg per mL. After randomization, midazolam bolus of 0.1 mg/kg and fentanyl bolus of 1 mcg/kg were given to both the groups prior to initiation of infusion of the drugs. Bolus dose of dexmedetomidine was not given in order to avoid bradycardia and hypotension. Starting doses of midazolam and dexmedetomidine were 1 mcg/kg/min and 0.25 mcg/kg/h, respectively. Sedation level was assessed using Penn State Children Hospital (PSCH) sedation algorithm for ventilated children [16]. The sedation targeted for primary outcome was Level 4 or 5. Level of sedation was assessed every 2 hours by the investigator or treating residents who were trained optimally regarding the appropriate application of sedation scale on mechanically ventilated children. Doses were titrated, based on the sedation score. While midazolam infusion was increased by 1 mcg/kg/min till maximum dose of 4 mcg/kg/min, dexmedetomidine infusion was increased by 0.25 mcg/kg/hr till a maximum dose of 0.75 mcg/kg/hr. The maximum infusion dose of dexmedetomidine was chosen as 0.75 mcg/kg/min to avoid side effects such as bradycardia. Fentanyl boluses

(2 mcg/kg/bolus) were administered in case of agitation and asynchronous ventilation. Infusion of drugs was continued till seven days or weaning from mechanical ventilation, whichever occurred earlier.

The number of fentanyl or vecuronium boluses received by children was recorded. Number of episodes of bradycardia (<60 bpm), hypotension (systolic blood pressure <5th centile for age) [17], duration of mechanical ventilation, ICU stay and hospital stay were recorded. The sum of the time periods of receiving continuous infusion of the sedative drug, the time periods for which the patient was monitored for sedation, the time periods in which the patient was at level of sedation 4 or 5, were calculated. Percentage of the total monitored duration of sedation, which was spent in level 4 or 5 sedation was calculated. Treatment failure was defined as self-extubation or inability to maintain desired sedation level score even after maximum doses of midazolam/dexme-detomidine infusion as decided by the treating team.

Our primary outcome was percentage of time spent in level 4 or 5 of PSCH sedation algorithm for ventilated children out of total duration of sedation monitored. Secondary outcomes were: top up doses of fentanyl and vecuronium, episodes of bradycardia/hypotension, length of mechanical ventilation, ICU stay and hospital stay. Treatment failure, hemodynamic status using vaso-active inotropic score (VIS), mortality were also compared between the groups

Statistical analyses: Data was entered into MS Excel spreadsheets, and analysis was performed using STATA ver. 13 (Stata Corp). Variables were compared by using Chi square test and Fisher exact test, as applicable. Normally distributed continuous variables were compared by applying unpaired *t* test. The mean difference in the percentage of time spent by mechanically ventilated children in level 4 or 5 of the Penn State Children Hospital sedation algorithm was compared between the two groups by Mann-Whitney test.

RESULTS

Of the 151 eligible children screened, 49 were randomized (24 in midazolam group and 25 in dexmedetomidine group) (**Fig.1**). Protocol was modified to relax strict exclusion criteria so as to improve recruitment rate. Fifteen children were enrolled after protocol modification (4 children were receiving sedative infusion, 3 had catecholamine refractory shock and 3 were receiving sedation as well as were in catecholamine refractory shock). Data were analyzed for 47 children (24 in midazolam group and 23 in dexmedetomidine group).

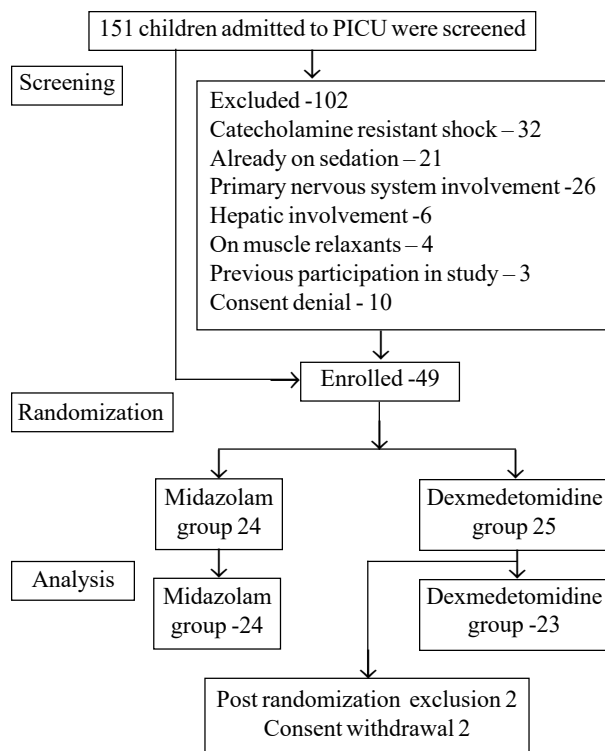


Fig. 1 Study flow chart.

Trial was stopped prior to completion of sample size due to higher rates of side effects in dexmedetomidine group and due to the time bound nature of study of 18 months.

Baseline characteristics of both the groups are shown in **Table I**. Ten (42%) children in the midazolam group and 2 (9%) in the dexmedetomidine group had congenital heart disease. In the midazolam group, 2 had underlying bronchiectasis, 2 had gastroesophageal reflux disease and one had airway malacia. In the dexmedetomidine group, 1 child each had underlying hepatic hemangio-endothelioma, congenital diaphragmatic hernia, Budd-Chiari syndrome, acute lymphoblastic leukemia, juvenile dermatomyositis, idiopathic pulmonary hemorrhage and primary immunodeficiency. Twenty-four children in midazolam group and 22 children in dexmedetomidine group received pressure controlled synchronized intermittent mandatory ventilation with pressure support

Table I Baseline Characteristics of Mechanically Ventilated Children Enrolled in the Study

Characteristics	Dexmedetomidine group (n=23)	Midazolam group (n=24)
Age (mo)	8 (3, 24)	5.5 (2.5, 11.7)
Boys, n (%)	12 (52)	12 (50)
%Predicted mortality ^a	13.5 (13.3, 27)	13.5 (13, 21)
Weight (z scores)	-2.52 (-3.61, -1.59)	-3.64 (-4.76, -2.65)
Length (z scores)	-1.84 (-2.48, -0.62)	-1.74 (-3.31, -0.87)
Admission diagnoses, n (%)		
Pneumonia	9 (39)	12 (50)
Gastrointestinal sepsis	3 (13)	1 (4)
Sepsis without focus	4 (17.5)	1 (4)
Postoperative ventilation	3 (13)	4 (17)
Others	4 (17.5)	6 (25)

Values in median (IQR) or as stated. PIM: Pediatric Index of Mortality; ^ausing PIM-2.

(PC-SIMV-PS). One child in dexmedetomidine group received high frequency oscillation ventilation (HFOV).

The dose range for midazolam was 1- 4 mcg/kg/min and for dexmedetomidine was 0.25-0.75 mcg/kg/hr. Median (IQR) duration of drug received in midazolam group was 64 (38, 135) hours and in dexmedetomidine group was 30 (14, 64) hours ($P=0.02$). Four (16.6%) children in midazolam group (16.6%) and 13 (56.5%) children in dexmedetomidine group (56.5%) had treatment failure ($P=0.005$).

The mean difference in the percentage of time spent by mechanically ventilated children in level 4 or 5 of the PSCH sedation algorithm between dexmedetomidine and midazolam groups was -10.94%. The lower end of 95% CI (confidence interval) for this difference breached the non-inferiority limit of -20% [difference= -10.94% (SE= 7.05); 95% CI: -25.15 to 3.25]. Hence, non-inferiority of dexme-detomidine as compared to midazolam could not be established (**Table II**). The secondary outcome parameters were comparable between the groups (**Table III**) While none of the children in midazolam group had bradycardia, 4 (17.4%) children in the dexmedetomidine

Table II Sedation Duration and Time Spent in PSCH Level 4 or 5 in Children Receiving Dexmedetomidine or Midazolam

Characteristics	Dexmedetomidine group (n=23)	Midazolam group (n=24)	P value
Sedation duration (h)	26 (14, 48)	53 (31, 83.5)	0.014
Time spent in level 4 or 5 of PSCH sedation algorithm (h)	20 (6, 28)	38 (20.5, 66)	0.006
Time spent in Level 4 or 5 of PSCH sedation algorithm (%) ^{ab}	56.5 (28.6)	67.3 (18.8)	-

PSCH: Penn State Children Hospital. Values in median (IQR) or ^amean (SD); ^bMean difference (95% CI)= -10.9 (-25.15 to 3.25)%.

Table III Comparison of Secondary Outcomes Between Dexmedetomidine and Midazolam Groups

Characteristics	Dexmedetomidine group (n=23)	Midazolam group (n=24)	P value
Fentanyl boluses	4 (2.2,5.7)	4 (2,6)	0.79
Adjusted boluses ^a	1 (1,3.4)	4 (1.5,6)	0.06
Vecuronium boluses	0 (0,1)	0 (0,1)	0.90
Mechanical ventilation (h)	162 (58,432)	132 (36,312)	0.90
ICU stay (d)	10.5 (4.8,20.8)	9.2 (5,15.2)	0.95
Hospital stay (d)	21 (11,33)	17.5 (13.5,37.5)	0.87

All values are in median (IQR); ^aadjusted for period of 24 hours per person sedation monitored.

group, developed persistent bradycardia (<60 bpm) necessitating withdrawal of the drug ($P=0.05$). Hemodynamic stability, assessed by vasoactive inotropic score, was not different between the groups [10 (IQR 0, 20) in midazolam group or 17.5 (IQR 0, 46) in dexmedetomidine group, $P=0.40$].

DISCUSSION

In our study, non-inferiority of dexmedetomidine compared to midazolam for desired sedation in mechanically ventilated children could not be established. Though the intended sample (36 in each group) size could not be attained due to the time bound nature of study of 18 months, wide margin of treatment failure rate in dexmedetomidine (56.5%) compared to midazolam (16.6%) group, and the adverse events such as bradycardia in dexmedetomidine group (14.4%) may not have changed even if the sample size was completed.

A study in ventilated adults [15] showed that, though the percentage time spent in the target sedation range was similar between dexmedetomidine (77.3%) and midazolam (75.1%) groups, the absolute duration of sedation was lower in dexmedetomidine group [3.5 days vs 4.1 days, $P=0.01$] like ours. Another recent trial in adults confirmed non-inferiority of dexmedetomidine when compared with midazolam with respect to the time spent in desired sedation range [18]. However, in contrast to our study, the duration of drug infusion was similar in both the groups. In our study, the median (IQR) number of fentanyl boluses received were similar in both groups, while the first reported pediatric trial that compared infusion of dexmedetomidine with midazolam in mechanically ventilated children found the number of rescue morphine boluses received in midazolam group was significantly higher [12]. The difference is perhaps due to the fact that the total duration of sedation in both

the groups was less than 24 hours in their study. In another trial in children undergoing open heart surgery, there was no difference in the need for rescue sedation between dexmedetomidine and fentanyl groups and sedation scores were comparable [13]. However, the mean duration of sedation infusion was only 13 hours, making it difficult to confirm effectiveness of dexmedetomidine infusion in providing adequate sedation in mechanically ventilated patients.

While studies in adults and pediatric population showed that sedation attained by dexmedetomidine is comparable to midazolam for mechanically ventilated population [10,12,15,18,19], our study could not establish the non-inferiority of dexmedetomidine compared to midazolam. This is likely to be due to individual patient traits, genetic polymorphisms in pharmacokinetics and pharmacodynamics [20] and a relatively conservative dexmedetomidine dose used in the study. Studies had shown that other factors like disease severity at admission was also associated with efficacy of dexmedetomidine [21,22]. Patients with lower baseline Simplified Acute Physiology Score (SAPS II) had higher clearance of dexmedetomidine [23] and those with lower Modified Acute Physiology and Chronic Health Evaluation (APACHE II) score had successful sedation with dexmedetomidine [24]. Since pharmacokinetic studies on dexmedetomidine have shown wide inter-patient variability of plasma levels [20], it is questionable whether adequate plasma levels are achieved in critically ill patients. Recent study from Japan in children less than 2 years old, on dexmedetomidine infusion (0.12-1.4 mcg/kg/hr) found that there was no correlation between plasma drug concentration and administered drug dose [25]. In our study, since majority of children were infants, possibly adequate plasma concentration of dexmedetomidine for sedation could not be attained. The trials in adults which established non-inferiority of dexmedetomidine compared to midazolam, used higher doses (>0.7 mcg/kg/h) to obtain desired sedation levels, thereby suggesting that adequate plasma levels may be attained with high doses [15,18,26]. It is possible that if a higher dose of dexmedetomidine *i.e.*, more than 0.75 mcg/kg/hr was used in our study, our results could have been different. Genetic polymorphisms in alpha-2 receptor may reduce affinity towards dexmedetomidine with resultant variation of its pharmacodynamic properties. Two important polymorphisms have been identified *i.e.*, ADRA2A*1291C/G SNP (single nucleotide polymorphism) and ADRA2A*753G. Study of ADRA2A*1291G polymorphism in 110 adult patients, who underwent coronary artery bypass graft, showed that patients carrying the G allele compared to those carrying C allele had better

WHAT IS ALREADY KNOWN

- Dexmedetomidine is shown to decrease the duration of mechanical ventilation, intensive care unit stay and sedation withdrawal, compared to midazolam in mechanically ventilated adults.

WHAT THIS STUDY ADDS

- For sedation in mechanically ventilated children, dexmedetomidine as continuous infusion, compared to midazolam, may not be as effective as seen in adults.
- Dexmedetomidine is associated with higher episodes of bradycardia compared to midazolam.

sedation [27]. Though we did not look at the genetic polymorphism of alpha-2 receptor in our study, this could be another reason for non-establishment of non-inferiority of dexmedetomidine compared to midazolam. Studies on the receptor polymorphism is lacking in Indian children.

Dexmedetomidine is known to cause hemodynamic adverse effects such as bradycardia, hypotension, and even transient hypertension in few patients [2]. Authors [15, 18] have reported between 14 and 42% of mechanically ventilated adult patients to have bradycardia in dexmedetomidine group with some requiring intervention for bradycardia. In pediatric population, incidence of bradycardia with dexmedetomidine infusion varied from 3% to 27% and majority not requiring intervention [4,8]. In our study, 4 children (17.4%) in dexmedetomidine group had persistent bradycardia (<60 bpm) which necessitated discontinuation of drug.

Strength of our study is that it is one of the few randomized controlled trials in mechanically ventilated children for sedation, especially in the Indian scenario. The limitations of the study include lack of assessment of withdrawal symptoms in either groups, targeted sample size not covered, observer bias due to the study being open label, exclusion criteria being relaxed for some children. Future studies on dexmedetomidine, with adequate sample size, for sedation in ventilated children are desirable.

Our study could not establish the non-inferiority of dexmedetomidine compared to midazolam for sedation in children on mechanical ventilation. Further studies are required to ascertain the utility of dexmedetomidine as a sedative for mechanically ventilated children.

Ethics clearance: The study was approved by Institute Ethics Committee, AIIMS, New Delhi; IEC/PG/403, dated June 29, 2016.

Contributors: KMG: design of the study, patient management, data collection, data analysis, and preparation of manuscript; JS,KRG,SKK: design of the study, patient management, reviewed manuscript; RL: design of the study, patient management and reviewed manuscript.

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I, Dr Devendra Mishra, hereby declare that the particulars given above are true to the best of my knowledge and belief.

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Duration of Viral Clearance in Children With SARS-CoV-2 Infection in Rajasthan, India

MANOHAR LAL GUPTA,¹ SUNIL GOTHWAL,¹ RAJ KUMAR GUPTA,¹ RAM BABU SHARMA,¹ JEETAM SINGH MEENA,¹ PAWAN KUMAR SULANIYA,¹ DEVESHWAR DEV¹ AND DEEPAK KUMAR GUPTA²

From Department of¹Pediatrics, SPMCH Institute, SMS Medical College, and²Centre for Data Analysis, Research and Training (CDART) Jaipur, Rajasthan, India.

Correspondence to: Prof RK Gupta,
Department of Pediatric Medicine,
SMS Medical College, Jaipur, India.
rkguptadr@hotmail.com

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Objective: To study the clinical and laboratory profile and to assess period for viral clearance in COVID 19 children. **Methods:** We reviewed hospital records of children (<18 years) admitted from 1 April to 31 May, 2020 at a tertiary-care public hospital and identified those positive for severe acute respiratory syndrome corona virus (SARS-CoV-2) by RT-PCR of respiratory secretions. **Results:** 81.2% of the 85 children studied were asymptomatic and 3 (8.5%) died. Severe lymphopenia (43.8%), raised C-reactive protein (93.8%), raised erythrocyte sedimentation rate (75%) and high (>500ng/mL) levels of D-dimer (37.5%) were common. Median (IQR) duration of viral shedding was 7 (5-10) days, with range of 2 to 45 days; 96.3% had viral clearance within 14 days. **Conclusions:** Majority of children aged <18 years with SARS-CoV-2 infection had viral clearance within 14 days.

Keywords: COVID-19, Management, Outcome, Viral shedding.

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Novel corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), has spread widely in India. Children account for 1-5% of diagnosed COVID-19 cases [1]. Clinical features, disease progression and outcome in children is milder compared to adults. To date, studies on COVID-19 in Indian children are scanty [2]. Moreover, there is limited literature over duration of viral clearance in COVID-19 children. We report profile of SARS-CoV-2 positive children and their viral clearance pattern at a public hospital in northern India.

METHODS

This study was hospital-based record review conducted in a tertiary care center attached to a government medical college. Data of all children (aged up to 18 years) positive for SARS-CoV-2 by RT-PCR of respiratory secretions (nasopharyngeal/oropharyngeal/nasal swab), admitted in COVID-19 ward of the hospital, from 1 April, 2020 to 31 May, 2020 were included in study. All children coming to COVID-19 OPD/ Influenza like illness OPD and suspected for COVID-19 according to ICMR guidelines, were tested by RT-PCR of respiratory secretions [3].

Nasopharyngeal or oropharyngeal or nasal swab was tested for SARS-CoV-2 by real time polymerase chain reaction (RT-PCR). We further tested all cases by RT-

PCR on day 0,3,6,9,12 and 14. We repeated the RT-PCR after 24 hours of first negative test, and viral clearance was considered after two consecutive negative tests. Those with inconclusive RT-PCR for SARS-CoV-2 were re-tested. We documented history, physical examination laboratory investigations, and chest X-ray from the records. Laboratory investigations included complete blood count, liver function tests, kidney function tests, inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin) and prothrombin time-international normalized ratio (PT-INR). High-resolution computed tomography chest was done in children with severe disease. Severity of illness was classified as per Dong, et al. [4] in four groups, viz. asymptomatic, uncomplicated illness, moderate disease, severe pneumonia/severe illness. All cases were treated as per institutional protocol and their clinical course was analyzed. Discharge criteria used was normal body temperature for >3 days plus two negative results on RT-PCR for SARS-CoV-2. This study was approved by the institutional ethics committee. Written consent was obtained from guardians of patients.

We took first negative RT-PCR, out of two consecutive negative tests, for deciding day of viral clearance. It was considered the number of days from symptom onset to the first negative sample defining the duration of clearance.

Statistical analyses: Data were summarized in proportions and median (IQR) was computed for viral clearance days. Chi square test was used for association between viral clearance days, age, sex and severity of disease. Results were computed using SPSS 22.0 (trial version).

RESULTS

Eighty-five eligible cases were enrolled in the study, of which 82 were discharged after fulfilling discharge criteria and three children died during the study. History of contact with COVID-19 cases could be traced in 52 children, out of which 24 (28.2%), 10 (11.8%) and 18 (21.2%) cases had contact with parents [father ($n=10$), mother ($n=9$) and both ($n=5$)], with family member other than parents (siblings and grandparents) and with COVID-19 cases other than family members, respectively. None of the children had no known medical co-morbidity.

All the three children who died had surgical comorbidities. One patient had ruptured liver abscess with peritonitis, another had multiple laryngeal papillomatosis, and the third child had been recently operated for ileal atresia.

Of the 16 (18.8%) symptomatic children, 7 (40.4%) had severe symptoms and 4 (25%, all >5 years of age) had moderate symptoms. Viral clearance distribution in terms of sex, age, and symptoms is shown in **Table I**. The median (IQR) duration of viral shedding was 7(5-10) days with range of 2 to 45 days. Almost all children (98.8%) showed viral clearance in 15 days. None of the cases presented as pediatric multisystem inflammatory syndrome (PIMS) in present study.

Among asymptomatic cases ($n=69$), we found leukocytosis ($>10,000/\text{mm}^3$) in 14.5% ($n=10$), leucopenia ($<4000/\text{mm}^3$) in 11.6% ($n=8$), lymphopenia ($<1100/\text{mm}^3$) in 29% ($n=20$), CRP $>6\text{ mg/dL}$ in 7.3% ($n=5$), and ESR $>20\text{ mm/hr}$ in 23.2% ($n=16$) cases. Among

symptomatic cases ($n=16$) we found lymphopenia in all (severe lymphopenia, ($<5\%$ of total leucocyte count) in 43.8%), leukocytosis in 37.5% ($n=6$), leucopenia in 31.3% ($n=5$), CRP $>6\text{ mg/dL}$ in 93.8% ($n=15$) and ESR $>20\text{ mm/h}$ in 75% ($n=12$) cases. D-dimer was evaluated in all symptomatic cases, and was found high ($>400\text{ ng/mL}$) in 37.5% ($n=6$) cases.

There were significant X-ray chest findings in 11 (68.8%) of symptomatic cases. Main X-ray findings were bilateral infiltrates (37.5%) and consolidation (31.3%). Computed tomography (CT) was not done as a routine for all study subjects but in three children with severe respiratory distress. All three cases showed typical multifocal, bilateral, peripheral ground glass opacities.

Three patients needed mechanical ventilation. Most of moderate to severe category patients were managed with supportive therapy, antibiotics, hydroxychloroquine and lopinavir/ritonavir as indicated. However, none of our patients received remdesivir or tocilizumab as both these drugs were not available at the time of study.

DISCUSSION

The present study shows that most SARS-CoV-2 positive children were asymptomatic and 60% of the cases had household contacts. A higher number (75.6%) of household contact was reported in a recent systematic review [5], though, others have reported majority (75%) without any known contacts [6].

Other authors have reported 9-28% asymptomatic cases in SARS-CoV-2 positive children [6-8]. Our findings differ from the description of the disease in previous studies, where the major presentation was a respiratory illness of varying severity [3-10], but are similar to findings from a recent meta-analysis [1,11]. This could be because of difference in population distribution of disease or difference in admission criteria. In contrast to above studies, we noticed cases with anosmia ($n=4$, 25% of symptomatic cases) and gastrointestinal features ($n=4$, 25% of symptomatic cases). Although anosmia has been reported frequently in adult COVID-19 cases, only few case reports were available for the pediatric population [12]. The laboratory features were similar to previous pediatric reports [13].

Chest X-ray was normal in all asymptomatic cases in our study while 19% of clinically asymptomatic children had radiological abnormalities in a recent meta-analysis [14]. In a recent systematic review, Kumar, et al. [14] reported bilateral ground glass opacities in 40% of symptomatic cases; we found similar findings in the three cases that underwent a CT scan. Death rate in our study was higher than reported previously from China (2.3%) and

Table I Trend of Viral Clearance in Children With SARS-CoV-2 Infection (N=85)

Patient characteristics	Viral clearance period		
	<7d ($n=43$)	8-14 d ($n=36$)	>14d ($n=3$)
Age, y			
Upto 1 y ($n=7$)	2 (28.6)	5 (71.4)	-
1 to <5 y ($n=15$)	6 (40.0)	8 (53.3)	1 (6.7)
5-10 y ($n=31$)	19 (61.3)	11 (35.5)	1 (3.2)
>10 y ($n=29$)	16 (55.2)	12 (41.4)	1 (3.5)
Male sex	32 (66.7)	14 (29.2)	2 (4.1)
Asymptomatic ^a	37 (54.4)	30 (44.1)	1 (1.5)

P > 0.05 for all comparisons except^a *P* = 0.007 for comparison of duration of viral clearance among symptomatic and asymptomatic children. All values in no. (%).

WHAT THIS STUDY ADDS?

- Median duration for 50% viral clearance was 7 days, and almost all patients had viral clearance within 14 days.
- Symptomatic cases required significantly longer time for viral clearance.

lesser than reported by WHO (4.4%) and from Italy (7.2%) [15-16]. A study from Italy showed a higher proportion (16% of admitted) of COVID-19 children needing ICU care [17], though the admission criteria were different.

Xu, et al. [18] found a median (IQR) duration of 15 (11.7-18) days for viral clearance in 85 adults [18]. We did not find any relation of age, sex, and symptoms to viral clearance of SARS-CoV-2, similar to previous studies [19]. However, we could not document the relationship of viral load and viral clearance as we did not measure the viral load.

Our study shows that majority of children with SARS-CoV-2 infection were asymptomatic, and viral clearance was seen in majority within 14 days. This data needs supplementation from other centers, but will be useful for deciding on further infection control and quarantine guidelines, especially after school re-opening.

Ethics clearance: Institutional ethics committee of SMS Medical College; No. 423/MC/2020 dated 27 June, 2020.

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Clinical Spectrum of COVID-19 in a Mexican Pediatric Population

EDGAR BUSTOS-CORDOVA, DANIELA CASTILLO-GARCIA, MAGDALENA CERON-RODRIGUEZ AND NADIA SOLER-QUINONES

From Emergency Department, Hospital Infantil de México Federico Gómez, Mexico.

Correspondence to: Dr Daniela Castillo-García, 162 Doctor Marquez Street, Col Doctores, Mexico City, Postal Code 06400, dracastillogarcia@gmail.com
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Objective: To describe the broader clinical spectrum of COVID-19 in children. **Methods:** In this descriptive, prospective study, we included confirmed pediatric patients with COVID-19 who presented to the emergency department of a pediatric tertiary care center from April to July, 2020. All patients were confirmed by the SARS-CoV-2 RT-PCR test, and we analyzed 24 symptoms and 25 signs. **Results:** Among the 50 patients with COVID-19, the most common symptoms were fever, excessive cry and dry cough; digestive symptoms were frequently found (24%). The most common signs were pharyngeal erythema and irritability. **Conclusion:** Clinicians should recognize that the clinical spectrum of COVID-19 in children is wider than previously described, often with nonspecific signs and symptoms, and digestive symptoms should raise suspicion.

Keywords: Diagnosis, Gastrointestinal symptoms, Presentation, SARS-CoV-2.

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The incidence of coronavirus disease (COVID-19) in Mexico began to escalate rapidly in April, 2020. By August 7, 12,052 cases of COVID-19 in children were confirmed in Mexico, with 188 deaths [1]. From the beginning of the COVID-19 pandemic, it has become evident that the spectrum of manifestations in children is different from those seen in adults. However, most of the clinical descriptions have been made from retrospective studies addressing a narrow number of manifestations. A meta-analysis [2] and a systematic review [3] evaluated fewer than ten signs and symptoms. The aim of this study was to describe a broader clinical spectrum of COVID-19 in children.

METHODS

We conducted a prospective study in the emergency department of a pediatric tertiary care center from April to July, 2020. We included patients <18 years of age, with a history in the week before inclusion of at least one of the following criteria: a) one respiratory symptom, b) one gastrointestinal symptom or c) fever and recent exposure to a confirmed COVID-19 case. Patients with tracheostomy, severe neurologic underlying conditions, use of sedatives in the last week or children not accompanied by the primary caretaker were excluded. All cases were tested with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swabs. For the patients who met the inclusion criteria, we looked for 24

symptoms present prior to evaluation at the emergency department and 25 signs at the physical exploration, and the information was gathered by attending physicians. Gastrointestinal symptoms were defined as the presence of diarrhea, vomiting, nausea or abdominal pain. We defined pneumonia as the presence of one of the following: increased work of breathing or oximetry <93%.

We analyzed the data from the COVID-19 confirmed patients; the information was analyzed using case counting and descriptive statistics, and calculating median (range), quartiles and percentages. To describe the chronology of the appearance of symptoms, we performed diagrams for each patient. A horizontal line represents the time (days) before admission. Time zero represents the day of onset of the first symptom. The time of appearance of each symptom was placed over the line.

RESULTS

A total of 92 children were evaluated. Fifty children (54%) were diagnosed with COVID-19 infection by a positive SARS-CoV-2 RT-PCR test. Since chronic patients may have different clinical manifestations, they were described separately from previously healthy patients.

Twenty-six patients (52%) with confirmed COVID-19 infection had a previous chronic medical condition. The most common condition was cancer (16%), followed by chronic lung disease (12%), obesity (8%), chronic kidney disease (6%) and neurological disorders (4%). Three patients had more than one chronic condition.

From the evaluated symptoms, 35 children presented with fever (70%), 36% excessive crying and dry cough; and 4% had hyposmia (**Table I**). Digestive symptoms were common; 24% of the patients presented only gastrointestinal symptoms. All patients without any respiratory or gastrointestinal symptoms were immunocompromised.

From the evaluated signs, 30 children presented pharyngeal erythema (60%), 24 with irritability (24%) and 10 with rhinorrhea and conjunctival hyperemia (20%) (**Table I**). The first symptom to appear was fever in 36% and cough in 12%, followed by fatigue, rhinitis, and excessive crying each in 8% of the patients. Manifestations intentionally sought but not found in any patient were expectoration, mucopurulent rhinorrhea, posterior nasal discharge, mucopurulent conjunctival discharge, and epistaxis. Manifestations intentionally sought that were found in only one patient were nasal mucosa edema, rhonchi, cyanosis, lymphadenopathy, grunting, and wheezing.

Analyzing the diagrams of the symptom appearance chronology, we defined three different patterns: Pattern A or almost asymptomatic: with only one or two symptoms; Pattern S or sudden: onset of $4 \geq$ symptoms in the first 24-36 hours; and Pattern D or disperse: sequential onset of symptoms over several days. The patterns were distributed in an irregular form in both groups; nonetheless, considering only the patients with pneumonia, the S pattern was found in seven of nine of the chronically ill patients, in two of eight immunocompromised patients, in four of the five patients with chronic lung disease and in three of four obese patients (**Table II**).

The rate of admission was significantly higher in chronically ill (61.5%) versus healthy individuals (31.7%); however, 7 of the 27 chronically ill individuals were admitted for previous disease decompensation. Of the 8 immunocompromised patients, two developed pneumonia. Four of the five patients with obesity also developed pneumonia.

All patients with pneumonia, except one, were admitted. Only one patient developed Kawasaki-like syndrome. Two patients required mechanical ventilation: one of them was a patient with cystic fibrosis, and the other was a kidney transplant patient who later died.

DISCUSSION

The clinical suspicion of SARS-CoV-2 infection in children has been a challenge for physicians worldwide. Many case series have been published; however, most of them are retrospective and collect few clinical features. A broader description of the disease is of paramount importance for the clinical suspicion of SARS-CoV-2

Table I Signs and Symptoms among 50 Pediatric Patients with confirmed COVID-19

<i>Symptoms^a</i>	<i>No. (%)</i>	<i>Signs</i>	<i>No. (%)</i>
Time of symptom onset ^b	72 (33-144)	Pharyngeal erythema	30 (60)
Fever	35 (70)	Irritability	12 (24)
Excessive crying	18 (36)	Rhinorrhea	10 (20)
Dry Cough	18 (36)	Conjunctival hyperemia	10 (20)
Rhinitis	13 (26)	Respiratory distress	6 (12)
Sore throat	12 (24)	Dehydration	6 (12)
Headache	11 (22)	Crackles	4 (8)
Abdominal pain	11 (22)	Fever	4 (8)
Conjunctival hyperemia	11 (22)	Rash	3 (6)
Vomiting	11 (22)	Diminished breath sounds	3 (6)
Diarrhea	11 (22)	Rhonchi	2 (4)
Shortness of breath	10 (20)	Nasal mucosa edema	2 (4)
Fatigue	9 (18)	Dysphonic	2 (4)
Hyporexia	9 (18)	Hyperemia of pillars	2 (4)
Myalgia	7 (14)	Somnolence	2 (4)
Dysgeusia	4 (8)	<i>Type of symptoms</i>	
Arthralgia	4 (8)	Only respiratory	25 (50)
Productive cough	4 (8)	Only gastrointestinal	12 (24)
Rash	4 (8)	Both	10 (20)
Hoarseness	5 (5)	Without any of them	3 (6)

^aHyposmia and cyanosis-2 children each; excessive daytime sleepiness in 3. ^bMedian (IQR) time from admission to onset of first symptom.

Table II Demographic and Clinical Characteristics, of Pediatric Patients With COVID-19 in Mexico (N=50)

<i>Characteristics</i>	<i>Chronic medical illness (n=26)</i>	<i>Previously healthy (n=24)</i>	<i>Total</i>
Age, ^a mo	108 (26-153)	18 (7.25-99.5)	56.6 (13-159)
Boys	20 (76.9)	15 (62.5)	35 (70)
Immunosuppression	8 (30.8)	0 (0)	8 (16)
Pneumonia	8 (30.8)	10 (41.7)	18 (36)
Admitted	16 (61.5)	9 (37.5)	25 (50)
Past antibiotic treatment	7 (26.9)	4 (16.7)	15 (30)
Past symptomatic treatment	19 (73.1)	16 (66.7)	35 (70)
<i>Clinical patterns</i>			
Pattern A	4 (15.4)	7 (29.1)	11 (22)
Pattern S	12 (50)	9 (37.6)	21 (42)
Pattern D	8 (30.8)	10 (38.8)	18 (36)

Values in no. (%) or ^amedian (IQR); Clinical patterns of disease: A: almost asymptomatic; S (sudden); D (disperse).

WHAT THIS STUDY ADDS?

- The clinical spectrum of COVID-19 in children is wider than previously described.
- Digestive symptoms and other symptoms like loss of taste or sensation should raise suspicion.

infection in children. Although our study included a limited number of patients, it explored a wider clinical spectrum in a heterogeneous population of pediatric patients.

The testing capacity for SARS-CoV-2 in Mexico is limited and reserved for patients who meet the national epidemiological definition. Many children with symptoms consistent with COVID-19 in the community are not tested and consequently not diagnosed. Our inclusion criteria allowed us to analyze patients who otherwise would not have been tested. These results may serve to reconsider epidemiological definitions for children with suspected COVID-19.

It is important to highlight that this study captured data from children who were seen or managed within a tertiary health-care institution; one-half of the patients had a chronic medical condition. Consequently, the study population is likely to primarily represent individuals with the more severe end of the disease spectrum. Statistical differences between the two groups were not calculated since the research was designed as a case series description, the sample was small, and there was a wide difference in age between both groups.

Adult patients with digestive symptoms without respiratory symptoms are rare [4], while in children it seems to be more frequent. Our results suggest that SARS-CoV-2 infection often presents with nonspecific signs and symptoms, and digestive symptoms, even in the absence of respiratory symptoms, should raise suspicion. Loss of taste and smell in adults has been reported in up to half of patients [5] and proposed as an important discriminatory symptom. Chemosensory dysfunction in children is seldom reported [6], but our results suggest that both hyposmia and dysgeusia are not so rare.

Pneumonia in patients with COVID-19 has been reported in up to 64.9% of children with COVID-19 using radiologic criteria [7], but it is rarely reported using clinical criteria. We found one-third of patients with pulmonary infection, exploring only clinical features. The recognition of different clinical patterns of COVID-19 may help us recognize patients with a higher risk of poor outcomes. Our results suggest that the 'S' or sudden pattern is associated with pneumonia in patients with underlying chronic conditions. Additionally, as shown in young adults [8], obesity appears to be an important risk

factor for poor outcomes (pulmonary involvement) in children with COVID-19.

Clinicians should recognize that the clinical spectrum of COVID-19 in children is wider than previously described and different from the adult presentation; often with nonspecific signs and symptoms, digestive symptoms should increase clinical awareness. The order of appearance of symptoms (clinical pattern) requires more investigations, as our results suggest that it could predict outcomes.

Ethics Clearance: Institutional ethics committee of Hospital Infantil de México Federico Gómez; No. HIM-AE-004-2020, dated September 14, 2020.

Contributors: EB: conceptualized the study design; EB,DC,NS,MC: recruited patients, collected demographic and clinical data. EB,DC: analyzed and interpreted the results; EB: wrote the manuscript in Spanish; NS,DC: translated the manuscript; DC,NS,MC,EB: commented on and revised the manuscript. All authors approved the final report.

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Supplementary Table 1 Signs and Symptoms among 50 Pediatric Patients with confirmed COVID-19

<i>Symptoms</i>	<i>Chronic medical illness (n=26)</i>	<i>Previously healthy (n=24)</i>	<i>Total (n=50)</i>	<i>Signs</i>	<i>Chronic medical illness (n=26)</i>	<i>Previously healthy (n=24)</i>	<i>Total (n=50)</i>
Time of onset of symptom ^a	72 (24-102)	72 (36-204)	72 (33-144)	Pharyngeal erythema	14 (53.8)	16 (66.7)	30 (60)
Fever	20 (76.9)	15 (62.5)	35 (70)	Irritability	5 (23.1)	7 (29.2)	12 (24)
Excessive crying	7 (26.9)	11 (45.8)	18 (36)	Rhinorrhea	5 (19.2)	5 (20.8)	10 (20)
Dry Cough	10 (38.5)	8 (33.3)	18 (36)	Conjunctival hyperemia	5 (19.2)	5 (20.8)	10 (20)
Rhinitis	6 (23.1)	7 (29.2)	13 (26)	Respiratory distress	3 (11.5)	3 (12.5)	6 (12)
Sore throat	6 (23.1)	6 (25)	12 (24)	Dehydration	4 (15.4)	2 (8.3)	6 (12)
Headache	7 (26.9)	4 (15.7)	11 (22)	Crepitations	2 (7.7)	2 (8.3)	4 (8)
Abdominal pain	6 (23.1)	5 (20.8)	11 (22)	Fever	2 (7.7)	2 (8.3)	4 (8)
Conjunctival hyperemia	4 (15.4)	7 (29.3)	11 (22)	Rash	0	3 (12.5)	3 (6)
Vomiting,	8 (30.8)	3 (12.5)	11 (22)	Diminished breath sounds	2 (7.7)	1 (4.2)	3 (6)
Diarrhea	5 (19.2)	6 (25)	11 (22)	Rhonchi	1 (3.8)	1 (4.2)	2 (4)
Shortness of breath	5 (19.2)	5 (20.8)	10 (20)	Nasal mucosa edema	2 (7.7)	0 (0)	2 (4)
Fatigue	5 (19.2)	4 (16.7)	9 (18)	Dysphonia	0	2 (8.3)	2 (4)
Hyporexia	6 (23.1)	3 (12.5)	9 (18)	Hyperemia of pillars	1 (3.8)	1 (4.2)	2 (4)
Myalgia	5 (19.2)	2 (8.3)	7 (14)	Somnolence	2 (7.7)	0	2 (4)
Dysgeusia	3 (11.5)	1 (4.2)	4 (8)				
Arthralgia	2 (7.7)	2 (8.3)	4 (8)				
Productive cough	3 (11.5)	1 (4.2)	4 (8)	<i>Type of symptoms</i>			
Rash	1 (3.8)	3 (12.5)	4 (8)	Only respiratory	16 (61)	9 (37.5)	25 (50)
Hoarseness	2 (7.7)	3 (12.5)	5 (5)	Only gastrointestinal	5 (19.2)	7 (29.1)	12 (24)
Excessive daytime sleepiness	3 (11.5)	0 (0)	3 (6)	Both	8 (30.7)	2 (8.3)	10 (20)
Hyposmia	1 (3.8)	1 (4.2)	2 (4)	Without any of them	3 (11.5)	0 (0)	3 (6)
Cyanosis	1 (3.8)	1 (4.2)	2 (4)				

All values in no.(%). ^aMedian (IQR) time from admission to onset of first symptom.

Congenital Lung Malformations: Experience From a Tertiary Care Center in India

KRISHNA MOHAN GULLA¹, MAN SINGH PARIHAR¹, KANA RAM JAT¹, SANDEEP AGARWALA², RAKESH LODHA¹ AND SK KABRA¹

From Department of¹Pediatrics and²Pediatric Surgery, All India Institute of Medical Sciences, New Delhi, India.

Correspondence to: Dr Rakesh Lodha, Professor, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India.
rakesh_lodha@hotmail.com
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Background: There are limited data on congenital lung malformations (CLM) and their clinical course from developing countries. **Methods:** A 10-year retrospective chart review of records of children with CLM attending pediatric chest clinic at an Indian tertiary care center was conducted. **Results:** Among the 48 children (24 boys) included in the review, the malformations included congenital lung hypoplasia/agenesis in 24 (50%), cystic pulmonary airway malformation in 9 (19%), bronchogenic/foregut cyst in 8 (18%), and congenital lobar emphysema in 4 (9%). Median (IQR) age at symptom onset and diagnosis were 1.5 (0.4,9.5) and 24 (3,62) months, respectively. Median (IQR) weight for age for age z-score at presentation was -2.4 (-1.4,-3.4). More than a third (37.5%) children underwent surgical removal of resectable lesions at median (IQR) age of 14 (6,42) months. 14 (27%) children had associated congenital heart disease. Median duration of follow-up was 13 months. In children with lung hypoplasia, median (IQR) number of hospitalizations in follow-up were significantly less than that prior to diagnosis 0 (0,0) vs 1(0,2) ($P=0.001$). Median (IQR) numbers of hospitalizations in follow up were significantly less than that of prior to surgical resection 0 (0,0) vs 1(1,1) ($P=0.016$) in children with CPAM. **Conclusion:** Lung hypoplasia was the most common congenital lung malformation in our setup. Detection of malformation during antenatal period was poor. Age of diagnosis and surgical intervention is often delayed. Regular follow up and definitive and/or supportive management decreased the morbidity.

Keywords: Bronchogenic cyst, Congenital lobar emphysema, Lung hypoplasia, Lung agenesis.

Congenital lung malformation (CLM) is a broad term which includes lung developmental disorders such as cystic pulmonary airway malformation (CPAM), bronchogenic cysts, pulmonary sequestration (PS), congenital large hyperlucent lobe and bronchial atresia [1]. They are rare diseases of childhood with cumulative incidence of 30–42 cases per 100,000 individuals [2]. The true prevalence of congenital lung malformations in developing countries is underestimated with data being limited to case reports and case series [3-5]. The clinical course of congenital lung malformations is largely unknown from the Indian subcontinent because of lack of antenatal diagnosis, lack of awareness among clinicians and misdiagnosis as pulmonary infections. Hence, authors share their experience with CLMs over a decade, from pediatric pulmonology service in a tertiary care center from India.

METHODS

In this retrospective chart review, records of children with CLM, attending the pediatric chest clinic of a tertiary care center in India, from 2009 to 2019, were evaluated.

Congenital lung malformations had been diagnosed based on clinical features, chest X-ray (CXR), Contrast enhanced computed tomography (CECT) of chest, and histopathology, if resection was done. Information on demographic profile, anthropometry, respiratory system symptoms, chest imaging, spirometry, hospitalizations, treatment, timing of surgical intervention, associated reactive airway disease and follow-up including final outcome was retrieved. Data regarding echocardiography, barium swallow, nuclear scan or bronchoscopy, wherever available, were also noted. Those who did not attend our clinic after first visit were considered as lost to follow-up. These children were contacted telephonically and any missing data were obtained. This study included the CLMs, namely, congenital small lung (agenesis, aplasia and hypoplasia) and congenital thoracic malformations (CPAM), sequestration, bronchogenic cyst, foregut cyst) [7]. We excluded congenital airway malformations and congenital diaphragmatic hernia. Congenital small lung was diagnosed based on clinical signs of volume loss on particular side, CECT chest showing low lung volume with ipsilateral small pulmonary

artery and bronchial hypoplasia/aplasia if bronchoscopy was performed. Differential diagnoses considered were lung collapse secondary to impacted mucous plug/foreign body or external airway compression. Bronchogenic cyst was diagnosed based on clinical signs, smooth bordered spherical mass, associated vertebral abnormalities on CECT chest and histopathology after surgical resection. Differential diagnoses for cystic lesions considered were lung abscess, hydatid cyst, fungal disease, tuberculosis, infected bullae, vascular malformations and neoplasm based on the clinical symptoms and investigations. Congenital lobar emphysema (CLE) was diagnosed based on signs of hyper-inflation of particular lobe after exclusion of intraluminal/extra luminal compression by CECT chest or bronchoscopy. Differential diagnoses for CLE considered were pneumothorax, foreign body bronchus/external compression of bronchus causing ball-valve mechanism leading to air entrapment. CPAM was diagnosed on solid/cystic mass lesion on CECT and later histopathology. Differential diagnoses for CPAM considered were necrotizing pneumonia, sequestration, congenital diaphragmatic hernia, and peripherally located bronchogenic cyst [7]. Institute ethics committee approved the study protocol with waiver of consent.

Statistical analyses: Data were entered in MS Excel and analyzed using STATA ver.12 (Stata Corp). Significance of difference among various groups were compared using Student t-test (uniformly distributed continuous data), Mann-Whitney test (skewed data) or Chi square test or Fisher exact test (for categorical data) as applicable. Statistical significance was set at P value of <0.05 .

RESULTS

Sixty-three children with congenital lung malformations were registered during study period and 48 case records could be retrieved. Major malformations were congenital lung hypoplasia 24 (50%), cystic pulmonary airway malformation 9 (19%), bronchogenic/foregut cyst 8 (17%) and congenital lobar emphysema 4 (8%). Baseline characteristics of enrolled children are shown in **Table I**.

The children with congenital small lung included right hypoplasia ($n=6$), right agenesis ($n=5$), left hypoplasia ($n=9$), left aplasia ($n=2$), and left agenesis ($n=2$). Of these, 3 children (13%) were treated as tuberculosis at other medical centers, prior to diagnosis, 7 (29%) were receiving cotrimoxazole prophylaxis and 17 (71%) children were advised pneumococcal and annual influenza vaccines. Two children with congenital small lung underwent pneumonectomy for repeated infections and associated lung sequestration, respectively. One child with right lung hypoplasia had systemic blood supply to the lung, which was coil embolized electively. None of

the children with congenital small lung were on home oxygen. Thirteen children with congenital small lung underwent echocardiography and findings included dextrocardia-3, ventricular septal defect-2, tetralogy of fallot-1, atrial septal defect-2, patent ductus arteriosus-2, patent foramen ovale-1, pulmonary arterial hypertension-1 and normal echocardiography-2. One child had horse-shoe lung. Median (IQR) number of hospitalizations during follow-up over 19 months were significantly less than that prior to diagnosis 0 (0,0) vs 1 (0,2) ($P=0.001$). Median (IQR) weight z score at diagnosis were than at follow-up [-2.4 (-3.4, -2.4) vs -1.7 (-2.6, -0.18), $P=0.13$].

Four children had bronchogenic cysts and another four had foregut duplication cysts. The hospitalization rate in follow up had significantly reduced from that prior to cyst removal, 0.5 (0,1) vs 4 (2,6) ($P=0.02$), respectively. Two children were treated as tuberculosis prior to referral. One of four children with foregut duplication cyst had features suggestive of gastric mucosa on nuclear scintigraphy study.

Table I Baseline Characteristics of Enrolled Patients (N=48)

Characteristics	Value
Type of malformation, n (%)	
Congenital lung hypoplasia/aplasia/agenesis	24 (50)
Cystic pulmonary airway malformation	9 (19)
Congenital lobar emphysema	4 (8)
Bronchogenic/foregut duplication cyst	8 (17)
Sequestration	1 (2)
Scimitar syndrome	1 (2)
Pulmonary AV malformation	1 (2)
Antenatal diagnosis, n (%)	1 (2)
Age of onset of symptoms (mo) ^a	1.5 (0.4,9.5)
Age of diagnosis (mo)	24 (3,62)
Weight at presentation, z score ($n=47$) ^a	-2.4 (-1.4,-3.4)
Male gender, n (%)	24 (50)
No. of hospitalizations per child prior to diagnosis for respiratory symptoms ($n=47$)	2 (0,3)
Operated/surgical resection done, n (%)	18 (37.5)
Age at surgical resection ($n=18$) (mo)	14 (6,42)
Lost to follow up, n (%)	9 (18.8)
Duration of follow-up (mo)	13 (1, 30)
Associated cardiac disease, n (%)	14 (27)
Treated as tuberculosis, n (%) ^b	5 (10)

^aData in median (IQR); ^bprior to diagnosis of malformation.

There were 9 children with CPAM (left lower lobe-3, right lower lobe-2, right upper lobe-2, left upper lobe-2). Median (IQR) number of hospitalizations before and after surgical resection were 1(1,1) vs 0(0,0), respectively ($P=0.016$).

Right lower lobe pulmonary arteriovenous malformation was diagnosed in a child, 60 months old, who underwent coil embolization 2 months later. Another child with Scimitar syndrome, underwent right lung pneumo-nectomy at 4 months of age. **Table II** depicts demography, clinical features and outcomes of major congenital lung malformations. All children presenting with CLM were symptomatic with almost half of them having associated reactive airway disease, receiving inhaled corticosteroids and 10% being treated as tuberculosis.

Barium swallow report was available for 18 children. Gastro esophageal reflux was seen in 1 child with right

lung hypoplasia, esophageal compression in 2 children with bronchogenic cyst and scimitar syndrome, respectively, while 15 children had normal study. Of the 14 children who underwent flexible bronchoscopy, 13 with suspected congenital small lung showed hypoplasia/aplasia/absent bronchus. Bronchoscopy had done in a child with CPAM revealed normal anatomy.

DISCUSSION

In our center, lung hypoplasia was found to be the most common CLM, followed by cystic pulmonary airway malformation (19%), bronchogenic/foregut duplication cysts (17%), and congenital lobar emphysema (8%). Around 60% of non-lung hypoplasia CLMs were operated at a median age of 14 months. Lung hypoplasia was the most common CLM to be associated with congenital heart disease. Almost half of children had concurrent reactive airway disease. Hospitalization rate for respiratory problems were significantly decreased

Table II Demography, Clinical Features and Outcomes of Major Congenital Lung Malformations

Characteristics	Lung hypoplasia (n=24)	CPAM (n=9)	CLE (n=4)	Bronchogenic cyst/foregut cyst (n=8)
Antenatal diagnosis, n (%)	0	1 (11)	0	0
Laterality, n (%)				
Left	14 (58)	5 (55)	3 (75)	0
Right	10 (42)	4 (45)	1 (25)	2 (25)
Midline	—	—	—	6 (75)
Age of symptoms onset (mo)*	2 (1,12)	1.5 (0.5,4)	0.5 (0.05,5)	2.5 (0.15,15)
Age of diagnosis (mo)*	24 (3,84)	30 (2,60)	6 (2,8)	19.5 (2.5,36.5)
Weight at diagnosis (z score)*	-2.47 (-3.45,-1.72)	-1.6 (-2.7,-1.0)	-2 (-3.6,-0.52)	-2.69 (-3.33,-1.43)
Weight at last visit (z score)*	-1.71 (-2.6,-0.18)	-0.2 (-1.52,-0.11)	-1.24 (-3.7,-0.72) ^b	-2.27 (-4.14,-1.61) ^c
No. of hospitalizations prior to diagnosis ^a	1 (0,2)	1 (1,1)	1.5 (0.5,6)	3 (2,6)
Age at surgical resection ^a	—	6 (5,42)	8.5 (7,10)	23.5 (10,32)
Duration of follow up (mo) ^a	19 (1,39)	9 (0.75,18.5)	1.5 (0,6.5)	17 (2,25)
Associated malformations, n (%)				
Cardiac	9 (37.5)	0	1 (25)	0
Non-cardiac	1 (4)	0	0	0
Predominant symptoms at presentation, n (%)				
Cough	19 (79)	8 (89)	4 (100)	8 (100)
Fast breathing	19 (79)	5 (55)	3 (75)	6 (75)
Recurrent fever	12 (50)	3 (33)	1 (25)	4 (50)
Hemoptysis	2 (8)	0	0	4 (50)
Noisy breathing	0	0	1 (25)	3 (38)
Chest pain	4 (16)	2 (22)	0	2 (25)
Treated as recurrent pneumonia	8 (33)	2 (22)	0	5 (62)
Associated hyper-reactive airway disease	13 (54)	3 (33)	1 (25)	5 (62)

^aValues are median (IQR); ^bn=3; ^cn=6. CPAM - cystic pulmonary airway malformation, CLE-congenital lobar emphysema.

WHAT THIS STUDY ADD?

- The most common congenital lung malformation was pulmonary hypoplasia/aplasia.
- Age of diagnosis and surgical intervention is often delayed due to lack of awareness.

after diagnosis and supportive management or surgical resection, whichever was applicable.

The high proportion of lung hypoplasia among all lung malformations may be due to referral bias for surgical intervention to pediatric surgery clinic. Lung hypoplasia is known to be associated with other lung malformations such as cystic adenoid malformations, congenital diaphragmatic hernia, pleural effusions etc. [4,5]. In our cohort, one each had associated horse-shoe lung and intralobar sequestration, respectively. Though hemoptysis is rarely reported in lung hypoplasia/agenesis [6], 2 children in our cohort had hemoptysis, with one of them requiring coil embolization for the same. The significant decline in hospitalization rate post enrolment in our clinic, was attributed to regular follow up, nutritional and immunization counseling, regular cotrimoxazole prophylaxis and vaccination against pneumococcus and influenza in addition to routine vaccination,

Unlike reports from other parts of the world, where CPAM was reported as the most common lung malformation [7-9], this pattern was not seen in our cohort, probably due to referral bias. The median age of diagnosis of CLM and its surgical intervention was relatively higher (24 months) in our cohort, compared to other reports [7,9-12] thus revealing the low awareness level among clinicians regarding CLMs. Further, in contrast to those cohorts [9,11], not a single child was asymptomatic at the time of presentation to our centre, highlighting the poor antenatal screening programs for lung malformations. Similar to previous reports [8,12], majority of children had associated hyper-reactive airway disease in our cohort. Our data shows that nearly 10% of the children were being treated empirically as pulmonary tuberculosis, prior to referral, underscoring the fact that persistent imaging abnormalities are often misdiagnosed in endemic countries.

The strength of this study is in its data from large numbers of children, along with a reasonable follow-up, unlike previously published data from India. Further the study brings out the limitations in diagnosing, treating and follow up of such children in lower middle income countries. The limitations of the study is its retrospective design, substantial loss to follow up (18%), non-availability of data on pulmonary function tests and absence of assessment of chest wall deformities.

Lung hypoplasia was the most common congenital lung malformation referred to a tertiary care pediatric pulmonology centre with almost none having been detected in the antenatal period. Age of diagnosis and surgical intervention was often delayed. Reactive airway disease was the most common associated respiratory morbidity. Further studies regarding follow-up of such children are required, from developing countries.

Ethics clearance: Institute Ethics Committee; Ref No. IEC-770/08.11.2019; RP- 10/2019, dated 27 November, 2019

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CLIPPINGS

Mutations disrupting neurogenetic genes confer risk for cerebral palsy (*Nature Genetics.* 2020;52:1046-56).

Cerebral Palsy (CP) is a neurodevelopmental disorder with multifactorial etiology including environmental and genetic factors. Previous studies have predicted deleterious CNVs in 10-31% cases of CP, however, insufficient availability of controls, limits the statistical inferences. In this study, whole exome sequencing (WES) was performed on 250 CP families from US, Australia and China. Within the 250 family cohort, 157 (62.8%) were classified as idiopathic, 84 cases (33.6%) had a known environmental insult and the remaining 9 trios (3.6%) were not able to be assigned to either category (unclassified). Control trios consisting of 1,789 unaffected siblings of autism cases and their unaffected parents were analyzed in parallel. WES was performed for 250 parent offspring trio which showed enrichment of damaging de-novo mutations. Eight genes had multiple damaging de novo mutations; of these, 2 met genome-wide significance (*TUB1A* and *CTNBN1*). Also, two novel monogenic etiologies were identified (*FBXO31* and *RHOB*). Candidate CP risk genes overlapped with neurodevelopmental disorder genes. It was estimated that 14% of cases could be attributed to an excess of damaging de novo or recessive variants.

The authors inferred that genomic variants should be considered alongside environmental insults when assessing the etiology of an individual's CP. Also, over time, mechanistic insights derived from the identification of core pathways via genomic studies of CP may help guide therapeutic development efforts.

Autism Spectrum Disorder may be linked to impaired production of myelin (*Nature Neuroscience.* 2020;23:375-85)

Research has revealed some mechanistic underpinnings of syndromic forms of autism spectrum disorder. A study at John Hopkins University performed transcriptomic analyses of seven independent mouse models covering three syndromic forms of ASD i.e. five models of Pitt Hopkins syndrome (PTHS) (a syndromic form of ASD caused by autosomal dominant mutations in the transcription factor 4 (TCF4) gene and characterized by intellectual disability, failure to acquire language, deficits in motor learning, hyperventilation, gastrointestinal abnormalities), 1 model of PTEN mutation and 1 model of *Mecp2* mutation. Then, they assessed dysregulated genes (DEGs) and their pathways in human post mortem brain from individuals with ASD and neurotypical controls. The PTHS mouse models showed cell-autonomous reductions in oligodendrocytes (OL) numbers and myelination, functionally confirming OL transcriptional signatures. Significant enrichment of overlapping DEGs and common myelination associated pathways were found in human idiopathic ASD post mortem brain also. Importantly, DEGs from syndromic ASD mouse models, and reduced deconvoluted OL numbers, differentiated human idiopathic ASD cases from controls. These results implicate disruptions in OL biology as a cellular mechanism in ASD pathology and opens a future prospect to tap therapeutic opportunity throughout the life span.

ARPITA GUPTA
arpita1517@gmail.com

Clinico-Etiological Profile of Pediatric Syncope: A Single Center Experience

SWETA MOHANTY,¹ C P RAVI KUMAR² AND SOWMYASHREE MAYUR KAKU³

From Department of ¹Pediatric Cardiology, ²Neurology, and ³Clinical Neurosciences and Child and Adolescent Psychiatry, Aster CMI Hospital, Bengaluru, Karnataka, India.

Correspondence to: Dr Sweta Mohanty, Valmark Apas, Bangalore 560 076, Karnataka, India. doctorsweta@yahoo.com
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Objective: To describe the clinical profile of children with syncope. **Methods:** Hospital records were reviewed for clinical and laboratory details of children presenting with real or apparent syncope. Five diagnostic categories were identified: neurocardiogenic syncope (NCS), psychogenic pseudosyncope (PPS), cardiac, neurological and indeterminate. **Results:** 30 children (aged 4 to 17 years) were included. The commonest cause of syncope was NCS (63.3%), followed by PPS (13.3%), cardiac (10%), neurological (10%) and indeterminate (3.3%). Exercise, loud noise or emotional triggers and family history were associated with cardiac etiology, and electrocardiogram (ECG) was diagnostic in the majority. Children with PPS and cardiac syncope had frequent episodes when compared with other groups. Indiscriminate antiepileptic use was found in 5 children, including two cardiac cases. **Conclusion:** Frequent recurrences of syncope may suggest PPS or cardiac cause. Cardiac etiology may be readily identified on history and ECG alone.

Keywords: Neurocardiogenic syncope, Psychogenic pseudosyncope, Head-up tilt table test, Management.

Syncope is defined as a transient loss of consciousness due to transient global cerebral hypo-perfusion, and is characterized by rapid onset, short duration and spontaneous complete recovery [1]. Syncope is commonest in adolescent age group with a peak in incidence between 15 to 19 years [2].

Various classification systems broadly categorize syncope as neurocardiogenic (NCS), cardiac, neurologic, or psychogenic pseudosyncope (PPS) [2], the commonest cause being benign NCS [2,3]. Although cardiac causes of syncope are rare, they can be potentially life-threatening [4]. Even a benign syncopal event can generate extreme anxiety. As a result, syncope evaluation often leads to a battery of expensive low-yield tests [4].

We performed this study to document common etiologies and identify clinical features that may assist in differentiating between various diagnostic categories.

METHODS

We reviewed records of patients aged 1 to 18 years presenting to our center with syncope, over a 14-month period from January, 2019 to February, 2020. Outpatient visits as well as inpatient hospitalizations of the first presentations were included. For the purpose of this study, syncope was defined as a sudden and transient (<2 hours) loss of consciousness and postural tone, with spontaneous recovery [5,6]. Children with dizziness

without loss of consciousness were excluded. Those with clinical presentation of seizure, focal neurological deficit or established causes of pathological syncope like cardiac disorder or trauma were excluded. The electronic medical records were retrospectively reviewed for demographic and clinical data and results of electrocardiography (ECG) or any additional testing.

Patients were classified into five diagnostic categories [1,2] viz., neurocardiogenic syncope (NCS), cardiac syncope, psychogenic pseudosyncope (PPS), neurological disorder and indeterminate cause. NCS was diagnosed by typical history, such as precipitating factors or prodromal symptoms, with supportive evidence on orthostatic vital testing or Head-up tilt table (HUTT) test in some cases. A confirmatory diagnosis of cardiac syncope was made based on ECG abnormalities and supplemental tests such as exercise stress test or 24-hour ECG monitoring (Holter). All cases of neurological disorder had abnormal electroencephalogram (EEG) with or without abnormal neuroimaging findings. Syncope was classified as indeterminate in absence of a clearly definable cause for an objective clinical manifestation. A diagnosis of PPS was made after the exclusion of other causes, and evaluation by a child psychiatrist.

Our pediatric syncope team follows a standardized clinical assessment and management plan to evaluate syncope patients. A standard 12-lead ECG is done in all

patients. Orthostatic vital sign testing in the clinic is considered positive when there is a drop in systolic blood pressure of greater than 20 mm Hg [7] or a rise in heart rate of more than 40 beats per minute on standing for 3 minutes [4]. Standard views for echocardiograms and standardized protocols for HUTT[8] and exercise stress testing[9] are followed. Holter monitoring consists of digital recording over 24 hours, analyzed using Digitrack (GE) software system with manual reviewing of all data. Psychological evaluation is done by the child psychiatrist, as indicated.

RESULTS

A total of 30 patients, aged 4 to 17 years, presented with syncope. Seven of these patients required hospitalization; the remaining were evaluated and managed on outpatient basis. Of the 30 patients, 19 (63.3%) were diagnosed to have NCS, 4 (13.3%) had PPS, 3 (10%) had a cardiac cause, 3 (10%) had a neurological cause and 1 (3.3%) was of indeterminate etiology. Two patients with NCS had convulsive syncope, where tonic clonic movements were observed following the loss of consciousness (EEG was normal in both).

Sixteen (53.3%) children had a history of recurrent episodes of syncope. All cases of PPS presented with multiple episodes in a week, with complete disappearance during hospital observation. Postural changes (15, 84%) or accompanying acute febrile illnesses (6, 31%) were the predominant precipitating factors for NCS (**Table I**). Exercise was precipitating event for a child with NCS, but syncope in this case was post-exertional (occurring a minute after cessation of exercise). Only two (10.5%) patients of NCS had a positive orthostatic exam.

Web Table I shows the investigations performed with their diagnostic yield. ECG was performed in all children and revealed a cardiac diagnosis in three children (long QT syndrome, 2; sinus node dysfunction, 1). One child with sinus node dysfunction had significant bradycardia on holter monitoring and required electrophysiology referral. EEG confirmed a diagnosis of idiopathic epilepsy in three patients, all of whom were started on antiepileptic medications. Lastly, a child with syncope following epistaxis, with similar parental history, was classified as indeterminate, after baseline investigations, including holter monitoring, revealed no abnormality.

All children with NCS were reassured, advised to increase fluid and salt intake and advised behavioral modifications on experiencing prodromal symptoms. The two siblings with long QT syndrome were started on beta-blockers and showed no recurrence on follow up at 3 months. For children with PPS, underlying stressors were

Table I Demographic Features and Precipitating Events in Different Etiological Categories of Pediatric Syncope (N=30)

	Cardiac (n=3)	NCS (n=19)	PPS (n=4)	Neurologic (n=3)
Age (y) ^a	13.7 (1.1)	10.3 (3.5)	12.5 (1.7)	10 (2.6)
Females	1	9	1	2
Recurrent syncope	2	8	4	2
Family history	2	0	0	0
Precipitating event				
Exercise	2	1	0	0
Loud noise/emotion	1	0	0	0
Postural factors	1	15	3	2
Fever/acute illness	0	6	0	0
Accompanying symptoms				
Nausea/sweating	0	3	0	1
Palpitation/chest pain	1	0	1	0
Headache	1	2	3	2
Visual change	0	2	2	0
Injury during fall	0	2	1	0
Urination	0	0	0	1
Vomiting on awakening	1	3	0	1

NCS: Neurocardiogenic syncope; PPS: Psychogenic pseudosyncope; Values in numbers except ^amean (SD).

identified, and two cases required psychotropic medications. Unindicated antiepileptic medications were being administered in five patients, with recurrent episodes (including children with cardiac syncope), and were discontinued.

DISCUSSION

In this retrospective study, the commonest diagnosis in children presenting with syncope was neurocardiogenic, followed by psychogenic pseudosyncope. Specific features on history that suggested a cardiac etiology, as reported previously [1,10], included syncope associated with exercise, loud noise or fright, and syncope preceded by chest pain or palpitations in the absence of prodromal symptoms.

The frequency of episodes tends to be significantly higher in cardiac causes as compared to non-cardiac [11], with the exception of PPS. In a patient with unusual loss of consciousness occurring multiple times per day, unrelated to posture, with varying presentations, or with events lasting longer than 3 minutes, conversion disorder should be considered [7].

ECG is an essential component of evaluation of all children who present with syncope [5] and clinched the

WHAT THIS STUDY ADDS?

- Detailed history of precipitating factors and accompanying symptoms and a baseline electrocardiogram helps identify the cause of syncope in most cases.

diagnosis for the cardiac cases in this cohort. Echocardiogram was found to be non-contributory, as also reported earlier [12]. HUTT is useful to differentiate NCS from PPS by the reproduction of symptoms during tilt testing in the absence of haemodynamic abnormalities in the latter [13]. However, as HUTT is time-consuming and not without risk [7], we selectively advised the test only when it was expected to bring about a change in management. EEG may be helpful in differentiating convulsive syncope, wherein extremity jerking usually occurs after loss of consciousness, from myoclonic jerks. It is common for syncope to be misdiagnosed and erroneously treated as an epileptic condition [14].

This study has the limitation of being a retrospective study, with a small sample size. However, our findings underscore that a detailed history is of paramount importance in making the diagnosis in syncope, and cases of syncope need an ECG to rule out potentially life-threatening cardiac causes.

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Web Table I Diagnostic Tests Obtained in Evaluation of Syncopal Episodes (N=30)

<i>Name of test</i>	<i>Obtained in n (%)</i>	<i>Indication (n)</i>	<i>Abnormal result, n (%)</i>	<i>Assisted in management, n(%)</i>
ECG	30 (100)	All cases of syncope (30)	3 (10)	3 (10)
HUTT	5 (17)	Parental anxiety in suspected NCS (3) Suspected PPS (1)		
		Suspected POTS (1)	2 (40)	4 (80)
Echo-cardiography	16 (53)	ECG abnormality (2) Past cardiac surgery (1) Injury during syncope (1) Required CPR (1) Parental anxiety (11)	0	0
Holter	6 (20)	Suspected LQTS (1) Sinus node dysfunction (1) Concerning family history (1) Frequent episodes in suspected PPS (2) Injury during syncope (1)	1 (17)	4 (66)
TMT	1 (3)	Suspected LQTS (1)	1 (100)	1 (100)
Genetic test	1 (3)	Suspected LQTS (1)	1 (100)	1 (100)
EEG	13 (43)	Suspected seizure (2) Unconfirmed diagnosis (11)	3 (23)	3 (23)
Neuro-imaging	7 (23)	Suspected seizure (1) At outside hospital (6)	1 (14)	1 (14)

HUTT: Head-up Tilt Table test; NCS: Neurocardiogenic syncope; PPS: Psychogenic pseudosyncope; POTS: Postural orthostatic tachycardia syndrome; Echo: Echocardiogram; CPR: Cardiopulmonary resuscitation; LQTS: Long QT syndrome; TMT: Treadmill exercise test.

Mumps Antibody Titer in MMR-Vaccinated and Vaccine Naïve Children at a Public Hospital in Delhi

BHOOMIKA SAXENA,¹ VG RAMACHANDRAN,¹ RUMPA SAHA¹ AND DHEERAJ SHAH²

From Department of¹Microbiology and²Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India.

Correspondence to:

Dr Bhoomika Saxena,

105, Gaytri Nilaya, 12th B Main Road,

6th Block, Rajajinagar,

Bengaluru 560 010, Karnataka, India.

bhoomika286@gmail.com

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Objective: To compare the mumps antibody titers in Measles-Mumps-Rubella (MMR)-vaccinated and vaccine naïve children. **Methods:** This cross-sectional study was conducted at a tertiary-care public hospital in Delhi from November, 2016 to April, 2018 among 78 healthy children (aged 16 month-12 years) attending the pediatric outpatient department. Serum IgG and IgM rubella antibodies were measured by ELISA for confirmation of MMR vaccination status. Qualitative determination of IgG mumps was done followed by quantitative determination in samples positive for IgG mumps antibodies. **Results:** IgG mumps was present in 69.2% of study population, with seroprotective titers in 32% taking endpoint titer as 1:4. Among MMR vaccinated children, 41.1% were sero-protected and in MMR vaccine naïve children 9.1% were seroprotected for mumps. **Conclusion:** Single dose of MMR vaccine does not provide effective (>90%) sero-conversion required for successful herd immunity to prevent mumps outbreak.

Keywords: Immunization, Measles, Rubella, Seroprotection.

Mumps is a vaccine preventable viral respiratory illness mainly in pediatric age group. Epididymo-orchitis is the most common complication and meningo-encephalitis is most common cause of mortality in mumps [1]. Sporadic outbreaks of mumps are reported from India and other countries indicating resurgence of disease in both vaccinated and unvaccinated population. Outbreaks in vaccinated young adults indicate waning of immunity with time. Outbreaks in India have been reported from various states [2-5]. Integrated Disease Surveillance Programme data shows 475, 124, 92 and 447 cases from year 2015-18 [6].

In India, MMR vaccine is a part of State immunization program of Delhi, Goa, Puducherry and Sikkim, administered as a single dose at 15-18 months [7]. National Technical Advisory Group on Immunization in June 2014, in view of India's commitment to eliminate Measles by 2020, recommended Measles-Rubella (MR) vaccine in National immunization program (NIP).

The Indian Academy of Pediatrics, on the other hand, recommended continuation of MMR vaccine in India as mumps is still an important vaccine preventable disease [8]. Considering the paucity of data regarding seroprotectiveness in children against mumps, this study aims at comparing level of mumps specific antibodies in MMR

vaccinated and vaccine naïve healthy children.

METHODS

This cross-sectional study was conducted at the departments of Microbiology and Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital from November, 2016 to April, 2018. Inclusion criterion was healthy children aged 16 months to 12 years attending hospital as outpatients. Children with chronic infection and acute febrile illness were excluded. The study was approved by the institutional ethics committee. Informed and written consent was obtained from parents/guardians of participating subjects, and assent obtained from children above seven years of age. Confidentiality was ensured by coding questionnaire and samples before data entry and analysis.

Blood samples were collected from healthy children attending pediatric OPD for routine checkup. Forty of the participants have received MMR vaccine and 38 were unvaccinated with MMR vaccine. The participant's details and history was noted in a case record form, which included age, MMR vaccination status, number of doses of MMR received, demographic details, past history of clinical mumps, history of exposure to any clinical mumps case in the past, maternal rubella history and antenatal history of mother. Vaccination history was

documented on basis the of immunization card. Data on history of rubella could not be collected as it was not recalled accurately by the family member.

All blood samples were centrifuged at 3000 RPM for 15 min and serum was extracted and stored at -20°C for further use. The samples were first subjected to IgG rubella ELISA test (Calbiotech Inc.) to confirm MMR vaccination status. To rule out any chance of recent vaccination, IgG rubella negative samples were also tested for IgM rubella (Calbiotech Inc). Samples were then subjected to IgG mumps ELISA test (Immunolab). The tests were performed and interpreted as per manufacturer's instructions. Due to resource constraints, only samples showing high optical density (2.0-3.5) were subjected to quantitative IgG Mumps ELISA for antibody titer calculation by standard reference graph plot method. Eleven samples were serially diluted from 1:5 to 1:40 and 15 samples were diluted from 1:2 to 1:8. End point titer was noted for each sample by extrapolation from standard graph obtained and antibody level was calculated for the undiluted and diluted samples showing optical density above cut off value as per kit instructions. Samples with OD in the grey zone were considered negative for statistical evaluation.

Statistical analyses: Data of subjects were categorized into two groups viz. MMR vaccinated and MMR-unvaccinated. Only children who tested positive for either IgG or IgM Rubella were considered as MMR vaccinated. Based on previous studies that correlated results of MuV PRNT and ELISA, end point titer of ≥ 4 was considered as sero-protective for mumps [9]. Chi-square test was used to find out *P* value between vaccination status and IgG Mumps antibody presence. Fischer's exact test was used to compare significance between vaccination status and sero-protective antibody titer. *P* value less than 0.05 was considered as significant.

RESULTS

Fifty-six of total 78 samples i.e., 71.7% (95% CI: 0.61, 0.81) were positive for IgG rubella and were designated as MMR vaccinated. Mean (SD) age of vaccinated children was 6.7 (3) years. Eighteen of the 78 samples were negative for IgG rubella, and four samples gave indeterminate results and were considered as negative test result. Mean age of unvaccinated children was 5.6 (2.6) years. None of the sample tested positive for IgM rubella.

Fifty four of total 78 samples [69.2% (95% CI: 0.58-0.78%)] were positive for IgG mumps antibody. Among MMR-vaccinated children, 45 (80.3%) had concurrent antibodies against both mumps and rubella. The mean age

of these children was 6.8 (3) years. End point titre of ≥ 4 , indicating sero-protection against mumps was seen in 41.1 % (95% CI: 0.29, 0.58), children, with mean (SD) age of was 7.3 (2.9) years. Nine samples showed qualitative presence of IgG mumps antibody even in the absence of IgG rubella Ab; only two had seroprotective levels. Correlation between IgG mumps antibody presence and seroprotection was insignificant ($P=0.46$).

DISCUSSION

In this study, 32.5% of total study population (41.1% of vaccinated and 9.1% of unvaccinated children) were found to be seroprotected for mumps. Low rate of seroprotection among MMR vaccinated children can be attributed to failure of development of immunity with a single dose of vaccine or failure of vaccine uptake. Rate of subclinical infection and atypical presentation in mumps are known to be very high. In a country like India, diagnosis is mainly clinical and laboratory confirmation is not routinely requested. Thus, seroconversion may arise as a result of clinical or subclinical infection as well as successful vaccination regardless of laboratory confirmation of the etiology. Sudden shift in age group of mumps affection from 5-9 years to 19-20 years made the Advisory Committee on Immunisation Practices (ACIP) to include a second dose of mumps vaccine at the age of 4 to 6 years [10]. Some of the countries are considering an adult third dose at 15-19 years of age as recent outbreaks are in this age group [11].

Host factors like immunological dysfunction, chronic diseases impacting the immune system, though rare are significant causes of vaccine failure. It may be pointed out that, of the 18 subjects who were seronegative for rubella, some could be due to primary or secondary vaccine failure. Moreover, indeterminate IgG rubella results for four subjects could be a consequence of waning IgG levels over time to levels below the threshold of the detection system.

There were limitations to our study including a small sample size whose results cannot be generalized to the entire population. Date of vaccination and time of blood sampling post vaccination could not be recorded for all participants as most of the participants did not carry vaccination card with them. MMR vaccination confirmation was done only by the presence of IgG or IgM Rubella estimation. Lastly, end point serial dilution was not done for all the samples seropositive for IgG mumps antibodies. Antigen used in ELISA was whole cell virus and not HN protein, which is the target against for neutralizing antibody production [12]. Thus, the antibodies detected in our study may not necessarily confer protection even with high end point dilution titers.

WHAT THIS STUDY ADDS?

- A large proportion of single dose recipients of MMR vaccine do not develop seroprotective titers against mumps.

Further, apparently seroprotective levels of mumps antibodies may also possibly arise due to antigenic cross-reactivity among paramyxoviruses.

Results of this study matches with previous reports that a single dose is not sufficient to prevent clinical mumps and natural immunity in Indian children is not sufficient to offer protection upon exposure [13]. In view of these results, decision of GOI and NTAGI on replacing MMR with MR vaccine may require reconsideration. Removing Mumps vaccine from states with <70% of MMR vaccine coverage can lead to potential outbreaks in future. Additionally poor efficacy in vaccinated individuals causes a rightward shift in epidemiology, resulting in affliction of older age group children and young adults. This phenomenon changes the epidemiology and also increases clinical severity of disease.

Blanket withdrawal of mumps component of MMR should not be a decision without a strong backup of long term epidemiological data. In a developing country like ours, with complex urban-rural divide and a varied spectrum of economic and social status with very variable healthcare access in different regions, a one-time decision to withdraw a vaccine can at best be an interim measure, which should be accompanied by regular sentinel surveillance of the status of protection of potentially vulnerable population.

Ethics clearance: Institutional Ethics Committee, UCMS; No. IEC-HR/130/18.10.2016 dated November 25, 2016.

Contributors: BS: Investigator, writing - original draft, review and editing; VGR: conceptualization and methodology; RS: project administration; DS: resources and supervision.

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Restrictive Threshold for the Management of Patent Ductus Arteriosus in Very Low Birth Weight Neonates

MANOJ MODI, SATISH SALUJA, ARUN SONI AND ANUP THAKUR

From Department of Neonatology, Sir Ganga Ram Hospital, New Delhi, India.

Correspondence to: Dr Manoj Modi,
Department of Neonatology,
Sir Ganga Ram Hospital, New Delhi,
India. drmanojmodi@gmail.com
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Objectives: To compare outcomes of very low birth weight (VLBW) neonates before and after the change in practice for treatment of PDA. **Methods:** Medical records of VLBW neonates were reviewed. Neonates were categorized in two groups: Period I (January, 2012 to July, 2015) and Period II (August, 2015 to December, 2016). The primary outcome of study was composite outcome of death or broncho-pulmonary dysplasia (BPD). **Results:** The composite outcome (Death/BPD) was comparable in two groups; adjusted OR (95% CI) 1.1 (0.6, 1.9). Mortality and severe BPD were also comparable. The pharmacological treatment for PDA was required in 8.4% vs 2.6% of VLBW neonates during Period I and II, respectively ($P=0.03$). Durations of invasive and noninvasive ventilation were comparable during two periods. **Conclusion:** Restrictive threshold for management of PDA in VLBW neonates may not be associated with increase in morbidities or mortality and possibly would reduce need for pharmacological treatment or surgical ligation.

Keywords: Indomethacin, Paracetamol, Ligation, Outcome.

A hemodynamically significant patent ductus arteriosus (PDA) in preterm neonates is considered a risk factor for mortality, and morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) [1]. A causal relationship between PDA and these adverse outcomes; however, has not been established [2,3]. Traditionally, therapeutic closure of hemodynamically significant PDA (hsPDA) in preterm neonates is considered based on certain clinical and echocardiographic criteria [4]. However, there is no unanimity regarding definition of hsPDA and guidelines for its management. Systematic reviews have not observed a significant reduction in respiratory morbidities or mortality with early inter-vention [5]. Moreover, both pharmacological treatment or surgical ligation for PDA could be associated with adverse effects on multiple organ systems [6,7].

Recent observational studies suggest that PDA closes spontaneously in most preterm neonates, and use of a conservative approach for its management does not result in an increase in morbidity or mortality [8-10]. With this background, we changed our unit practice in July, 2015, and adopted more restrictive guidelines for therapeutic closure for PDA in preterm neonates. We planned this study with an objective to compare outcomes of very low birth weight (VLBW) neonates before and after the change

in practice for treatment of PDA.

METHODS

Medical records of all VLBW neonates admitted to neonatal intensive care unit, Sir Ganga Ram Hospital, New Delhi, between January 2012 and December 2016 were reviewed after approval by institutional ethics committee. Neonates admitted beyond 72 hours of age or those with major congenital malformations were excluded. Baseline characteristics of enrolled neonates were recorded in a predesigned proforma. Based on date of admission, neonates were categorized in two groups: Period I (January, 2012 to July, 2015) and Period II (August, 2015 to December, 2016). The primary outcome of this study was composite outcome of death or BPD. The secondary outcome measures were need for pharmacological or surgical treatment for PDA, duration of ventilation, and need for postnatal steroids and diuretics.

During both periods, evaluation for PDA was considered, if a neonate required invasive ventilatory support with $\text{FiO}_2 > 0.3$ and/or mean airway pressure (MAP) > 8 cm H_2O beyond 48-72 hours of life or had other clinical features suggestive of hsPDA. All echocardiograms were performed by pediatric cardiologists. During Period I, PDA was considered hemodynamically significant and therapeutic closure of

PDA was attempted, if duct size was >1.5 mm and left atrium to aortic root ratio (LA: Ao ratio) was >1.5. During Period II, PDA was considered hemodynamically significant, if echocardiographic assessment revealed an unrestrictive duct (laminar flow with peak velocity <1.5 m/sec) and LA: Ao ratio >2. During both periods, oral ibuprofen was used as first line medication. If pharmacological treatment was unsuccessful after two courses or was contraindicated, surgical ligation of PDA was considered.

The overall management of VLBW neonates was similar during both the study periods. Fluid intakes were adjusted as per daily weight pattern, allowing 1-2% physiological weight loss per day during the first week of life. Cumulative days on respiratory support and supplemental oxygen were noted, BPD was defined as per NIH consensus definition 2001 [11].

Statistical analyses: Statistical analysis was done using SPSS version, 17.0. Statistical differences between two study periods were computed with chi square test for categorical variables and Student *t* test or Mann-Whitney U test as applicable for quantitative variables. Logistic regression analysis was applied to adjust for possible confounders among demographic and perinatal characteristics. *P* value <0.05 was considered statistically significant.

RESULTS

Of 528 VLBW neonates admitted during the study period, 509 were enrolled and analyzed; 394 in Period I and 115 in Period II. Remaining neonates were excluded from analysis; 17 were admitted 72 hrs after birth and 2 were shifted to another NICU during first week of life. Baseline characteristics of study groups are depicted in **Table I**.

The mortality and composite outcome of death/BPD were comparable during the two periods (**Table II**). On univariate analysis, BPD rate was higher during Period II. After adjustment for potential confounders (gestation <28 weeks, antenatal steroid, surfactant administration and culture positive sepsis), all outcomes were comparable. The pharmacological treatment for PDA was required in 8.4% vs 2.6% of VLBW neonates during Period I and II, respectively (*P*=0.03). Two (0.5%) neonates in Period I and none in Period II required surgical ligation for PDA. Among neonates requiring ventilatory support, durations of invasive and noninvasive ventilation were comparable during the two periods (**Table II**).

DISCUSSION

There is a wide variation in thresholds for PDA treatment across different NICUs with available options of

prophylactic closure, early targeted treatment or a conservative approach where intervention is delayed beyond 1st week [12-14]. We changed our unit practice for therapeutic closure of PDA in July, 2015 to a more conservative approach. We observed a high spontaneous closure rate during period II, only 3 (2.6%) neonates received treatment for PDA and all were below 28 weeks of gestation. These findings are consistent with recent reports of high spontaneous closure rates with a more conservative approach for PDA [8-10].

Respiratory morbidity among preterm neonates with PDA is a major concern, prompting neonatologists to attempt early therapeutic closure of ductus. We found that all grades of BPD, death and combined death/BPD were comparable during the two periods. Our observations are similar to recent reports, where, a conservative approach towards PDA was associated with spontaneous closure of PDA in most neonates without increase in morbidities or mortality [8-10]. In fact, Sung, *et al.* in a before-after study reported a lower BPD rates among neonates with gestation of 23-26 week, with a non-intervention approach compared with a mandatory closure of PDA [15]. The authors observed that with non-intervention and restrictive fluid intakes, 95% PDA closed spontaneously by discharge from NICU; only 3 neonates required transcatheter occlusion later during infancy. These observations of high spontaneous PDA closure rate with a conservative approach without an increase in neonatal morbidities and mortality are reassuring and warrant

Table I Characteristics of VLBW Neonates (N=509)

Characteristics	Period 1 (n=394)	Period 2 (n=115)
Birthweight, g ^a	1112 (254)	1130 (269)
Gestational age, wk ^a	29.9 (2.6)	29.6 (2.6)
Gestation <28 wk ^b	68 (17.2)	30 (26.0)
Small for gestation	126 (31.9)	42 (36.5)
Antenatal steroids ^b	309 (78.4)	79 (68.6)
Complete course	239 (60.6)	65 (56.5)
UA Doppler flow		
Reduced	72 (18.2)	13 (11.3)
Absent/reversed	65 (16.4)	20 (17.4)
Need for respiratory support		
Non-invasive	103 (26.1)	41 (35.6)
Invasive	147 (37.3)	51 (44.3)
Surfactant use ^b	122 (31)	50 (43.4)
Caffeine usage	230 (58.4)	62 (53.9)
Culture positive sepsis ^b	94 (23.9)	38 (33)

ANS- antenatal steroid; UA- umbilical artery. Data expressed as n (%), or ^amean (SD); *P* >0.05 for all comparisons except ^b*P*<0.05.

WHAT THIS STUDY ADDS?

- Restrictive threshold for management of PDA in VLBW neonates may not be associated with an increase in morbidities or mortality and possibly would reduce pharmacological treatment.

Table II Outcomes of VLBW Neonates During Two Study Periods

Outcome	Period I (n=394)	Period II (n=115)	Period I vs II
Death/BPD ^b	106 (26.9)	38 (33)	1.1 (0.6, 1.9)
Death ^b	80 (20.3)	24 (20.9)	1.1 (0.63, 2.0)
BPD ^b	31 (7.9)	17 (14.8)	1.7 (0.83, 3.5)
Severe BPD ^b	9 (2.3)	2 (1.7)	2.3 (0.4, 12.8)
Pharmacological treatment	33 (8.4)	3 (2.6)	0.03
Age at medication, d ^{a,c}	4 (3, 7.5)	6 (4, 14)	0.81
Duration of ventilation, d ^{a,c}			
Invasive	1 (3, 7)	3 (1, 15)	0.22
Non-invasive	4 (1, 10)	4 (1, 15)	0.69
Duration of hospitalization, d ^{a,c}	29 (14, 44)	28 (15, 56)	0.32
Postnatal steroid use ^c	10 (2.5)	6 (5.2)	0.21
Intraventricular hemorrhage ^c			
Any grade	19 (4.8)	5 (4.3)	1.0
Grade III/IV	6 (1.5)	3 (2.6)	0.42
NEC stage >2 ^c	11 (2.8)	3 (2.6)	1.0

Data expressed as n (%) or ^amedian (IQR); BPD; bronchopulmonary dysplasia; comparison between two study periods in ^badjusted OR (95% CI) or ^cP value. 2 children each in period I underwent surgical ligation or had diuretic use as compared to none in period II.

revisiting conventional liberal treatment practices. In the absence of proven therapeutic benefits of the traditional approaches, there is a need to devise more restrictive guidelines for the management of PDA that would limit exposure to possible harmful effects of medical or surgical treatment in these tiny neonates.

The limitations of our study include the single center, non-randomized study design, and few extremely preterm neonates <27 weeks in this cohort, making our findings less generalizable for this subset. Further, in before-after study, impact of changes in NICU practices over the year and improvement in overall care cannot be denied.

In conclusion, restrictive threshold for management of PDA in VLBW neonates may not be associated with increase in morbidity or mortality, and possibly would reduce need for pharmacological treatment or surgical ligation. There is need for adequately powered random-

mized controlled trials to evaluate impact of restrictive approach for the management of PDA on both short-term and long-term outcomes.

Ethical clearance: Institutional ethics committee, Ganga Ram Hospital; No. EC/11/171285, dated 31 March, 2018.

Contribution: MM, SS: planned the study; MM, AT: collected data; MM, SS: analyzed the data; MM, SS, AT: wrote the manuscript. AS edited the manuscript.


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CLIPPINGS

 **Reduced tactile neural repetition suppression is an early marker of later ASD traits in infants**
(*J Neurodevelop Disord.* 2021;13:1)

This longitudinal study from 2013-2019 was done to investigate behavioural and neural markers of tactile sensory processing in ninety one 10-month-old infants at elevated likelihood of ASD or ADHD (i.e. by virtue of having a first-degree relative with a clinical diagnosis of ASD or ADHD) compared to infants at typical likelihood of the disorders. A tactile repetition suppression paradigm administering repeated pairs of vibrotactile stimuli (S1-S2) was used and coupled with the recording of EEG. Behavioural markers were quantified by coding looking and moving behaviours before and after receiving the pair of tactile stimuli by a computerized frame-by-frame coding system. The longitudinal associations between early neural and behavioural markers of tactile processing and later ASD traits [by Autism Diagnostic Observation Schedule (ADOS-2)] or ADHD traits [by Early Childhood Behaviour Questionnaire (ECBQ)] were assessed at 24 months. It was observed that all infants, independent of their likelihood status, exhibited a decrease in screen-directed looking and an increase in body movement from the pre to the post-stimulus phase. Infants with an elevated ASD likelihood manifested reduced neural repetition suppression to tactile stimulation ($P=0.02$). The hierarchical linear regression with Tactile Suppression Index (TSI) as predictor and ADOS as outcome was statistically significant ($P < 0.001$), indicating that infants with lower neural repetition suppression of tactile stimulation at 10 months exhibited higher levels of ASD traits at 24 months. In contrast, there was no significant main effect of ADHD likelihood status.

The authors underlined the need for future research to assess the existence of continuity between the marker identified in the current study and the heterogeneous spectrum of sensory features documented later in development, including sensory hyper/hyposensitivity manifestations.

 **Viloxazine as a new drug for treatment of Attention Deficit Hyperactivity Disorder in school-aged children**
(*Clin. Therap.* 2020 Aug;42(8):1452-1466)

A phase III, multisite, randomized, double-blind, placebo-controlled, 6-week trial was conducted in United States to assess the efficacy and safety of a newer drug viloxazine (SPN-812) in treatment of ADHD in school aged children. It is a multimodal serotonergic and noradrenergic modulating agent (SNMA) having activity at serotonin receptors and norepinephrine transporters, although the mechanism of action remains to be fully elucidated. Side effect profile is usually mild, comprising of somnolence, decreased appetite, headache, fatigue, nausea, and irritability and is usually reversible after discontinuation. A total of 477 children (6-11 year old) with ADHD were randomized into 3 arms (159 in placebo, 157 in 100mg/d and 161 in 200mg/d) between October 2017 and September 2018. The efficacy endpoints were the change from baseline in total score of ADHD-RS-5, Clinical Global Impression-Improvement (CGI-I), Conner's 3 scale and Weiss Functional Impairment Rating Scale (WFIRS-P). The majority of subjects were male (63%) with similar demographic and baseline characteristics between groups. Statistically significant improvements in ADHD-RS-5 Total score were observed in both the 100- and 200-mg/day SPN-812 treatment groups compared to placebo at week 1 of treatment, which was maintained through end of the study ($P < 0.0004$ and $P < 0.0001$). Significant improvements were also observed in the CGI-I scale, Conner's 3-Composite T-score, and WFIRS-P average score. Treatment-related adverse events (AEs) were reported in $\geq 5\%$ of subjects and the discontinuation rate due to AEs was $< 5\%$. The authors deduced that SPN-812 is an effective and well tolerated pharmacotherapy that could be future treatment option for children with ADHD, though more evidence is required.

ARPITA GUPTA
arpita1517@gmail.com

Extended-Spectrum β -Lactamase-Producing Enterobacteriaceae Causing Community-Acquired Urinary Tract Infections in Children in Colombia

JHON CAMACHO-CRUZ,¹ JAVIER MUNOZ MARTINEZ,¹ JULIO MAHECHA CUFINO,¹ GERMAN CAMACHO MORENO,¹ CAROLINA RIVERA MURILLO,¹ MARIA ALEJANDRA SUAREZ FUENTES,¹ AND CARLOS ALBERTO CASTRO²

From Departments of ¹Pediatrics and ²Medical Epidemiology, Fundación Universitaria de Ciencias de la Salud (FUCS) – Hospital de San José and Hospital Infantil Universitario de San José de Bogotá, Colombia.

Correspondence to: Dr Jhon Camacho, Associate Instructor, Department of Pediatrics FUCS, Calle 10, No. 18-75 Bogota, Colombia.

jhcamacho@fucsalud.edu.co

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Objective: To characterize the pediatric patients presenting at the two pediatric centers in Bogotá, with first isolate urine culture of community-acquired extended-spectrum β -lactamase (ESBL)-producing enterobacteriaceae. **Methods:** Review of microbiological data of children between January, 2012 and December, 2018, obtained using the WHONET software. **Results:** A total of 2657 *Escherichia coli*, *Klebsiella spp* and *Proteus mirabilis* - positive urine cultures were obtained within a 6-year period; data of 132 patients were finally selected. Frequency of ESBL-producing bacteria infections in community-acquired urinary tract infections (UTI) was 5%: 123 *E. coli* (93.2%), 7 *K. pneumoniae* (5.2%), 1 *K. oxytoca* (0.8%), and 1 *P. mirabilis* (0.8%). **Conclusion:** A predominance of female sex, preschool children, and lower tract urinary infections were found, as well as a low frequency of comorbidities. Adequate sensitivity to amikacin and nitrofurantoin was found in this study.

Keywords: *Escherichia coli*, *Klebsiella spp*, Management, Prevalence, Sensitivity.

Gram-negative bacteria are a common cause of urinary tract infections (UTIs) in children, and are frequently being reported as extended-spectrum β -lactamase (ESBL)-producing bacteria [1]. Actual incidence of urinary infections due to ESBL-producing bacteria in children is difficult to estimate; however, over the last 10 years, resistance has been gradually increasing around the world [2].

Adult studies report a prevalence of 3% to 16.3% among all UTI patients [1], whereas a prevalence of 10.9% has been reported in a pediatric study [3]. There are few pediatric studies, estimating the prevalence and the incidence of ESBL-producing enterobacteriaceae in community-acquired UTIs. We report the frequency and the clinical characteristics of children presenting with urinary infections and a urine culture with community-acquired ESBL-producing bacteria in two hospitals of Bogotá.

METHODS

A hospital record review of patients younger than 18 years was done from the emergency department of Hospital de San José and Hospital Infantil Universitario de San José in Bogotá. Children included were those with urinary symptoms or febrile condition without focus and

initially an ESBL-producing bacteria was isolated for the first time in the urine culture from January, 2012 to December, 2018. Those with positive urine cultures for healthcare-associated infections (defined as hospital-acquired infections during treatment or care for a medical condition) and reinfections (two or more UTI by ESBL-producing bacteria) were excluded. Socio-demographic and clinical variables were evaluated, including additional diagnoses, underlying pathologies, inpatient management, and characteristics related to antibiotic treatment. Information was collected using an instrument developed by the investigators, which was completed based on the review and selection of medical records that met the inclusion criteria. Microbiological information was obtained using the WHONET 5.6 software (World Health Organization). Minimum inhibitory concentrations (MIC) were also rated and interpreted in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI) of 2017 [4], measured based on the MicroScan (Baxter) parameters in Hospital San José and on the VITEK2 (bioMérieux) automated method, in the Hospital Infantil Universitario de San José.

Statistical analyses: Information was stored in a database to be then validated selecting 10% of the records, and compared against the instruments. A descriptive analysis

of the information was conducted in STATA 12; qualitative variables were presented with absolute and relative frequencies, while quantitative variables included central tendency and scatter measurements, in accordance with the distribution of the data. This study was submitted and approved by the ethics and the research on humans committees in both hospitals.

RESULTS

A total of 2657 positive urine cultures were obtained, of which 240 were reported as ESBL-producing bacteria; the medical records were reviewed, and in the end, 132 (81.8% girls) patients were eligible for the final analysis (**Fig. 1**). Frequency of community-acquired ESBL-producing bacteria isolates in first UTI was 5%. Of the 132 community-acquired ESBL-producing bacteria isolates, 123 (93.2%) were from *E. coli*, 7 (5.2%) from *K. pneumoniae*, and 1 (0.8%) each from *K. oxytoca*, and *Proteus mirabilis*.

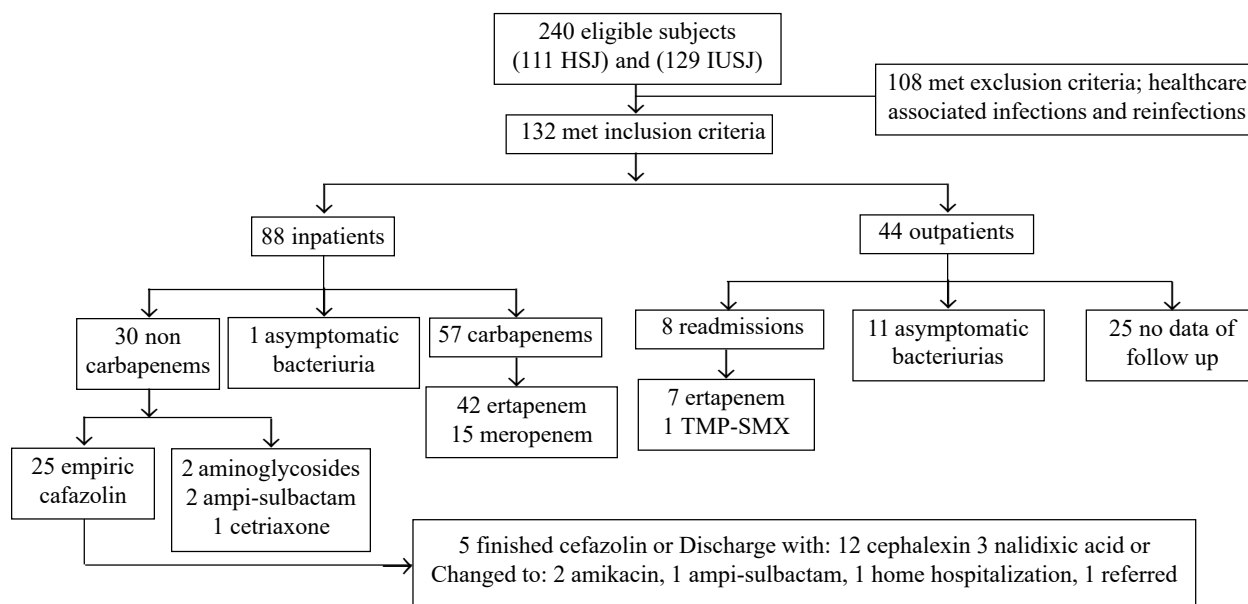
The median (IQR) age of girls and boys age 4 (1-6.5) year and 0.5 (0.2-1) year, respectively. Other characteristics of the population are shown in **Table I**.

Additionally, 49 patients (37.1%) had a previous history of UTIs, 25 patients (18.9%) had UTI-associated congenital malformations, 19 (76%) had renal or urologic conditions (hydronephrosis ($n=9$), pyelectasis ($n=5$), horseshoe kidney ($n=2$), renal hypoplasia ($n=1$), duplex collector system ($n=1$) and renal duplication ($n=1$) and 6 patients (24%) presented with neurological malfor-

mations (myelomeningocele ($n=5$), hydrocephalus ($n=1$). Among this group of malformations, 18 (69.2%) presented a history of previous UTI. Furthermore, four patients (3.0%) were in immunosuppressive therapy: two cases of nephrotic syndrome, one case of systemic lupus erythematosus and one due to chronic kidney failure. Nine patients (6.8%) exhibited an additional risk because of self-medication with amoxicillin, cephalexin, trimethoprim sulfamethoxazole (TMP-SMX) or metronidazole. 50 patients (37.9%) had no relevant history or risk factors for UTI.

Imaging findings showed 92 (69.6%) patients undergoing kidney and urinary tract ultrasound, of which 52 (56.5%) had normal results, 13 (14.1%) exhibited enlarged kidneys, 9 (9.8%) had evidence of pyelocaliceal ectasia, 7 (7.6%) with kidney atrophy, 6 (6.5%) sediments in urine, 3 (3.2%) hydronephrosis, 1 (1.1%) duplicated pyelocaliceal system, and 1 (1.1%) neurogenic bladder). Out of 24 patients undergoing cystourethrography, 12 (50%) were normal, 7 (29.2%) had vesicoureteral reflux, and 2 (8.3%) bladder diverticula; the remaining three patients (12.5%) had penile hypospadias, postvoid residual urine, and decreased posterior urethral diameter. Finally, of 22 patients undergoing renal gammagraphy, 12 (54.5%) had documented pyelonephritis, 8 (36.4%) were normal, and 2 (9.1) had kidney scarring.

Sensitivity profiles and co-resistance for *E. coli* and *K. pneumoniae* are illustrated in **Table II**.



TM-SMX: trimethoprim-sulfamethoxazole; HSJ: Hospital de San José; IUSJ: Hospital Infantil Universitario de San José.

Fig. 1 Flowchart of the study.

Table I Clinical and Demographic Characteristics of Children With First Episode of Urinary Tract Infection by Community-Acquired ESBL-Producing Enterobacteriaceae (N=132)

Characteristics	No. (%)
<i>Age (mo)</i>	
<12	28 (21.2)
13-24	22 (16.7)
25-60	45 (34.1)
61-144	30 (22.7)
>145	7 (5.3)
<i>Comorbidities</i>	
Renal and urological comorbidities ^a	18 (13.6)
Other comorbidities ^b	15 (11.4)
<i>Diagnosis</i>	
Asymptomatic bacteriuria	12 (9.1)
Lower UTI	102 (77.3)
Upper UTI	18 (13.6)
History of hospitalization ^c	28 (21.2)
History of surgery ^c	8 (6.1)
Previous antibiotic therapy ^c	50 (37.9)
UTI ^d	49 (37.1)
Congenital malformation ^e	26 (19.7)
Hospital stay (d), median (IQR)	9 (6-11)

UTI: Urinary tract infection; ESBL; Extended spectrum beta lactamase; ^aRenal and urological comorbidities: hydronephrosis, pyelectasis, horseshoe kidney, nephrotic syndrome, bladder diverticula, vesicoureteral reflux, kidney transplant and nephrostomy; ^bOther comorbidities: myelomeningocele, anemia, chromosomo-pathy, cholestasis, hydrocephalus, systemic lupus erythematosus, pulmonary hypertension. ^c3 months prior to ED visit; ^ddue to ESBL non-producing germs; ^epredisposing to UTI.

Supplementary Fig. 1 shows the detailed MICs for *E. coli* for the most important antibiotics, using automated methods and their relationship to the CLSI to define sensitivity and resistance.

After the initial assessment 44 patients, empiric outpatient therapy was administered with cephalexin in 39 cases (88.7%), nalidixic acid in 2 cases (4.5%), no antibiotic therapy was prescribed in 2 cases (4.5%), while TMP-SMX was used in 1 case (2.3%). Of these patients, 8 (18.2%) relapsed and were admitted for ertapenem treatment (7) and 1 was discharged with TMP-SMX. The remaining 36 patients (81.8%); 11 were considered to develop asymptomatic bacteriuria and 25 patients had no outpatient follow-up information available.

88 patients received hospitalized management, 70 (79.5%) were initially treated with cephalosporins, 7 (7.9%) with aminoglycosides, and 11 (12.6%) received other antibiotic therapies. Once the results of the urine culture were available, 57 (64.8%), received specific therapy with carbapenems: ertapenem ($n=42$) and meropenem ($n=15$); 31 patients (35.2%) received another betalactamic antibiotic therapy ($n=28$) and aminoglycosides ($n=3$).

Of the 107 patients followed, 12 were considered asymptomatic bacteriurias, and 95 received empirical treatment. Of these 95 patients, 74 (77.8%) required switching over to carbapem management and 21 (22.2%) patients experienced no change in their antibiotic treatment.

In terms of outcomes, one 7-month old patient died, with Down syndrome admitted with a diagnosis of upper

Table II Specific Sensitivity CLSI 2017 of Each Antibiotic According to the ESBL-Producing Bacteria Isolated in Positive Urine Culture (N=130)^a

Antibiotic	<i>Escherichia coli</i>			<i>Klebsiella pneumoniae</i>		
	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
Ampicillin sulbactam, $n=130$	46 (35.4)	25(19.2)	52 (40)	3 (2.3)	0	4 (3.1)
Piperacillin-tazobactam, $n=68$	56 (82.4)	3 (4.4)	5 (7.4)	4 (5.8)	0	0
Amikacin, $n=130$	121 (93)	1 (0.8)	1 (0.8)	7 (5.4)	0	0
Gentamicin, $n=130$	88 (67.7)	1 (0.8)	34 (26.1)	6 (4.6)	0	1 (0.8)
TMP-SMX, $n=128$	33 (25.8)	0 (0.0)	88 (68.8)	3 (2.3)	0	4 (3.1)
Nitrofurantoin, $n=129$	92 (71.3)	28 (21.7)	2 (1.5)	5 (3.9)	1 (0.8)	1 (0.8)
Fosfomycin, $n=57$	52 (91.3)	0	1 (1.7)	3 (5.3)	0	1 (1.7)
Ciprofloxacin, $n=129$	59 (45.7)	2 (1.6)	61 (47.3)	4 (3.1)	0	3 (2.3)
Meropenem, $n=130$	130 (100)	0	0	130 (100)	0	0

^aOne case each of *P. mirabilis* and *K. oxytoca* were excluded; Values in no. (%); all n not equal to 130 because not all isolates had the disks for that antibiotic in the antibiogram.

UTI and *E. coli* isolate. The patient received empirical treatment with ampicillin sulbactam, which was switched on day three to ertapenem, based on the urinary culture results. However, the condition of the patient progressed to septic shock.

Hospitalization in last three months ($n=28$, 21.2%), recurrent urinary tract infection ($n=49$, 37.1%), previous use of antibiotics ($n=50$, 37.9%) and urinary tract abnormalities were findings for ESBL producing community-acquired UTI.

DISCUSSION

This study presents the frequency of UTI associated with community acquired ESBL-producing bacteria similar to the levels reported in the international literature [1,5]. Demographic characteristics include a higher frequency of females, with an age group distribution similar to the reported in the world literature [6,7]. The factors related with ESBL-producing bacteria UTIs are: a history of a previous UTI non ESBL-producing bacteria, urinary tract malformations, hospitalization, or antibiotic therapy during the last 3 months (40% first generation cephalosporins) [5,8,9]. In terms of comorbidities, surprisingly most patients were previously healthy (without any comorbidities), which correlates with the circulation of ESBL-producing enterobacteriaceae phenotype in the community.

Median for hospital days is high, similar to previous studies [10], in addition to a more than two-fold increase in costs [9,11]. This may be due to the fact that patients with infections from ESBL-producing bacteria have a higher risk of hospitalization because of their past history [6]. Findings of imaging studies were mostly normal and among the most frequent ultrasound alterations were enlarged kidneys, followed by pyelectasis; the number of patients who underwent cystourethrographies and renal gammagraphies was low in contrast with literature [6] as for most in our population it was their first infection [12].

The most commonly isolated bacteria was *E. coli*, so a more detailed analysis was performed of the resistance to 8 antibiotics. A very high sensitivity was found to fosfomicin, nitrofurantoin and amikacin, with similar findings to those in the Spanish study by Pérez, et al. [1]. A variable sensitivity and resistance was also identified in the group of betalactamase inhibitors, with a higher resistance in the ampicillin sulbactam group and intermediate sensitivity, with MIC approaching the resistance to piperacillin-tazobactam. It is therefore hypothesized that these are not sound therapeutic options in this scenario, because of the risk if increased resistance as has been stated by other authors [11,13]. A proportion

of inpatients were treated with initial empirical management with cephazolin, achieving a satisfactory clinical evolution with a negative control urine culture. The correlation of urinary concentrations that the drug can reach should be studied [14]. In this series of patients, the typical risk factors described in the literature were uncommonly seen [7,15].

It can be suggested that this pathology may be underdiagnosed or even treated incorrectly, impacting on bacterial resistance and as a result in prognosis; forcing health professionals treating this disease to explore the presence of ESBL in a non-hospital population and without the risk factors specified in the literature. Other studies should be done to confirm if there are strains of multi-resistant bacteria circulating in the community.

Taking into account the observational nature of this study and the retrospective collection of data, it is not possible to determine causality. However, this drawback was offset using different sources of information. Further analytical and experimental studies are needed to validate the hypotheses herein discussed and propose an analytical study to confirm if there are strains of multi-resistant bacteria circulating in the community. Another limitation of study was that discs of antibiotic for antibiogram were not uniformly available for all cases.

UTIs from community acquired ESBL-producing enterobacteriaceae are a serious public health issue as a result of the increasing number of cases over the last decade. This population presents a frequency of 5% for *E. Coli* and *K. pneumoniae*. A predominance of low urinary infection was found in previously healthy girls of preschool age. The typical risk factors associated with ESBL-producing bacteria infections in community acquired UTI were low in this population. This study reveals the epidemiological and microbiological profile of these hospitals, good sensitivity was found in this population for amikacin and nitrofurantoin, so as to select an adequate treatment and to design alternative non-carbapenem antibiotic protocols for outpatients, with a view to promote the rational use of antibiotics. Fosfomicin, piperacillintazobactam, and other antibiotics require further investigation.

Ethics Clearance: Ethics and the research on humans committees in both hospitals. Hospital ethics review board (Comité de ética en investigación con seres humanos Hospital de San José, CEISH-HSJ). No. 0369-2018, dated September 17, 2018.

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Contributors: JCC, JMM, JMC: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; GCM, CRM, MASF, CCM: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All authors critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Predictive Value of IAP 2015, IAP 2007 and WHO Growth Charts in Identifying Pathological Short Stature

RIDDHI PATEL,^{1,2} CHETANKUMAR DAVE,^{1,2} NEHA AGARWAL,^{1,2} HEMANGKUMAR MENDPARA,^{1,3} RISHI SHUKLA¹ AND ANURAG BAJPAI^{1,2}

From the ¹Department of Pediatric Endocrinology, ²Regency Center for Diabetes Endocrinology and Research, Kanpur and ³GROW Society, Growth and Obesity Workforce, ³Department of Pediatric Critical Care, Kanpur, India.

Correspondence to: Dr Anurag Bajpai, Department of Pediatric Endocrinology, Regency Center for Diabetes Endocrinology and Research, Kanpur 208 001, Uttar Pradesh, India. dr_anuragbajpai@yahoo.com

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Objective: To compare the diagnostic accuracy of IAP 2015, WHO and IAP 2007 growth charts in identifying pathological short stature in Indian children.

Methodology: The predictive value of the growth charts for pathological short stature was assessed in 500 (266 boys) short subjects (age 5-17.9 years) presenting to our pediatric endocrine clinic.

Results: WHO, IAP 2015, IAP 2007 criteria classified 500, 410 (82%) and 331 (66.2%) subjects short respectively. A total of 218 (43.6%) subjects had a pathological cause. Two out of 90 subjects short by WHO criteria but normal as per IAP 2015 had a

pathological cause (2.2%) whereas 38 out of 79 subjects short as per WHO and IAP 2015 criteria but normal by IAP 2007 had pathological short stature. The diagnostic measures of IAP 2015 and IAP 2007 charts in identifying pathological short stature showed a sensitivity 99.1% and 81.7%, negative predictive value 97.8% as against 76.3%, positive predictive value 52.7% and 53.8%, and specificity of 31.2% and 45.7%, respectively.

Conclusions: IAP 2015 growth charts are superior in identifying pathological growth failure compared to WHO and IAP 2007.

Keywords: Growth chart, Growth failure, Validation.

Short stature is the one of the most common complaint presenting to a pediatrician. Most short children have a physiological cause not requiring extensive evaluation, a substantial proportion; however, have a serious underlying cause [1]. Differentiating physiological from pathological short stature is pivotal to allow a rational evaluation where growth charts are used as a non-invasive tool.

Currently used growth charts for Indian children include WHO, IAP 2007 and IAP 2015 [2-5]. Significant impact of ethnicity and environmental factors on growth makes country specific charts desirable. The Indian Academy of Pediatrics (IAP) growth monitoring committee in 2007 recommended growth charts developed from major urban affluent zones of India in 1989-91 [3]. These were replaced by IAP 2015 charts based on collated data of 33,148 Indian children of age 5 to 18 years across 14 centers [5]. The use of WHO criteria has shown to classify greater number of children as short compared to IAP 2015 and IAP 2007 charts [6,7]. These studies have; however, not addressed predictive value of these criteria in identifying pathological short stature [8,9]. We conducted this study to compare WHO, IAP 2007 and IAP 2015 criteria to identify pathological short

stature in children and adolescents between the age of 5 and 18 years.

METHODS

Case records of children and adolescents between 5-18 years of age presenting to the pediatric endocrine clinic of our hospital with short stature from January 2015 to December 2018 were reviewed after institutional ethics committee approval. Height was measured using a portable stadiometer (Model 213, Seca scale, Germany) up to an accuracy of 1 mm. Subjects were asked to stand on the platform with heels together, toes apart and back of the occiput, shoulder blades, buttocks and heels in contact with the backboard. Readings were taken in triplicate and averaged. The stadiometer was calibrated daily with Seca Calibration Rod. Weight was measured using Seca Scale till 100 grams which was calibrated daily.

The anthropometric parameters were converted to Z-score using WHO Anthroplus software, and macros derived from IAP 2007, and IAP 2015 growth charts. Children with height Z-score less than -2 as per WHO criteria were evaluated for etiology of short stature as per institutional protocol. The work-up included a

comprehensive clinical examination and screening tests (complete blood count, alanine aspartate transferase, creatinine, free T4, thyroid stimulating hormone, tissue transglutaminase antibody, and serum electrolytes) in all and further work-up as required (karyotype in girls, growth hormone stimulation test, genetic tests, venous blood gas, etc.). Subjects with normal work-up and growth velocity over a six-month period were diagnosed as physiological short stature. Children short by WHO but normal by IAP 2007 and 2015 criteria were excluded from the study if their weight SDS was below -2 as per the IAP 2007 or 2015, indicating the need for evaluation irrespective of height. A sample size of 340 was required considering a prevalence of pathological short stature of 33% [10], 95% confidence and a standard error of 0.05.

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS version 25.0, SPSS, Inc) for Macintosh, and expressed as mean (standard deviation) and frequency (percentage). Sensitivity, specificity, positive predictive value, negative predictive values and likelihood ratio of IAP 2015, IAP 2007 criteria were calculated. P value less than 0.05 was considered significant.

RESULTS

Seven hundred and forty children (377 boys) presented with a concern of short stature to our clinic during the study period. Forty children with incomplete data and 190 with normal stature were excluded. The WHO, IAP 2007 and IAP 2015 criteria labelled 510 (72.6%), 410 (58.2%) and 331 (47%) subjects short, respectively. Ten subjects labelled short by WHO, and normal by IAP 2007 and IAP 2015 were excluded as their weight z-score was below -2 by IAP 2007 or IAP 2015 criteria. The final analysis was performed in 500 subjects (266 boys) with mean (SD) age of 11.8 (3.1) years. The height z-score was above -2 in 90 (18%), between -2 to -3 in 245 (49%), and below -2 in 165 (33%) as per IAP 2015 criteria.

A pathological cause of short stature was identified in 218 (43.6%) and included celiac disease (83, 16.6%), growth hormone deficiency (78, 15.6%), hypothyroidism (33, 6.6%), Turner syndrome (8, 1.6%), chronic illness (8, 1.6%) and other syndromes (8, 1.6%). Among the 218 subjects, 216 (99%) were short by IAP 2015 and 178 (81.6%) by IAP 2007 criteria. Ninety subjects short by WHO criteria had normal stature as per IAP 2015. A pathological cause was identified in 38 of the 79 subjects (48.1%) short as per both WHO and IAP 2015 but normal by the IAP 2007 criteria. The sensitivity, specificity, negative predictive value and positive predictive value specificity of IAP 2015 and 2007 in identifying pathological short stature are shown in **Table I**.

Table I Diagnostic Performance of IAP 2007 and IAP 2015 Criteria for Identifying Pathological Short Stature (N=500)

Diagnostic measure	IAP 2007	IAP 2015
PPV	53.8%	52.7%
NPV	76.3%	97.8%
Sensitivity	81.7%	99.1%
Specificity	45.7%	31.2%
Positive likelihood ratio	1.5	1.4
Negative likelihood ratio	0.4	0.03

PPV: Positive predictive value; NPV: Negative predictive value.

Identification of one child with pathological cause would have required evaluation of 45 subjects short by WHO but normal by IAP 2015.

DISCUSSION

Findings of our study suggest that IAP 2015 criteria have the best diagnostic accuracy in identifying pathological short stature in Indian children and adolescents. The use of WHO criteria causes unwarranted work-up in a substantial number of subject, while that of IAP 2007 misses pathological causes.

Studies have shown a higher prevalence of short stature as per WHO charts compared to IAP 2007 and IAP 2015 in privileged school children around Pune, and New Delhi [6,7]. These studies; however, did not evaluate predictive accuracy of these charts for pathological short stature. The present study demonstrated that IAP 2015 criteria correctly reduced the number of Indian children with short stature requiring evaluation. The use of IAP 2007 growth charts lowered the number of subjects requiring evaluation at the cost of missed pathology in many.

To the best of our knowledge, this is the first study determining the predictive accuracy of currently available growth charts in India in identifying pathological short stature. The conduct of the study in a pediatric endocrine clinic may have increased the proportion of subjects with pathology. Retrospective analysis of case records represents another limitation of this study. However, a protocol-based evaluation by a single pediatric endocrinologist across the study period and review of structured records ensured diagnostic categorization in most of the cases.

Our observations suggest a superior diagnostic accuracy of IAP 2015 over IAP 2007 and WHO growth charts in identifying pathological short stature. Further studies looking into the predictive accuracy of these criteria in identifying pathological short stature in different clinical settings are required.

WHAT THIS STUDY ADDS?

- IAP 2015 criteria have superior diagnostic accuracy in identifying pathological short stature in Indian children compared to WHO and IAP 2007.

Acknowledgement: Dr Vaman Khadilkar for providing macro for calculation of standard deviation score as per WHO, IAP 2007 and IAP 2015 criteria.

Ethical clearance: Regency Hospital Limited Institutional ethics committee; RHC-IEC-16036 dated September 11, 2019.

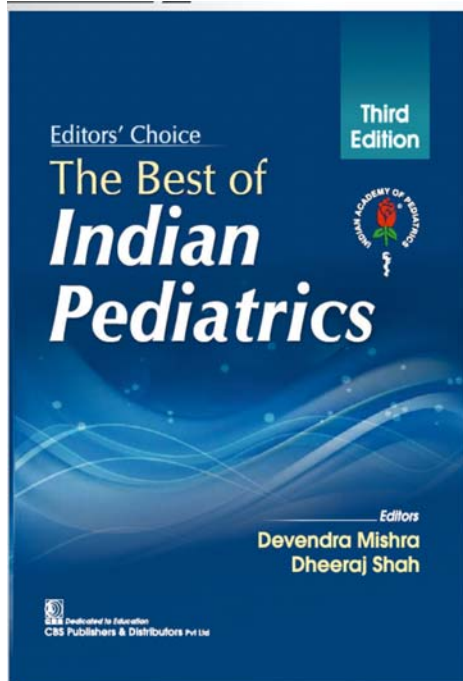
Contributors: RP, NA, CD, HM, RS: patient management and data collection; RP did literature review, statistical analysis and drafted the initial manuscript; AB: patient management, conceptualization and planning of the study, critical review of the manuscript and would act as guarantor of the paper.

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RECOMMENDATIONS

Indian Academy of Pediatrics Guidelines for Pediatric Skin Care

R MADHU,¹ VIJAYABHASKAR CHANDRAN,¹ V ANANDAN,² K NEDUNCHELIAN,³ S THANGAVELU,⁴ SANTOSH T SOANS,⁵ DIGANT D SHASTRI,⁶ BAKUL JAYANT PAREKH,⁷ R REMESH KUMAR⁸ AND GV BASAVARAJA⁹

From ¹Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai, Tamil Nadu; ²Department of Dermatology, Venereology and Leprosy, Govt Stanley Medical College, Chennai, Tamil Nadu; ³Research and Academics and ⁴Department of Pediatrics, Mehta Multispeciality Hospitals, Chetpet, Chennai, Tamil Nadu; ⁵AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka; ⁶Killol Children Hospital, Surat, Gujarat; ⁷Bakul Parekh Children Hospital and Multispeciality tertiary care centre, Mumbai, Maharashtra; ⁸Apollo Adlux Hospital, Cochin, Kerala; and ⁹Indira Gandhi Institute of Child Health, Bangalore, Karnataka; India.

Correspondence to: Dr C Vijayabhaskar, No 4, Gandhi Street, SS Nagar Extension, Thirumullaivoyal, Chennai 600 062, Tamil Nadu, India. buskibuski@gmail.com

Objective: To develop standard recommendations for skin care in neonates, infants and children to aid the pediatrician to provide quality skin care to infants and children. **Justification:** Though skin is the largest organ in the body with vital functions, skin care in children especially in newborns and infants, is not given the due attention that is required. There is a need for evidence-based recommendations for the care of skin of newborn babies and infants in India. **Process:** A committee was formed under the auspices of Indian Academy of Pediatrics in August, 2018 for preparing guidelines on pediatric skin care. Three meetings were held during which we reviewed the existing guidelines/ recommendations/review articles and held detailed discussions, to arrive at recommendations that will help to fill up the knowledge gaps in current practice in India. The initial draft of the manuscript based on the available evidence and experience, was sent to all members for their inputs, after which it was finalized. **Recommendations:** Vernix caseosa should not be removed. First bath should be delayed until 24 hours after birth, but not before 6 hours, if it is not practically possible to delay owing to cultural reasons. Duration of bath should not exceed 5-10 minutes. Liquid cleanser with acidic or neutral pH is preferred, as it will not affect the skin barrier function or the acid mantle. Cord stump must be kept clean without any application. Diaper area should be kept clean and dry with frequent change of diapers. Application of emollient in newborns born in families with high risk of atopy tends to reduce the risk of developing atopic dermatitis. Oil massage has multiple benefits and is recommended. Massage with sunflower oil, coconut oil or mineral oil are preferred over vegetable oils such as olive oil and mustard oil, which have been found to be detrimental to barrier function.

Keywords: Cleanser, Emollients, Infant, Massage, Newborn.

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Skin is the largest organ in the human body with vital functions such as barrier integrity, thermoregulation, immunological function, protection from invasion of microbes and ultraviolet rays [1]. The skin of a newborn or an infant is different from the adult skin. Skin of the term newborn is 40-60 times thinner, less hydrated and has reduced natural moisturizing factor (NMF) compared to the adult skin. The skin of a preterm baby is thinner than that of a term baby and is vulnerable to impaired thermoregulation, increased skin permeability, increased transepidermal water loss (TEWL), dehydration, predisposition to trauma and increased percutaneous absorption of toxins. The fragile and delicate nature of the skin of the neonate calls for special care in cleansing. It has been observed that skin of the newborn undergoes various structural and functional changes from birth to first five years of life [2,3]. About 30% of children who attend the pediatric out-patient departments present with dermatological disorders, which makes it essential to

prioritize skin health from the very beginning [4]. Skin care in newborn or a child is not given the due attention that is required, and in addition, in India, there are varied community and culture-based practices that can adversely affect the healthy skin in babies [5]. Hence, there is an urgent need for formulation of standard recommendations for skin care of newborns and infants in India based on the available literature.

PROCESS

To accomplish the goal of preparing guidelines on pediatric skin care, a committee comprising of pediatricians and dermatologists with experience in pediatric dermatology (**Annexure I**) was formed under the auspices of Indian Academy of Pediatrics (IAP) in August, 2018. We performed a literature search across multiple search engines, namely Pubmed, MEDLINE, Cochrane and Google Scholar for the terms, “newborn/preterm/infant skin care”, “first bath”, “WHO guidelines”, “recommendations”, “cord care”, “nappy

care”, “cleanser”, “emollients”, “massage.” Search was limited till September, 2019. We did a systematic review of the evidence available on skin care for babies in the various headings such as bathing, cleansing, care of the umbilical cord, nappy care, care of hair, cleansers, oils used for baby massage, atopic dermatitis and dry skin. Three meetings were held, during which we reviewed the existing guidelines/recommendations and review articles, and held discussions, with regard to skin care practices in neonates, infants and children, to arrive at recommendations that will help to fill up the knowledge gaps in current practice in India. The first meeting was held in Mumbai on 5 August, 2018 and the two subsequent meetings were held at Chennai on 12 May, 2019 and 20 October, 2019. An initial draft was prepared based on the available evidence and experience, and then sent to all the other members for their inputs, after which, the final recommendations were drafted.

GUIDELINES

Newborn Skin Care

Care of the skin of newborn babies encompasses assessment of the skin, identification of the risk factors that will affect the barrier function and routine care of skin.

Assessment of the skin of the neonate: During the first examination of the newborn, it is essential to do a head to foot examination of the skin. Various parameters to be observed are dryness, scaling, erythema, colour, texture and physiological changes. Neonatal skin condition score (NSCS) based on the score (1 to 3) given to the condition of neonate’s skin related to dryness, erythema, and break down/excoriation is useful for daily evaluation of newborn skin. Perfect score is considered to be 3, while worst score is 9 (**Fig. 1**) [6].

Identification of risk factors that will affect the barrier function: Epidermal barrier function will be affected due to immaturity of the skin, phototherapy, iatrogenic injuries, extensive epidermolysis bullosa, septicaemia and environmental temperature. Treatment related risk factors may occur due to antiseptics, adhesives and vehicles in topical medications. Term babies with either physiological or pathological jaundice on phototherapy and preterm babies in incubator are susceptible to increased transepidermal water loss (TEWL).

Routine care of skin in term and preterm

Ideal care of skin of newborn comprises of gentle cleansing, protection of barrier function, prevention of dryness of skin, avoidance of maceration in the body folds and exposure to toxins, prevention of trauma and promotion of normal development of skin.

Skin to skin care

WHO recommends that soon after birth, baby is placed on the abdomen of the mother before the cord is cut or over the chest after the cord is cut, after which entire skin and hair is wiped with a dry warm cloth. It is strongly recommended that the baby dressed only in a diaper (maximises the skin to skin contact between the baby and the mother), be left on the mother’s chest with both of them being covered with pre-warmed blankets, for at least 1 hour after birth, as this will help to promote breast feeding and prevent hypothermia. WHO strongly recommends skin-to-skin care (SSC) for all mothers and newborns without complications, irrespective of the mode of delivery immediately after birth [7]. (*Strong recommendation; Level of evidence VII*). If the mother is unable to keep the baby in skin to skin contact due to complications, then the baby should be well wrapped in a warm, soft dry cloth. Head of the baby should be well

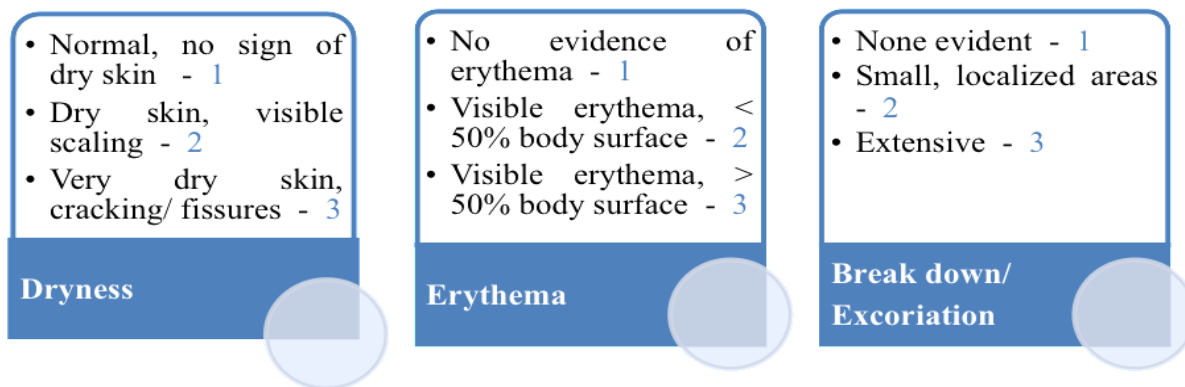


Fig. 1 Neonatal skin condition score.

covered with a dry cloth to minimize the heat loss.

Vernix caseosa

Vernix caseosa is a natural cleanser and moisturiser known for its anti-infective, antioxidant and wound-healing properties. Development of acid mantle is facilitated by vernix caseosa, which also supports the normal bacterial colonization [8,9]. WHO and the European round Table meeting recommend that vernix caseosa should not be removed because of the various beneficial functions [10-12] (*Strong recommendation; Level of evidence VII*). Vigorous rubbing of the baby should be avoided. If the baby's skin is stained with blood or meconium, wet cloth should be used to wipe followed by a dry cloth.

First Bath of the Newborn

It is a well-known fact that bathing in newborn can lead to hypothermia, increased demand of oxygen, unstable vital signs and disruption of behavior. WHO recommends that the first bath should be delayed until 24 hours after birth but not before 6 hours, if it is not practically possible to delay owing to cultural reasons. But while bathing a baby after 6 hours of life, one must ensure that the baby is normothermic with a stable cardiorespiratory status [10-14]. (*Strong recommendation; Level of evidence VII*). This holds good for a term baby weighing more than 2.5 kgs. Delayed bathing promotes successful initiation of breast feeding, and facilitates bonding and skin to skin care [15]. Bath should always be given in a warm room and the temperature of bath water should be between 37°C and 37.5°C [11]. Temperature of the water should be checked by the health worker or caregiver by immersing their hand. Duration of bath should not exceed 5-10 minutes as an over hydrated skin is fragile with increased threshold for injury [11] (*Strong recommendation; Level of evidence VII*).

If choosing to give a tub bath, depth of the water should be 5 cm, up to the hip of the baby. As bath tub and bath toys are potential sources of infection, they must always be disinfected [11]. It would be ideal for the health workers to use gloves while giving the first bath [11]. In those babies born to mothers infected by hepatitis B and/or HIV, bath should be given at the earliest when the baby is physiologically stable, with stringent aseptic precautions [16,17].

It will be ideal to use a synthetic detergent (syndet) rather than a soap to cleanse the baby as the latter tends to damage the epidermal barrier. It has been observed that it takes about an hour for the regeneration of skin pH after use of soaps. Syndet liquid cleansers are preferred over syndet bars. Liquid cleansers with acidic or neutral pH

(appropriate blend of ionic, non-ionic and amphoteric surfactants) do not affect the skin barrier function or the acid mantle and hence recommended. AWHONN (Association for Women's Health, Obstetric and Neonatal Nurses) neonatal skin care guidelines recommends the use of minimal amount of pH neutral or slightly acidic cleanser [17]. (*Strong recommendation; Level of evidence VII*). In case of cost constraint, a mild soap with low alkaline pH may be minimally used; although, soaps are best avoided in neonates [11,18].

Routine Bathing in Neonates, Infants and Children

Routine bathing of newborn and infants is mainly need based and dependent on the regional, cultural and climatic conditions. Daily bath not exceeding 15 minutes is preferable, except during winter or in hilly regions, wherein bath may be given twice or thrice in a week or as per the local culture [11]. After bathing, baby should be dried from head to foot using a dry warm towel. Use of bubble baths and bath additives should be avoided as these may increase the skin pH and cause irritation.

Care of the Diaper Area

Diaper area exposed to excessive hydration, maceration, occlusion and friction has an increased pH due to the action of fecal ureases on urea. This increase in pH potentiates the action of fecal enzymes, which are highly irritant to the skin. Hence, diaper area should be always kept clean and dry [19]. Moistened cloth or cotton ball soaked in lukewarm water could be used to clean the area after defecation [20] (*Strong recommendation; Level of evidence VII*). Dry soft cloth/towel can be used to pat dry the skin. Cloth should not be dragged on the skin during removal of faeces or urine or while drying. Only a mild cleanser with slightly acidic to neutral pH that will not disturb the barrier function should be used in the perineal area [11,18,21,22].

Diapers should be changed frequently in order to prevent diaper dermatitis [11,17]. (*Strong recommendation; Level of evidence I*). Duration could vary from every 2 hours in neonates to every 3-4 hours in infants. Cloth napkins are preferable. These are to be washed in warm water and dried in sunlight. Frequent exposure of the nappy area to air would be beneficial [18,22]. If frequent change of napkins is not possible, application of mineral oil to the skin over the diaper area will act as a barrier [18,22]. Baby wipes that are mild on the infant skin may be used [23]. (*Strong recommendation; Level of evidence III*). Wipes should be free of fragrance and alcohol. If disposable diapers have to be used, superabsorbent gel diapers may be used.

Application of barrier creams containing zinc oxide, dimethicone and petrolatum-based preparation at each change of diaper will be beneficial in babies with diaper dermatitis [24] (*Strong recommendation; Level of evidence I*).

Care of the Umbilical Cord

Umbilical cord should be cleaned with lukewarm water and kept dry and clean. Care taker's hands should be washed before and after cord care. If the stump is soiled, it should be washed with water and syndet /mild soap and dried thoroughly with soft, clean cloth. WHO recommends that nothing should be applied on the cord stump [10,12] (*Strong recommendation; Level of evidence VII*). Diaper should be cladded below the stump. No bandage should be applied on the stump [10,12].

Care of the Scalp

First hair wash in a newborn baby may be given after the cord falls. Cradle cap of the scalp is the common problem in newborn babies. Application of mineral oil to the crust and removal after 2 to 3 hours will be helpful. Baby shampoos which are free from fragrance could be used. They should not cause irritation to the eyes [18,22]. Hair wash can be given once or twice a week or as and when required in case of soiling [18,25]. In case of children, hair wash can be given twice a week using a mild shampoo.

Care of Nails

Nails should be cut and kept short [18,26].

Use of Baby Talcum Powders

Routine use of powders is not advocated in neonates and young infants. In the case of infants, if desired, mother should be advised to smear the powder on the hands and then gently apply on the skin of the baby. Puffs should not be used as it may result in accidental inhalation of powder [18,25]. Powder should not be applied in the groins, neck, arm and leg folds.

Care of Skin of Preterm Baby

Preterm baby should be kept in a warm environment. Gentle and minimal handling of the preterm babies would be ideal. Hand hygiene measures are to be followed strictly by the mother/caregiver/healthcare workers. Kangaroo mother care is recommended for the routine care of preterm and low birth weight newborns weighing 2000 g or less at birth, as soon as the neonates are clinically stable [12] (*Strong recommendation; Level of evidence VII*).

Tub-bathing which results in less heat loss, is recommended as a safer and comfortable option than sponge bathing in healthy, late preterm infants with gestational age (GA) between 34-36 weeks [27,28]. In a randomized clinical trial (RCT) [29], swaddle immersion bathing method was found to maintain temperature and reduce stress in preterm babies with GA between 30-36 weeks from 7-30 days of postnatal age compared to conventional bathing, and hence was concluded as an appropriate and safe bathing method for preterm and ill infants in NICUs [29]. Swaddled bathing was found to be more effective at maintaining body temperature, oxygen saturation levels and heart rate compared to tub bathing. AWHONN recommends the use of only warm water without use of cleansers, during the first week of life in infants less than 32 weeks of gestation [17]. UK Neonatal skin care guidelines state that babies less than 28 weeks of gestation should not be bathed and instead recommends the use of sterile pre-warmed water to pat dry the skin [30]. Sponge bathing given in stable preterm neonates resulted in a transient drop of temperature at 15 minutes, but not to the extent of causing hypothermia and subsequently temperature began to rise by 30 minutes and normalized by 1 hour post-bath. Hence, it appears to be a safe method of routine cleansing of stable preterm babies [31]. A RCT [32] documented that bathing preterm neonates every 4 days decreases the risk of temperature instability [32].

To summarize, preterm babies with GA less than 28 weeks should not be bathed, and in case of soiling, sterile pre-warmed water could be used to cleanse with gentle patting of the skin to dry [30] (*Strong recommendation; Level of evidence IV*). In India, sponge bathing is the most common method, currently in vogue, to cleanse babies with GA between 28-36 weeks. However, as the comparison studies between sponge bathing and swaddle immersion bathing, have documented that the latter method is more efficacious in thermoregulation and maintenance of oxygen saturation, swaddle immersion bathing could be adopted, with the training of nursing staff [29] (*Strong recommendation; Level of evidence II*). As there is paucity of Indian literature in this area, the need for more research is highlighted.

Preterm babies are more vulnerable to develop percutaneous toxicity because of the thin skin and larger body surface area. Hence stringent care should be taken while using topical antiseptics in these babies. Alcohol containing solutions have been shown to cause skin burns and hence best avoided in preterm babies. 2% Chlorhexidine is a safer alternative topical antiseptic agent used in newborn units. Use of gentle medical adhesives to secure intravenous cannulas is to be

practiced because epidermal stripping secondary to removal of adhesive dressing is the main cause of skin injury in preterm babies. Adhesive should be loosened with mineral oil or petrolatum based emollient and removed gently avoiding the use of adhesive removers. Position of the baby must be frequently changed. Gentle application of appropriately selected emollients will help to decrease the TEWL and maintain the barrier function [11].

Ideal Cleanser

An ideal cleanser is one that is mild and fragrance free with neutral or acidic pH and does not irritate the skin or eyes. It should not affect the acid mantle of the skin surface, remove the lipids/ natural moisturizing factor (NMF) or disrupt the barrier function [25]. Soapless liquid cleansers appropriately formulated for use in babies could be preferred by virtue of the maintenance of barrier function [11,33]. In children with normal skin, mild soaps are to be used. Syndets are preferred in children with skin disorders that disrupt the barrier function such as atopic dermatitis, ichthyosis, eczema, psoriasis etc.

Shampoos

They are soapless, and consist of principal surfactant for detergent and foaming power, secondary surfactants to improve and condition the hair, additives to complete the formulation and special effects. Shampoos that are used in babies should be mild, fragrance free and should not irritate the eyes [33,34].

Use of Emollients

Dry skin is seen in preterm, post term, intra uterine growth retardation babies, neonates under radiant warmers and phototherapy, and in children with conditions like atopic dermatitis, ichthyosis, contact dermatitis and psoriasis. Various factors like bathing in hot water, frequent washing and use of harsh detergents, exposure to low humidity like air-conditioned environment and cold climate will worsen the dryness of the skin. Ceramides, cholesterol, free fatty acids and NMF present in the stratum corneum contribute to the maintenance of the skin hydration and integrity of the barrier function. NMF and free fatty acids play an important role in the maintenance of low pH in the stratum corneum and in turn barrier integrity [35]. Skin of neonate has been observed to have less hydration of the skin surface, thinner stratum corneum and epidermis, less NMF and increased water loss [36]. Similarly, reduced levels of NMF has been observed in the stratum corneum of infant skin. Washing the skin with soaps removes the lipids and NMF resulting in an increase in the pH of the

stratum corneum and altered homeostasis of the skin. Hence liquid cleansers or if not affordable, judicious use of mild cleansing bars would be the ideal recommendation in babies prone for dry skin [35,36]. The baby's skin is clinically dry but may not appear so. Dry skin leads to micro and macro fissure formation which results in easy penetration of allergens and bacteria. Hence, the use of emollients is very important in order to restore the barrier integrity, prevent infections and further damage. Gentle application of emollients will help to enhance and maintain the skin barrier function [11,37] (*Strong recommendation; Level of evidence VII and IV*).

Natural olive oil and mustard oil have been used for many years as emollients. Studies have shown that these disrupt the skin barrier and hence should not be used [5,38] (*Strong recommendation; Level of evidence II*). Vegetable oils high in linoleic acid such as safflower oil or sunflower oil are recommended for infant's skin. Skin barrier recovery occurs faster with sunflower seed oil and petrolatum, whereas it gets delayed with mustard seed oil, soybean oil and olive oil [5,38]. Oleic acid content of olive oil inhibits synthesis of arachidonic acid, increases membrane permeability and TEWL. Mineral oil has been found to be an effective skin moisturiser by virtue of emollient and occlusion property. In addition, mineral oil, which has limited penetration, does not contain the carcinogenic polyaromatic hydrocarbons and hence has been found to be very safe [39]. Appropriately selected emollients which are petrolatum-based, water miscible, and free of preservatives, dyes and perfumes could be used in pre/post term/IUGR babies, neonates under radiant warmers/ phototherapy and in those infants and children with atopic dermatitis, contact dermatitis, psoriasis and ichthyosis. Emollients decrease the risk of invasive infection in preterm infants by prevention of access to deeper tissues and the blood stream through skin portals of entry [36].

In the case of healthy babies, in whom the stratum corneum function has been disturbed by use of harsh soaps, emollients play a significant role, especially during winter. Simpson et al have shown that application of emollient in babies born in families with high risk of atopy tends to reduce the risk of developing atopic dermatitis [40] (*Strong recommendation; Level of evidence II*). Emollients marketed as natural, herbal and organic have to be used with caution as there are limited study data on these and hence, are to be avoided unless proved to be effective and safe.

Massage

Systematic application of touch is termed as massage.

Massage promotes circulation, suppleness and relaxation of the different areas of the body and tones of the muscles. It relieves the physical and emotional stress in the baby and supports the baby’s ability to fulfill the individual developmental potential. Massage increases the activity of the vagus nerve which results in increased levels of gastrin, insulin and insulin like growth factor 1 that enhances the food absorption, weight gain contributing to increase growth. There is greater bone mineralization, more optimal behavioral and motor responses in infants who were given massage. It has been observed that preterm infants who were given massage had reduced cortisol level and parasympathetic response, reduced stress response, increased vagal activity and gastric motility, release of gastrin, improved weight gain and enhanced motor development. Massage of hospitalized preterm or low birth weight babies resulted in improved daily weight gain, reduced length of stay in the hospital and had positive effect on postnatal complications and weight at 4 to 6 months. In summary, benefits of massage are improved barrier function, decreased TEWL, improved thermo-regulation, stimulation of circulatory and gastrointestinal

systems, improved sleep rhythm and enhanced neurological and neuromotor development [41-45].

Touch therapy –massage – by whom? when? where? how?: Massage may be given by mother, father, grandparents, caregiver or nurse. Full body massage will need fifteen to thirty minutes of uninterrupted time and is to be given when the baby is quiet, alert and active, preferably one to two hours after feed. Massage is to be given in a warm room. Massage provider should avoid having long nails or wearing any jewelry in the hands. Massage should be slow and gentle but firm enough for the baby to feel secure.

Oil Massage

Oil acts as a source of warmth and nutrition and helps in weight gain of the babies. Coconut oil, sunflower oil, synthetic oil and mineral oil are being used for massage [5,38,46,47]. Babies massaged with oil showed less stress behavior and lower cortisol levels than those who were given massage without oil [48]. Thus, oil massage has multiple benefits and hence is recommended

Table I Evidence Based Recommendations for Skin Care in Neonates and Infants

<i>Recommendation</i>	<i>Level of evidence [50]</i>	<i>Strength of recommendation</i>
Skin-to-skin care (SSC) for all mothers and newborns without complications at least for one hour [7,12]	Level VII	Strong
Vernix caseosa should not be removed [11,12]	Level VII	Strong
First bath should be delayed until 24 hours after birth but not before 6 hours [13]	Level VII	Strong
Duration of bath should not exceed 5-10 minutes [11]	Level VII	Strong
Liquid cleanser with acidic or neutral pH preferred as it will not affect the skin barrier function or the acid mantle [11,17]	Level VII	Strong
Prevention of diaper dermatitis - Frequent change of diapers [24]	Level I	Strong
In babies with diaper dermatitis, frequent change of diapers, use of super absorbent diapers and protection of perineal skin with a product containing petrolatum and or zinc oxide [24]	Level I	Strong
Use of soft clothes and water for cleansing the diaper area is encouraged [20]	Level VII	Strong
Only fragrance free baby wipes can be used [23]	Level III	Strong
Nothing should be applied on the cord stump [10]	Level VII	Strong
Kangaroo mother care is recommended for the routine care of preterm and low birth weight newborns weighing 2000 g or less at birth, as soon as the neonates are clinically stable [12].	Level VII	Strong
Swaddle immersion bathing could be adopted, with the training of nursing staff [29]	Level II	Strong
Gentle application of appropriately selected emollients will help to maintain the barrier function [11,37]	Level VII	Strong
Application of emollient in babies born in families with high risk of atopy tends to reduce the risk of developing atopic dermatitis [40]	Level II	Strong
Vegetable oils such as olive oil and mustard oil should not be used [5,38]	Level II	Strong
Oil massage has multiple benefits and hence is recommended [38,46,48]	Level II	Strong

[38,46,48] (*Strong recommendation; Level of evidence VII*). Mustard oil has been shown to cause irritant and allergic contact dermatitis while olive oil is reported to cause erythema and disruption in skin barrier function [44,45]. Oil massage is to be avoided during summer, if miliaria rubra is present. Oil massage should be given before bath during summer and after bath during winter [38,48,49].

Synopsis of evidence-based recommendations for skin care in neonates and infants is given in **Table I** [50] and assessment of recommendations in **Supplementary Table I**.

Care of Skin in Special Situations

Atopic Dermatitis

Atopic dermatitis (AD) occurs in genetically predisposed children with impaired epidermal barrier function and immune dysregulation. AD is characterized by chronic relapsing dermatitis with pruritus and age dependent distribution of skin lesions. Initially, skin lesions start over the face and trunk followed by extensor aspects and later involves the flexural areas. Emollients containing ceramides, lipids and n-palmitoyl ethanolamine and natural colloid oatmeal are useful in children with atopic dermatitis. Emollients are to be applied within 3 to 5 minutes after a quick bath (5–10 minutes) in lukewarm water and patting the skin dry. Frequency of application should be every 4 to 6 hours depending on the degree of dryness. Emollients should be applied 30 minutes before the application of topical corticosteroid cream. Proper application of sufficient quantity of emollients will help to reduce the frequency of flares. In babies at high risk for atopic dermatitis, application of emollient from birth has been observed to be safe and effective towards primary prevention of atopic dermatitis [40, 51-53].

Seborrheic Dermatitis

Seborrheic dermatitis occurs mostly in the sebum rich areas of the body like scalp, face and body. The exact etiology is not known but may be associated with various factors like genetic predisposition, *Malassezia* colonization of the skin, dryness of the body and environmental factors like cold weather. In newborn period, the maternal hormones may trigger this condition. Usually seborrheic dermatitis appears by third or fourth week of life and peaks by 3 months of age. Scaling over the scalp, around the eyes, nose and the folds of the skin and diaper area may be present. It is usually asymptomatic and disappears by one to six months of age. Emollients are useful in infantile seborrheic dermatitis. Hydrocortisone 1% cream has been found to be of use for lesions on the face. Topical azole antifungal agents could be used for lesions in the groin [54].

Photoprotection

Routine use of sunscreens has not been a common practice in the community at large in India. But, in the recent years, there is increased interest and awareness evinced among the parents, especially those with children involved in sports. Sunscreens used in children should ideally provide broad spectrum (ultraviolet A and ultraviolet B) coverage, good photo stability and should not cause irritation. Those that contain physical or inorganic filters such as zinc oxide or titanium oxide are preferable. Liquids, sprays and alcohol-based gel formulations are likely to cause irritation and hence are best avoided in children below 12 years. Sunscreens that contain para amino benzoic acid (PABA), cinnamates and oxybenzone may cause allergic contact dermatitis. In infants below 6 months of age, photoprotection with appropriate clothing and headgear is recommended, rather than use of sunscreens. American Academy of Pediatrics recommends limitation of sun exposure between 10.00 am and 4.00 pm, use of protective, comfortable clothing, wide-brimmed hats, sunglasses with ultraviolet (UV) protection and broad-spectrum sunscreen with Sun protection factor (SPF) ≥ 15 in infants older than 6 months and children. Sunscreen should be applied 30 minutes before going outdoors with reapplication every 2 hours and after swimming, excessive sweating, vigorous exercise and toweling. Application of appropriate quantity (2 mg/cm²) to all the sun-exposed areas is necessary to provide good photo protection [55-57].

CONCLUSION

Evidence based standard recommendations for care of the skin of newborn babies and infants will facilitate the improvement of quality of skin care of the babies which in turn will have a positive impact on their future health. These recommendations could be further revalidated with advent of more scientific data in the years to come.

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ANNEXURE 1

Expert Members of the Committee

(in alphabetical order)

Anandan V (Chairperson, IAP Dermatology chapter), *Chennai*; Bakul Jayant Parekh, *Mumbai*; Basavaraj GV, *Bengaluru*; Digant D Shastri, *Surat*; Madhu R (Secretary, IAP Dermatology chapter), *Chennai* (Co-convener); Nedunchelian K (Executive Board member, IAP Dermatology chapter), *Chennai*; Remesh Kumar R, *Cochin*; Santosh T Soans, *Mangalore*; Thangavelu S (Executive Board member, IAP Dermatology chapter), *Chennai*; Vijayabhaskar C (Treasurer, IAP Dermatology chapter), *Chennai* (Convener).

Comparative Efficacy and Safety of Non-Steroidal Anti-Inflammatory Drugs in Patients With Juvenile Idiopathic Arthritis: A Systematic Review and Network Meta-analysis

CHUN-LIAN SHI, YU ZHANG, ZHI-YONG ZHANG, JUAN ZHOU AND XUE-MEI TANG

From Department of Rheumatology and Immunology, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Child Infection and Immunity, Children's Hospital of Chongqing Medical University, Chongqing, PR China

Correspondence to: Dr. Xue-mei Tang, Department of Rheumatology and Immunology, Children's Hospital of Chongqing Medical University, Yuzhong District, Chongqing 400 014, China. tangxuemei_2019@163.com

Objective: We conducted a systematic review and network meta-analysis to compare the efficacy and safety of nine non-steroidal anti-inflammatory drugs (NSAIDs) in treating patients with juvenile idiopathic arthritis (JIA). **Methods:** Randomized controlled trials (RCTs) of NSAIDs for the treatment in children with JIA were searched systematically by using MEDLINE, EMBASE, and the Cochrane Library for available literature up to January 1, 2019. Bayesian network meta-analysis was used to combine direct and indirect evidence on treatment effectiveness and safety. **Results:** Eight eligible RCTs involving 1112 patients with JIA were identified, addressing 9 interventions. The ranking probability plot based on the surface under the cumulative ranking curve (SUCRA) indicated that celecoxib (6 mg/kg twice-a-day) had the highest probability of being most effective (SUCRA = 76.4%) among four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen). Also, rofecoxib (0.3 mg/kg once-a-day) and piroxicam demonstrated a higher probability of safety in treating children with JIA (SUCRA = 33.0% and 35.5%, respectively), compared with other interventions. **Conclusions:** The quality of available evidence limits the formation of powerful conclusions regarding the comparative efficacy or safety of NSAIDs used to treat JIA.

Keywords: *Drugs, Juvenile chronic arthritis, Management, Pain, Rheumatoid arthritis, Side-effects.*

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and one of the leading causes of pediatric acquired disability. It encompasses a heterogeneous group of disorders characterized by chronic arthritis, of unknown etiology, lasting for 6 weeks or more, with disease onset before 16 years of age having excluded arthritis caused by other diseases [1]. Treatment is aimed to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. Currently, early diagnosis and treatment of JIA with conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) have vastly improved outcomes for children with these diseases.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as an adjunct therapy for symptomatic management, particularly during initiation or escalation of therapy with DMARDs or biologic agents [2]. NSAIDs exert their analgesic and anti-inflammatory effects by blocking prostaglandin formation *via* inhibition of cyclooxygenase (COX) isoenzymes, a rate-limiting enzyme in the prostaglandin biosynthetic pathway. Both non-selective (which suppress both COX-1 and COX-2 enzymes) and selective (suppress COX-2 only) NSAIDs

have been used in JIA [3].

Previous comparative studies of NSAIDs were mostly performed to evaluate the efficacy and safety of two NSAIDs or one NSAID versus placebo [4,5]. However, the preferred NSAID in the treatment with JIA still remains unclear. To comprehensively compare and rank different NSAIDs in the treatment of children and adolescents with JIA, we conducted a systematic review and network meta-analysis [6,7].

METHODS

This systematic review with meta-analysis was conducted and reported according to the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [8].

Eligibility criteria and search strategy: Randomized controlled trials (RCTs) were included if they met the following criteria: (i) the study compared any NSAID with placebo or another NSAID in the treatment of JIA; (ii) the study provided endpoints for the efficacy or adverse events; and (iii) the study included patients diagnosed with JIA. The details of eligibility criteria are provided in **Web Table**

1. For this network meta-analysis, MEDLINE (via PubMed), EMBASE, and the Cochrane Library were searched for RCTs published from January 1, 1965, to January 1, 2019, comparing the efficacy and (or) safety of NSAIDs in the treatment of JIA. The following search terms were used: “#1 “Juvenile Idiopathic Arthritis” OR “Arthritis” OR “Still Disease” OR “Rheumatoid” AND #2 “NSAIDs” OR “Agents” OR “Non-Steroidal Anti-Inflammatory Drugs” OR “Analgesics” OR “indomethacin” OR “naproxen” OR “Naprosyn” OR “aspirin” OR “acetylsalicylic acid” OR “celecoxib” OR “Celebrex” OR “rofecoxib” OR “piroxicam” OR “ibuprofen” OR “meloxicam” OR “tolmetin” OR “diclofenac” OR “Voltaren” OR “voltarol” AND #3 “randomized controlled trial” OR “controlled clinical trial” OR “placebo” OR “drug therapy” OR “groups”. In order to ensure the authenticity of data, we also searched the list of references included in the articles.

Data extraction: The following information was extracted from each study: *i*) study characteristics (author, year, study design); *ii*) patient characteristics (sample size, race, age, sex, duration of JIA, subtype); *iii*) interventions: any NSAID, dosage, concomitant therapy, follow-up time when outcomes were evaluated; and, *iv*) outcomes (efficacy, and adverse events). Data were extracted from original studies by two independent investigators, and any discrepancy between the investigators was resolved by after discussions along with a third investigator.

The primary outcomes were efficacy (the number of patients who had improvement in symptoms of arthritis) and safety (the number of patients who experienced adverse events).

Quality assessment: The risk of bias was assessed using Cochrane risk of bias tool [9], evaluating for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias like sample size, [10] (labeling them as low risk of bias with 200 participants or more per treatment group, unclear risk with 50 to 199 participants per treatment group, or high risk with fewer than 50 participants per treatment group), multiple publications, financial declarations, and participants with conflicts of interest.

Statistical analyses: First, we divided the three-arm or more-than-three-arm tests into combinations of any two arms, and performed the evidence network diagram for the comparison of each treatment. We assessed the inconsistency or extent of disagreement between direct and indirect evidence. For closed loops, we tested the transitivity assumption by examining loop-specific consistency

between direct and indirect effects using network side splits and global consistency by comparing a model assuming consistency with an inconsistent model. When the global Wald test indicated no significant differences between the consistency and inconsistency models [11] and no significant differences in estimates based on side splits, we presented consistency model estimates. The Markov chain Monte Carlo (MCMC) method was used to obtain pooled effect sizes [6]. We calculated the risk ratio (RR) with 95% credible interval (CI; or Bayesian confidence interval). The efficacy and safety of NSAIDs in different arms were ordered according to the probability of being ranked as the best performing regimen. We did a network meta-analysis within a Bayesian framework with WinBUGS (version 1.4.3) and further analysis with Stata (version 15.1). Information on relative effects and safety was converted to a probability that a treatment is the best, second best, etc., or to the ranking of each treatment, called the surface under the cumulative ranking curve (SUCRA) [12]. The SUCRA value was 100% when a treatment is certain to be the best for efficacy but the worst for safety.

RESULTS

The selection of studies is shown in the flowchart (**Fig. 1**). Overall, 8 studies provided data of 1112 individual JIA patients receiving the following NSAIDs: celecoxib,

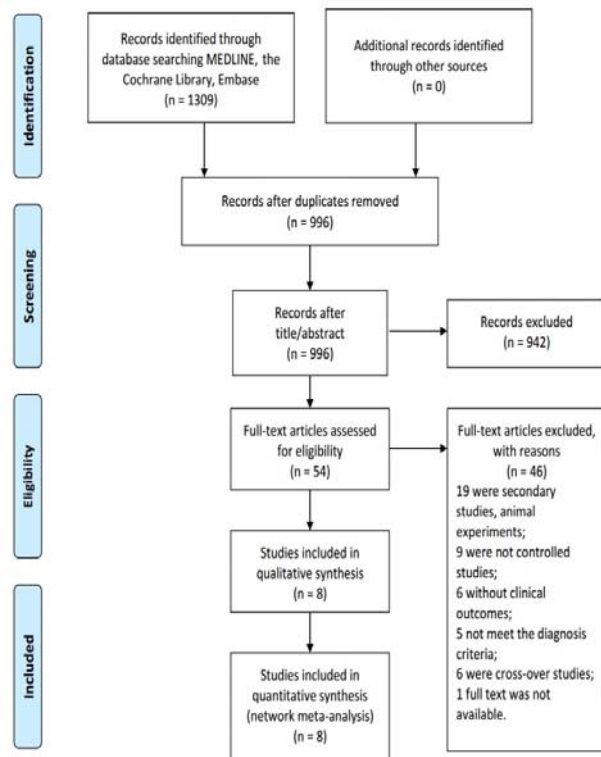


Fig. 1 PRISMA 2009 flow diagram.

rofecoxib, meloxicam, diclofenac, ibuprofen, naproxen, piroxicam, and tolmetin. The study sample size ranged from 26 to 310. The duration of treatments was from 2 weeks to 24 weeks. It was reported that there was no significant difference in age, sex, course of disease between the groups. The subtype of JIA contained poly-articular JIA, oligoarticular JIA, and systemic JIA. The details of each included trial were listed in **Table I**. Risk of bias within individual studies was assessed (**Fig. 2**).

Network meta-analysis for efficacy: Network meta-analysis was only performed when studies were sufficiently homogeneous regarding outcome criteria. Thus, for efficacy, three studies [14-16] with the efficacy criteria of achieving an American College of Rheumatology Pediatric-30 (ACR Pedi 30) response [22-23] were eligible. Four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen) were compared with at least

one other active drug directly and indirectly. There were no significant differences between any two NSAIDs regarding efficacy (**Fig. 3**). The ranking of treatments based on cumulative probability plots and SUCRAs is shown in **Web Fig. 1**. In terms of efficacy, celecoxib (6 mg/kg bid) had the highest probability of being most effective (SUCRA = 76.4%), while two doses of meloxicam ranked last.

Network meta-analysis of the safety: Nine NSAIDs (celecoxib, rofecoxib, meloxicam, naproxen, ibuprofen, aspirin, diclofenac, piroxicam, and tolmetin) were directly compared with at least one other active drug. There were no significant differences between any two NSAIDs regarding safety (**Fig. 4**). Ranking probability based on SUCRA values indicated that rofecoxib (0.3 mg/kg/d) had the highest probability of being the safest treatment (SUCRA=33.0%), followed by piroxicam (SUCRA =35.5%). Tolmetin and aspirin appeared to have the worst safety probability (SUCRA=82.3% and 82.0%, respectively) (**Web Fig. 2**).

Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility of inconsistencies that might significantly affect the results. In addition, the results of the random and fixed-effects models yielded the same interpretation, indicating that the results were robust.

DISCUSSION

We conducted a network meta-analysis of currently available literature regarding NSAIDs for children and adolescents with JIA. Unlike previous meta-analyses, we were able to generate a ranking order for the relative efficacy and safety of NSAIDs in patients with JIA. We found that the rate of efficacy observed in all treatment groups in our study were above the pooled composite placebo response rate (28.9%) reported in a meta-analysis of six placebo-controlled trials [25]. However, no statistically significant differences were observed between NSAIDs in terms of efficacy or safety. The findings are similar to the previous meta-analysis on NSAIDs for osteoarthritis in adults [26,27]. The SUCRA ranking suggests that celecoxib had better efficacy, while piroxicam and rofecoxib have higher safety probabilities, compared to other NSAIDs.

The most common adverse effects across all treatment groups were gastrointestinal side effects, rash, headache, and pyrexia. These side effects occurred more frequently within the aspirin, tolmetin, and ibuprofen groups, resulting in more non-compliance. Estimates of NSAIDs-associated gastropathy range from 0.7-75%, depending on different study designs [28-32]. Most of the gastrointestinal

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Edward H 1990	+	+	+	?	?	+	-
Foeldvari 2009	+	?	+	?	+	+	?
Haapasaari 1983	?	+	+	?	?	+	-
Kvien 1984	?	+	+	?	?	+	-
Levinson 1977	?	?	+	?	?	+	?
Morteo 1987	?	?	+	?	?	+	-
Reiff 2006	+	+	+	?	+	+	?
Ruperto 2005	?	?	+	?	+	+	?

Fig. 2 Risk of bias assessment.

Table 1 Randomized Controlled Trials Included in the Systematic Review and Network Meta-analysis of Efficacy and Safety of Non-steroidal Anti-inflammatory Drugs in Juvenile Idiopathic Arthritis

Study, year	Size of sample (t1/t2/t3)	Mean age (y) (t1/t2/t3)	Subtype	Mean duration (y) t1/t2/t3 (wk)	Treatment			Concomitant therapy			Treatment duration (wk)
					t1	t2	t3	DMARDs (%)	Biologic agents (%)	CS (%)	
Foeldvari, et al. [14], 2009	77/82/83	10.4/10.2/10.4	pJIA, oJIA	2.71 (2.8)/ 3.77 (3.4)/ 3.41 (3.2)	Celecoxib 3 mg/kg bid	Celecoxib 6 mg/kg bid	Naproxen 7.5 mg/kg	50.6/47.6/51.8	0/3.7/3.6	NA	12
Reiff, et al. [15], 2006	109/100/101	9.7/9.4/10.7	pJIA, oJIA	4.0 (3.6)/ 3.4 (3.0)/ 3.7 (3.3)	Rofecoxib 0.3 mg/kg qd	Rofecoxib 0.6 mg/kg	Naproxen 7.5mg/kg	53.2/51.0/45.5	NA	19.3/22/14.9	12
Ruperto, et al. [16], 2005	73/74/78	8.9/9.0/7.5	pJIA, oJIA	3.47 (3.4)/ 2.5 (2.8)/ 2.31 (2.1)	Meloxicam 0.125 qd	Meloxicam 0.25 mg/kg	Naproxen 5 kg	24.7/28.4/37.2	NA	NA	12
Edward, et al. [17], 1990	92,1:1	7.7	pJIA, oJIA, sJIA	NA	Ibuprofen 30-40 mg/kg/d	Aspirin 60-80 mg/kg/d	—	0	0	NA	12
Haapasaari, et al. [18], 1983	45,1:1:1	N/A	pJIA, oJIA, sJIA	NA	Diclofenac 2-3 mg/kg/d	Aspirin 50-100 mg/kg/d	Placebo	NA	NA	NA	2
Morteo, et al. [19], 1987	26,1:1.06	8.5	pJIA	2.7/1.6	Piroxicam*	Naproxen 12.5 mg/kg/d	—	NA	NA	11.5	12
Kvien, et al. [20], 1984	80,1:1	10.2	pJIA, oJIA	1.0/1.3	Naproxen 10 mg/kg/d	Aspirin 75 mg/kg/d	—	0	0	0	24
Levinson, et al. [21], 1977	107,1:1.02	9.2	pJIA, oJIA, sJIA	3.7/3.4	Tolmetin 15 mg/kg/d	Aspirin 50 mg/kg/d	—	NA	0	0	12

End points for all studies were efficacy and adverse events. NA: not applicable; pJIA: polyarticular juvenile idiopathic arthritis; oJIA: oligoarticular juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis; DMARDs: disease-modifying anti-rheumatic drugs; CS: corticosteroid; AEs: adverse events. *Piroxicam dose. 15-30 kg: 5 mg/kg/d; 31-45 kg: 10 mg/kg/d; 46-55 kg: 15 mg/kg/d.

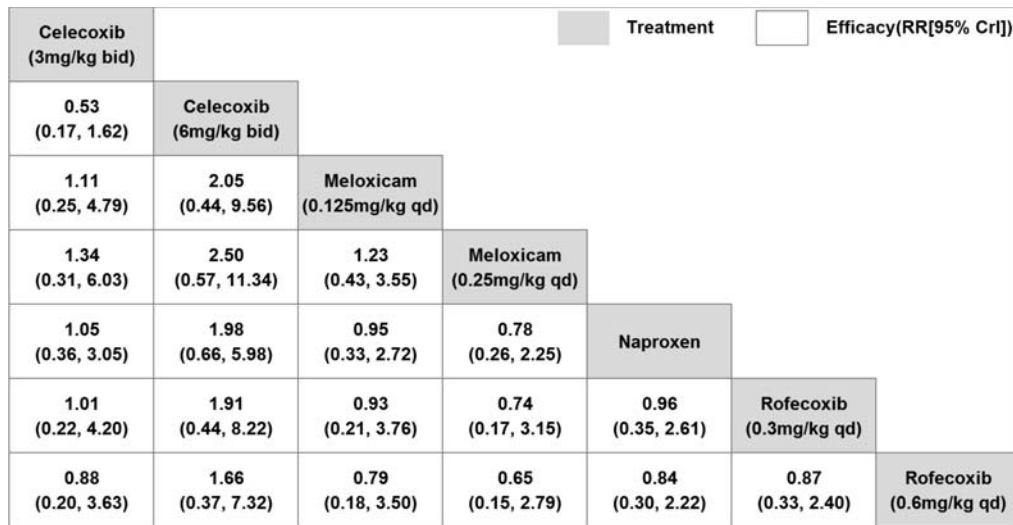


Fig. 3 Network meta-analysis of efficacy of non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.

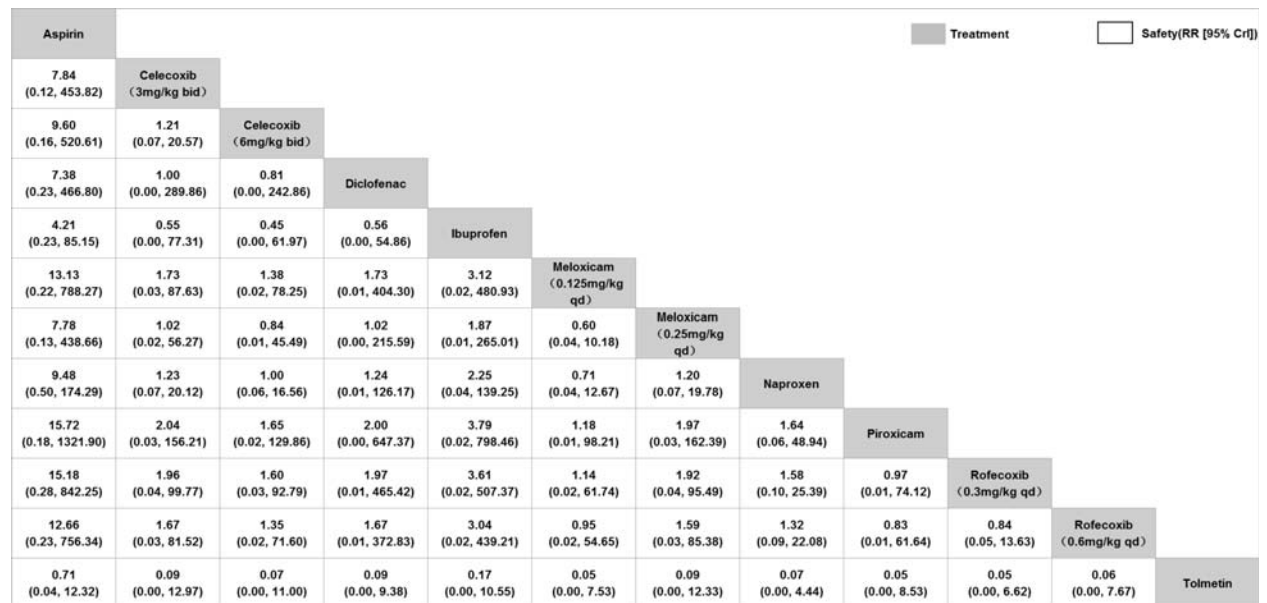


Fig. 4 Network meta-analysis of safety of non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.

disorders were mild, while serious gastropathy such as gastrointestinal perforation and massive gastrointestinal hemorrhage was lower than adults. The combination of glucocorticoid, leflunomide, and methotrexate can aggravate gastrointestinal adverse reactions. While children have a very low risk of cardiovascular thromboembolic and serious gastro-intestinal events, prolonged use of NSAIDS into adulthood could make them vulnerable to such risks, especially when associated with other risk factors such as obesity or smoking [36].

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the quality of the evidence related to our outcomes. The eight included studies themselves were of moderate quality; however, there may be circumstances where the overall rating for a particular outcome would need to be adjusted per GRADE guidelines [37]. The sample size for some comparisons was assessed as a high bias of risk, which largely restricts the quality of meta-analysis. Among the included studies, there were no two studies

that investigated the same type of NSAID compared with another type of NSAID, which might overestimate the efficacy and safety of treatments. Additionally, the inconsistent criteria of efficacy make it impossible to make a comprehensive comparison of some NSAIDs. Also, there was no data on the stratification of subtypes and concomitant therapy, thus it is unlikely to eliminate the impact of these factors on efficacy and safety. The follow-up time points were limited from only 2 to 24 weeks. The quality of the evidence (GRADE rating) for the efficacy and safety of NSAIDs is very low, meaning there is no evidence to support or refute the findings.

In conclusion, this Bayesian network meta-analysis involving eight RCTs with low quality of evidence showed that, in terms of efficacy, celecoxib (6 mg/kg bid) ranked best among the four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen). In terms of safety, rofecoxib, piroxicam, and meloxicam may be better than others. However, the limitations of the study and suboptimal quality of evidence bar us from making strong conclusions about the comparative efficacy or safety of NSAIDs used to treat JIA. Further well-designed RCTs are needed to figure out the best NSAID for JIA.

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Contributors: TX: conceived and designed the study, critically revised the manuscript; SC: acquired data, interpreted data, and drafted and critically revised the manuscript. ZY, ZZ, ZJ: critically revised the manuscript; SC, TX: screened and selected articles; SC, ZY, TX: assessed the quality of included trials. All the authors read and approved the final manuscript.

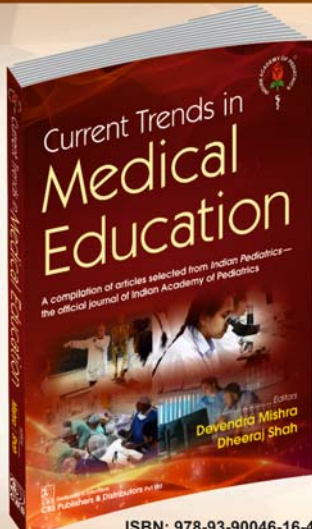
Competing interests: None stated. **Funding:** None.

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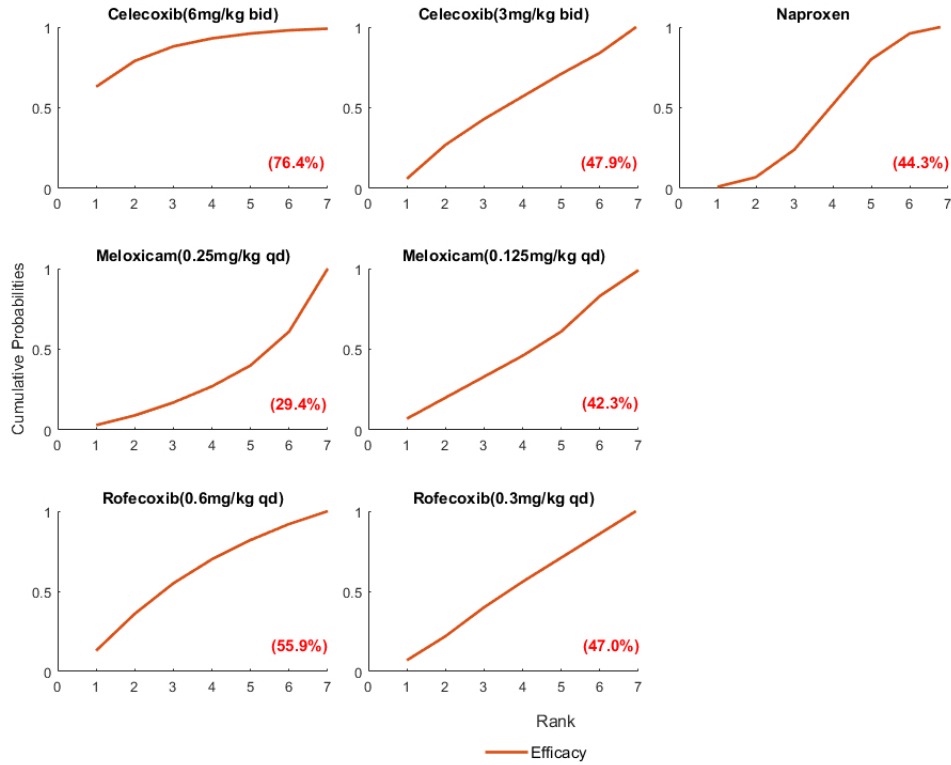
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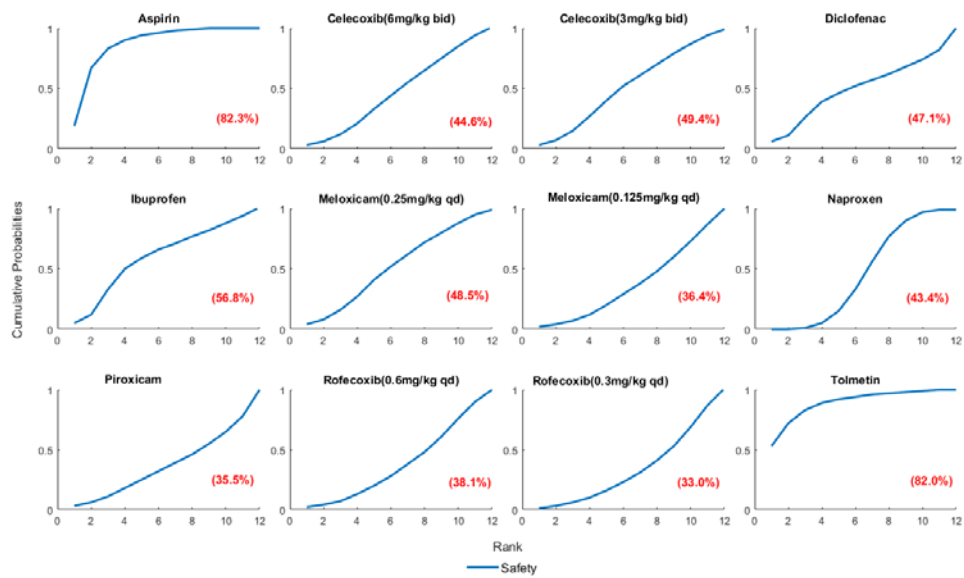
Web Table I Eligibility Criteria for The Selection of Studies

<i>Inclusion criteria</i>	<i>Rationale</i>
<i>Population</i>	The population was restricted to patients of both genders with a diagnosis of JIA.
Gender: any	
Race: any	
Disease: JIA	
<i>Intervention</i>	
Any NSAIDs	NSAIDs used to treat JIA. Different formulations or routes of administration were included.
<i>Comparison (if applicable)</i>	
Any NSAID	Comparative studies were selected if a NSAID was compared to any NSAID or placebo
Placebo	
<i>Outcomes</i>	
The efficacy and (or) safety	We select studies to assess their effect on efficacy and (or) adverse events.
<i>Language</i>	
No language restrictions were applied to the search strategy	The systematic review was meant to be as comprehensive as possible
<i>Publication timeframe</i>	
No timeframe restrictions were applied to the search strategy	The systematic review was meant to be as comprehensive as possible
<i>Study design</i>	
RCTs	RCTs are the standard of clinical evidence due to their design
<i>Exclusion Criteria</i>	
<i>Population</i>	
Not JIA	Due to the primary objective of this review, studies with multiple disease states were excluded.
<i>Study design</i>	
Unpublished data (conference abstracts, oral and poster presentations), reviews, meta analyses and editorials	Only original research, published in a peer-reviewed journal, was included in this review

JIA: Juvenile idiopathic arthritis; NSAID: Nonsteroidal anti-inflammatory drug; RCT: Randomized clinical trial.



Web Fig. 1 Cumulative efficacy rankings of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis in children.



Web Fig. 2 Cumulative safety rankings of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.

X-Linked Agammaglobulinemia With Chronic Meningoencephalitis: A Diagnostic Challenge

ARUSHI GAHLOT SAINI,¹ BISHAN DASS RADOTRA,² DHARMAGAT BHATTARAI,¹ AMIT RAWAT¹ AND VIKAS BHATIA³
From Departments of ¹Pediatrics, ²Histopathology and ³Radiology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Correspondence to: Dr Bishan Dass Radotra, Departments of Histopathology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. bishanradotra@gmail.com

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X-linked agammaglobulinemia (XLA) is a primary disorder of humoral immunity characterized by *Bruton tyrosine kinase* gene mutations resulting in a primary antibody deficiency. While an intact T-cell function largely protects against majority of viral infections, enteroviruses are notorious for infecting these patients due to impaired mucosal immunity. Although the incidence of enteroviral meningoencephalitis in XLA is only 1-5%, yet the mortality is quite high. A typical presentation of enteroviral encephalitis in XLA is a subacute to chronic nervous system infection. A progressive loss of motor and cognitive milestones, spastic quadriplegia, coma, and death are common presentations. The histopathological features reflect gliosis, gradual neuronal loss, neuronophagia, and microglial proliferation. We describe the clinical and brain histopathological findings in a 2-year-old boy with XLA and progressive encephalitis, possibly due to an enteroviral infection.

Keywords: Central nervous system infection, Enterovirus, Encephalitis, Epilepsia partialis continua, Immunodeficiency.

A 3-year-old boy was admitted with recurrent febrile illnesses and neurological symptoms. The first illness, at 21 months of age, manifested as a high-grade fever with non-paroxysmal cough, respiratory distress, and a generalized macular rash, present over one week. The perinatal period and development were normal. Computed tomography scan of the chest showed nodules in the bilateral lower lobe with necrotic conglomerating mediastinal lymph nodes suggestive of infective etiology. A clinical diagnosis of probable measles with pneumonia was considered. At 24 months of age, he again presented to our center with a febrile illness. Examination showed the absence of tonsils and peripheral lymph nodes, and presence of a BCG scar. Family history revealed that two of his maternal uncles had died in early childhood due to an undiagnosed infection. A clinical diagnosis of X-linked agammaglobulinemia (XLA) was considered and confirmed by specific investigations as per the diagnostic criteria proposed by European Society for Immuno-deficiencies [1]. Monthly intravenous immunoglobulin (IVIg) (400 mg/kg) was initiated, and he showed symptomatic improvement. At 26 months of age, he developed left-sided focal motor status epilepticus and left-sided hemiparesis without associated fever, altered sensorium, cranial nerve involvement, or features of raised intracranial pressure. Investigations are shown in **Table I**. Magnetic resonance imaging (MRI) of the brain showed focal signal changes (details in the

section on investigations). A clinico-radiological diagnosis of XLA with probable focal enteroviral encephalitis was considered. Intravenous acyclovir (30 mg/kg/d for 15 days) and high-dose IVIg (1g/kg) were given. He recovered with residual left hemiparesis. He was readmitted a month later with persistent vomiting, intermittent lethargy, redness of eyes with watery discharge, and brief intercurrent seizures over the past one week. He had been on regular monthly IVIg replacements, and trough IgG level was 600 mg/dl. He continued to have altered sensorium and residual left hemiparesis with radiological progression of the focal encephalitic changes (details in the section on investigations). He had two further admissions, one and six months later, with persistent left-sided, focal seizures and residual left hemiparesis. By 34 months of age, he developed subacute neurological deterioration (progressive lethargy and reduced interaction), visual deterioration, and recurrent right-sided focal tonic-clonic seizures followed by right hemiparesis. At this time, examination showed weight 10 kg (-2 to -3 z), length 90 cm (-1 to -2 z) and head circumference 48 cm (-1 to -2 z). His Glasgow Coma Scale was 11 (E₃M₅V₃₋₄), and pupils were 2mm bilaterally equal and reacting to light. He had chronic left-sided motor weakness with lower limb spasticity, acute-onset right-sided weakness with diminished tone, brisk deep tendon reflexes and bilateral extensor plantar response. Rest of the systemic examination was unremarkable.

Table I Relevant Investigations During Multiple Hospitalizations

<i>Investigations</i>	<i>First admission</i>	<i>Subsequent admissions</i>	<i>Last admission</i>
Platelets (10 ⁹ /L)	179	504	565
TLC (10 ⁹ /L)	16	95	76.3
DLC (%)	N ₃₂ L ₃₈ M ₂₈ E ₂	N ₄₉ L ₃₅ M ₉ E ₆	N ₅₃ L ₃₁ M ₈
ANC (cells/mm ³)	512	4655	4043
Serum galactomannan ^a	0.4	0.18	0.3
<i>Microbiological and radiological investigations</i>			
Blood, urine and CSF cultures	Sterile	Sterile	Sterile
Toxoplasma PCR	Negative	-	Negative
Mycoplasma serology	Negative	Negative	Negative
HIV serology	Non-reactive	-	-
Cerebrospinal fluid	No cells, glucose 59 mg% protein 21 mg%	No cells, glucose 61 mg% protein 21 mg%	No cells, glucose 183 mg% protein 438 mg%
Cryptococcal antigen	Negative	Negative	Negative
Herpes PCR	Negative	-	Negative
Enterovirus	Negative by PCR and cultures		
Electroencephalogram	Right-sided centro-parietal periodic lateralized epileptiform discharges		Encephalopathic pattern with interictal discharges
<i>Immunological investigations</i>			
Immunoglobulin G (mg/dL)	<92 (370-1580)		
Immunoglobulin A (mg/dL)	<17 (30-130)		
Immunoglobulin M (mg/dL)	<25 (50-220)		
CD3+ T-lymphocytes	83.93% (56-75%)		
CD20+ B lymphocytes	0.07% (14-33%)		
CD56+ natural killer cells	9.74% (4-17%)		
CD3+/56+ natural killer T-cells	3.35 (normal)		
Btk protein expression on CD14+ monocytes	11.5% positive; Median Fluorescence Intensity (MFI): 1.89 (Control 87.4% positive; MFI: 5.84)		

HSV: herpes simplex virus; PCR: polymerase chain reaction; TLC: total leucocyte count; DLC: differential leucocytes count; ANC: absolute neutrophil count; ^aSerum galactomannan index normal <0.5.

Investigations (Table I): XLA being a prototype primary humoral immunodeficiency disorder, T cells and their subsets were not tested in the blood or on the brain sections at autopsy. Stool sample was negative for both polio and non-polio viruses. Baseline MRI of the brain at the onset of seizures showed presence of a right-sided, frontal, subcortical white matter lesion, which showed gliosis later. New lesions appeared in bilateral occipital and parietal subcortical white matter, and the thalamus, suggesting a progressive, subcortical, multifocal involvement (**Fig. 1A-H**). MR spectroscopy revealed reduced NAA with a small lactate peak.

Course and Management: Multiple anti-epileptic drugs (phenytoin, valproate, levetiracetam, phenobarbitone, midazolam infusion) were sequentially given for right-sided epilepsy partialis continua. He was intubated and

ventilated for worsening sensorium. Intravenous acyclovir and high dose IVIg (2g/kg total dose) were restarted. Brain biopsy was deferred due to the poor general condition of the patient. Newer therapies such as pleconaril and pocapavir were considered but could not be tried due to resource-constraints. The patient further developed high-grade fever secondary to nosocomial infection and/or aspiration pneumonia. Intravenous antimicrobials were sequentially upgraded (ceftriaxone, meropenem, vancomycin). He suffered a cardiac arrest on day 19 of hospital stay and could not be revived.

Unit's Final Diagnosis

X-linked agammaglobulinemia with recurrent seizures and encephalopathy probably due to chronic enteroviral encephalitis complicated with nosocomial pneumonia.

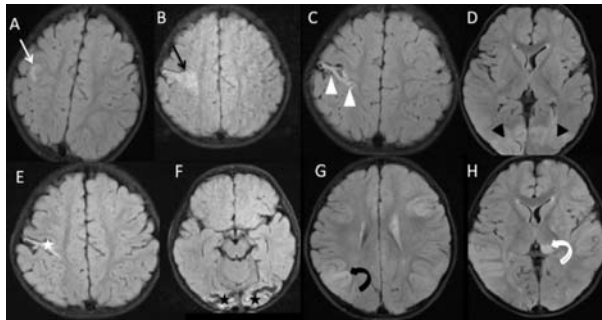


Fig. 1 Sequential axial flair MR images of the patient: Baseline MRI *a*) shows the presence of frontal subcortical white matter lesion (white arrow). MRI after 24 days *b*) shows the progression of frontal subcortical white matter lesion (black arrow). Interval MRI after one month, *c,d*) shows gliosis in the right frontal subcortical lesion (white arrowheads) and appearance of bilateral occipital subcortical lesions (black arrowheads). Interval MRI after 1.5 months (*e,f*) shows gliosis in the frontal (white star) and occipital (black stars) subcortical lesions. Interval MRI after five months (*g,h*) shows the appearance of new parietal subcortical (curved black arrow) and thalamus (curved white arrow) lesions. No evidence of any diffusion-weighted abnormality, susceptibility-weighted abnormality, contrast enhancement, or angiographic abnormality was noted in all the MRI examinations.

DISCUSSION

Clinical discussant: We had a 34-month-old boy with recurrent sinopulmonary infections, absent tonsils, lymph nodes and peripheral B-cells, pan hypogammaglobulinemia, reduced Btk protein expression on CD14+ monocytes and progressive neurocognitive decline. The family history supported an X-linked inheritance pattern. Based on the standard diagnostic criteria, a diagnosis of underlying XLA is beyond doubt [1].

Regarding the central nervous system (CNS) manifestations, the patient had an acute CNS event, which progressed both clinically and radiologically over the subsequent 12-14 months with intermittent exacerbations. CNS manifestations in children with XLA can be either due to an inability to clear the opportunistic infections, or due to a dysregulated immunity, or both. XLA is a prototype of humoral immunodeficiency disorders with B-lymphocyte differentiation arrest, resulting in recurrent infections with encapsulated bacteria like pneumococcus and *H. influenza*, gastrointestinal infections with giardia and chronic enteroviral infections [2]. However, the chronic and indolent clinical course, presence of significant neutropenia and absence of fever during all episodes of clinical deterioration make bacterial infection unlikely. Moreover, the patient being on regular IVIg replacement therapy had adequate trough level (>600 mg/dL) to control the bacterial infections [3]. Although there are anecdotal reports of fungal and mycobacterial infections causing primary CNS manifestations in XLA

patients, overall, these infections primarily concern the cell-mediated immunity, which is intact in XLA patients.

In the index case, toxoplasma serology (IgG and IgM) and PCR were negative. In neuroimaging toxoplasmosis lesions usually appear as hypointense (on T1-weighted) with high or mixed signal intensity (on T2-weighted and FLAIR images) signals, typically in basal ganglia, cortico-medullary junction, white matter, and the periventricular regions [4]. Few case reports of toxoplasmosis in acquired immunodeficiency syndromes have shown hyperintense lesions involving basal ganglia, thalamus and cerebral hemispheres [5,6]. However, in our case, neuroimaging was not in favour of toxoplasmosis.

Enteroviral infections are known to cause difficult, persistent CNS disease in children with XLA. As opposed to other viruses, which are dealt with by cell-mediated immunity, the host response to enteroviral infections in XLA is by forming neutralizing antibodies. In one of the largest series of 36 patients of XLA seen over two decades, CNS infections constituted a significant proportion (25%) of all infections [7] with enteroviral infections including echo, polio and coxsackie being the most problematic [8]. As seen in our case, enteroviral encephalitis in XLA are described as insidious onset, slowly progressive loss of motor and cognitive milestones over 2-3 years, followed by spastic quadriplegia, coma with mortality in nearly 44% of cases [9, 10]. CSF samples remained negative for all enteroviruses, tested both by PCR and by viral cultures in the index case, which may be falsely negative and does not exclude the infection. Though adequate trough levels by IVIg replacement therapy may prevent bacterial infections it protect against enteroviral infections [3].

Besides enteroviruses, astrovirus, measles and herpes viruses need to be considered in XLA [11, 12]. Though, the index case had a measles-like past illness, and had been immunized with a live vaccine, measles inclusion body encephalitis was unlikely, because it is a disease of patients with depressed cell-mediated immunity with a rapid and fatal course. The clinical and radiological presentation in the index case did not favor subacute sclerosing pan-encephalitis. Moreover, the measles serology was negative and measles virus inclusion bodies were absent on the histopathology. Other than these, clinical presentations described in the anecdotal reports of other viruses such as adenovirus, influenza virus, cytomegalovirus, and John Cunningham (JC) virus [13] did not fit into our clinical scenario. Progressive multifocal encephalopathy, reported with XLA was also unlikely [14,15]. Dysregulated immunity leading to autoimmune encephalitis, abnormal immune response to

drugs [2] or IVIg therapy induced progressive, chronic neuro-regression [3] were other differential diagnosis, but unlikely in this case.

Pediatric immunologist 1: In the present case, the trough level of immunoglobulins being well above 600 mg/dL, he was protected against the common bacterial pathogens, thus making bacterial infection of CNS unlikely. The most common CNS pathology in such patients is an enteroviral infection, which can occur even when the patient is on regular IVIg therapy. Therefore, this is consistent with a case of chronic enteroviral infection with XLA.

Neurologist 1: The diagnosis of chronic enteroviral infection with XLA seems most likely in this case. The early onset of gliosis in the MRI brain of this patient suggests a vascular invasion. As pointed rightly by the clinical discussant, measles inclusion body encephalitis is a fulminant infection that does not follow such a chronic indolent course. Additionally, there is no contrast enhancement in any of five sets of MRIs probably due to the lack of immunity to mount an inflammation. JC virus could be another possibility.

Virologist: Enterovirus is the most common etiology for this clinical presentation. Astrovirus, as the discussant highlighted, is also being reported. Sensitivity of detection of enterovirus by CSF PCR ranges from 75-100%. It would be ideal to take a throat swab along with CSF samples. Studies have shown that sensitivity has improved when throat swab is being examined along with CSF PCR.

Pediatric pulmonologist: Although the case strongly points towards a viral infection, yet the presence of necrotic lymph nodes in computed tomography chest and persistent mastoiditis might be suggestive of other infectious agents such as fungus or an invasive hospital-acquired infection. As the autopsy was done for brain only, infection elsewhere in the body could not be identified.

Pediatric hemato-oncologist 1: One could consider granulomatous amoebic infections such as *Balamuthia*, which have been previously reported from the center, although the MRI picture does not conform to it.

Pediatric immunologist 2: The patient received 4-5 doses of oral polio vaccine in routine immunization schedule, along with a dose on the national immunization day, 15 days prior to the onset of illness. Live viral vaccines are contraindicated in such patients as well as in siblings and their surroundings.

Physician: Measles seems more likely in the index case

than enteroviruses as the posterior parts of the brain are more involved. The absence of enhancement and cells in the CSF and the presence of high protein and gliosis in the brain are described in measles. However, the clinical course in measles is shorter for 1-3 months, as compared to the chronic course in the index lasting nearly 12 months.

Clinical discussant: Measles inclusion body encephalitis is primarily a disease of cell-mediated immunity, seen more commonly in adult patients, and follow a rapid fulminant course. Subacute-chronic measles virus infection could not be completely excluded. Serological testing for measles virus was not feasible as B-cells are deficient in XLA. JC virus infection would be unusual as the virus is carried to the brain by B-cells, which are deficient in XLA patients. Polioviruses are also a type of enteroviral infections. XLA patients are prone for atypical manifestation of enteroviruses, which includes fulminant polio encephalitis as well as paralytic poliomyelitis. The abnormal chest findings on computed tomography described the lung pathology at the time of first illness when the child was admitted with a viral prodrome, bacterial pneumonia and neutropenia suggestive of an acute bacterial necrotizing pneumonia. Additionally, investigations for tuberculosis and fungal infections had been non-corroborative at that time. It would be very unusual for a mycobacterial or fungal infection to present with such CNS manifestations over several months. However, systemic infection with pneumocystis carinii is described in patients with XLA.

Pediatric hemato-oncologist 2: As progressive multifocal leukoencephalopathy secondary to JC virus infection is common in hematological conditions treated with rituximab, a similar mechanism may be proposed for XLA patients also. The patient also had persistent microcytic, hypochromic anemia with thrombocytopenia, which could be due to an enteroviral inflammatory bowel disease or an intestinal giardiasis, which is common in XLA patients.

Pediatric immunologist 1: As part of an international collaborative study, 32 children of the institute, with XLA were screened for poliovirus. None of them had poliovirus infections. In Iran, 4% of children with XLA had poliovirus infection [16]. The negative stool samples for poliovirus make this infection unlikely in the case.

Pediatric neurologist 1: Chronic herpes encephalitis type 1 and human herpes virus-6 infection may be additional possibilities.

PATHOLOGY PROTOCOL

A partial autopsy was performed in this case. The external

examination of the brain weighing 1142 grams, showed slightly congested meninges, without any exudate. A mild tonsillar herniation was noted. Blood vessels of circle of Willis and brainstem appeared normal. Bilateral parieto-occipital and temporal lobes were discolored, collapsed and soft (**Fig. 2**). The coronal sectioning of the brain revealed softening, shrinkage and thinning of the cortical ribbons of left inferior frontal, left frontal, paramedian area above cingulate gyrus and right middle and inferior frontal gyrus (**Fig. 2**). Both temporal lobes and bilateral parietal cortices had similar changes with a shrunken left temporal lobe. The right occipital lobe showed cystic encephalomalacia. While the left putamen and adjacent internal capsule showed necrosis explaining his right hemiparesis, the right lentiform nucleus was normal (**Fig. 2**). The affected areas of the brain corresponded to the anterior, middle, and posterior cerebral artery territories indicating global hypoxia. The hippocampi, thalami and midbrain appeared normal grossly. The white matter was mostly spared. The brainstem axial cuts revealed mild congestion of the dorsal parts of the pons, with unaffected medulla and cerebellum.

Microscopic examination revealed sparse meningeal infiltrates, predominantly lymphocytic (**Fig. 2**). The grossly affected cortical areas showed laminar and transcortical necrosis, replaced by large number of foamy macrophages admixed with few lymphocytes, accompanied by reactive glial proliferation (**Fig. 2**). The adjacent cortical areas showed evidence of hypoxic changes, more marked at the base of the sulci than the crests. Hippocampi showed diffuse hypoxic damage and patchy neuronal loss. The posterior parts of the occipital cortex showed extensive neuronal loss, cyst formation and calcium deposits indicating chronicity (**Fig. 2**). Therefore, the cerebral cortex, in nutshell, showed presence of hypoxic damage and varying degree of cortical necrosis, explained by recurrent seizures. Histological examination of the dorsal pons demonstrated neuronal loss, neuronophagia and microglial proliferation with nodule formation, highlighted by CD68 immuno-staining. The perivascular lymphocytic infiltration consisted of CD3-positive T-cells without any CD20-positive B-cells. Similar changes were noted in the midbrain, dentate nucleus of the cerebellum and grey matter around 4th ventricle with cerebellar folia being unremarkable. The dorsal motor root of vagal nucleus and the anterior horn cells of the cervical segment of the cord were affected. Immunohistochemistry for herpes simplex virus 1 and 2, cytomegalovirus, simian virus 40 (SV40), Epstein Barr and parvovirus were negative. In addition, PCR for enteroviruses was negative in the brain tissue. The post-mortem biopsy samples of brain, lung and liver tissues did not contribute any significant information.

The topography of the lesions in this brain namely the involvement of dorsal pons, dentate nucleus, medulla, part of the hypothalamus and sparing of thalamus and cortical zone favours enteroviral infection, even though PCR was negative. PCR positivity depends on multiple factors and at best gives 50% positive results. The lesions and the histological features favour a chronic enteroviral infection over JC virus. SV40 antibody, which recognizes both JC virus and BK polyoma virus failed to show any positivity. The final autopsy diagnosis was XLA with probable enteroviral encephalitis and cystic cerebral encephalomalacia.

Open Forum

Pediatric neurologist 2: Considering a remarkably similar case of XLA with seizures reported by the CDC, where RNA separation method detected astrovirus, infection with other single-stranded RNA viruses could be a possibility. The presence of hemorrhage and calcification in the occipital lobe could also suggest Posterior reversible encephalopathy syndrome-like changes.

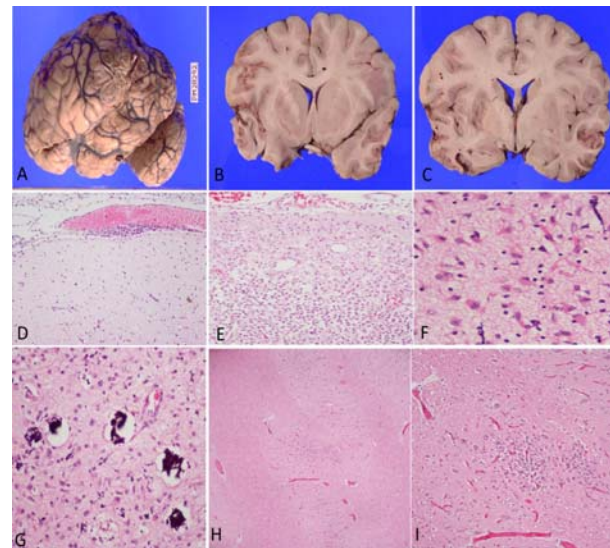


Fig. 2 a) The parietal convexity is discolored and collapsed due to softening of underlying cortex of the brain; b) Coronal section of the brain shows shrinkage and softening of the cortical ribbons affecting left inferior frontal gyrus and both temporal lobes. The white matter is relative spared, c) The left putamen and internal capsule are soft and necrotic in this coronal slice. The right basal ganglia and both thalami are spared. Note that left temporal is affected more than right temporal lobe; d) Sparse lymphocytic inflammation is seen in the cortical leptomeninges; e) The affected cortical areas showed neuronal loss and necrosis and replacement by macrophages and lymphocytes; f) Reactive hypertrophied astrocytes. The occipital cortex demonstrated foci of micro-calcification and microglial proliferation, g-h) The dentate nucleus of the cerebellum shows neuronal loss, microglial proliferation, and vascular congestion.

Neurologist 2: As none of the viral studies yielded an etiological agent, autoimmune encephalitis could be a possibility. The response to ongoing IVIg therapy could also be a pointer toward an underlying autoimmune process.

Pathology discussant: The case has been a clinical and histopathological challenge. While Posterior reversible encephalopathy syndrome mostly involves the white matter, gray matter involvement was seen in this case. Autoimmune encephalitis should only be considered when infectious causes have been excluded. A negative PCR does not exclude an enteroviral infection. Enterovirus A71 infection has been prevalent in India, Bangladesh, Malaysia, and Taiwan. Enterovirus D68 can present similarly in an XLA patient. Other uncommon enteroviruses and single-stranded RNA viruses also remain a possibility. In the presence of normal limbic organs, cingulate gyrus, and amygdala on histopathology, a limbic encephalitis is most unusual. Other forms of autoimmune encephalitis such as anti-NMDAR and anti-AMPA need specific testing. The California encephalitis project has reported that 63% of the probable encephalitis cases remain unknown despite extensive investigations for infectious causes. The hypoxic changes in the brain in the case were probably due to recurrent seizures.

Pediatric immunologist 3: The histopathology shows typical features of viral encephalitis with infiltration by CD3 lymphocytes alone, CD20 lymphocytes being absent, as expected in XLA patients. The diagnosis of astrovirus infection in the CDC case alluded to in the previous discussion was based on highly advanced pyrosequencing PCR technique which is not routinely available.

DISCUSSION

The case highlights the unique presentation of a child with XLA and recurrent infections. A simple throat examination for the presence of tonsils is a vital bedside clue and helps clinch the diagnosis. CNS infections are tough to treat and constitute a significant cause of mortality in these children as seen in the index case [17]. Although the presence of good T-cell functions protects the patients from common childhood viral infections, yet enteroviruses notoriously cause chronic infections [18,19]. The brain pathology was not consistent with the diagnosis of JC virus-related multifocal leukoencephalopathy, where multifocal discrete white matter demyelination occurs initially, progressing to form confluent large demyelinating lesions appearing as granular soft discolored plaques. As mentioned in the pathology description, the white matter was spared in this case with a predominantly grey matter disease. No

demyelination is seen in the index case. There were no oligodendroglia inclusions or bizarre astrocytes and anti-SV40 antibody on immunohistochemistry did not show any viral antigen in brain tissue. The typical involvement of brainstem nuclei, dentate nucleus of cerebellum and hypothalamus showing neuronal loss, microglial hyperplasia is characteristic of an enteroviral infection [19]. Although JC virus could not be tested in the CSF, SV40 antibody used for immunostaining on the brain sections did not show any positivity for the same. The collections of foamy macrophages with a few lymphocytes on histopathology are from multiple infarcts involving various regions of the cerebral cortex. This is the second pathology in brain, which occurred due to severe hypoxia in this child because of repeated seizures. The cerebral infarcts were of different durations.

Hence, with the available investigative work-up possible in a resource-limited setting, we could conclude that the case was a probable enteroviral meningoencephalitis. The topography of the lesions, the peculiar preponderance of enteroviral infections in children with XLA, the histological features and immunohistochemistry favour an enterovirus over JC virus, although the virus could not be demonstrated by PCR in the brain tissue. This is a common scenario in several pediatric centers in India and needs to be brought out, even if an organism could not be identified. Prevalence of enteroviral encephalitis in XLA is reported between 1% and 3% [8]. Echovirus, poliovirus, coxsackievirus and several uncommon enteroviruses may cause chronic progressive encephalitis with neuroregression [17,20] with enteroviruses being one of the most common causes of meningoencephalitis in patients with XLA [21]. The sensitivity of CSF PCR-based assays for enteroviruses ranges from 75%-80%. Combining the CSF PCR with a throat swab may increase the sensitivity of detection [22, 23]. Regular IVIg therapy with adequate trough levels protects against severe bacterial infections [3]. However, the role of high dose peripheral and intraventricular immunoglobulin for enteroviral encephalitis is debatable [9,17].

Contributors: AGS: Concept and design of the study, data collection and interpretation, drafting manuscript data interpretation, editing of draft, critical revision, Clinical discussant of CPC; BDR: Design of the study, drafting manuscript, acquisition of data and data analysis; pathology discussant of CPC; DB: Concept and design of the study, patient care, data collection and interpretation, drafting manuscript data interpretation, editing of draft, critical revision; AR: Acquisition of immunological data and data analysis, critical revision of manuscript; VB: Acquisition of radiological data and data analysis, critical revision of manuscript, radiology discussant of the CPC.

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Type 2 Diabetes Mellitus in Adolescents From Southern India – A Single Center Experience

This 1-year follow-up study was conducted on 21 subjects with type 2 diabetes mellitus. We found reduction in glycosylated hemoglobin from 10.5% to 8.1%, and maintenance of BMI z-scores from 3.9 to 3.8. Majority of the patients could be weaned-off from insulin. Heterogeneous presentation, frequent co-morbidities and complications, and familial clustering were observed.

Keywords: *Diabetic nephropathy, HbA1C, Outcome.*

Pediatric data on T2DM from various Indian centers been described [1-3], but there is paucity of studies on response to therapy. We, herein, describe the profile of children and adolescents with T2DM and response to one year of therapy from a single center in Southern India. With the increasing prevalence of obesity [4,5], type 2 diabetes mellitus (T2DM) in young is also increasing [1,2].

With institutional review board approval, we recruited newly diagnosed children with T2DM: Fasting blood sugar ≥ 125 mg/dL, 2 hour post 75 gram glucose challenge ≥ 200 mg/dL (screening in asymptomatic obese adolescents), glycosylated hemoglobin (HbA1C) $\geq 6.5\%$, C-peptide >4 ng/mL and negative anti-glutamic acid decarboxylase antibody titre (<10 mIU/mL) [6]. Data on demography, history, clinical presentation, anthropometry and Tanner staging collected. T2DM complications assessed: urine albumin creatinine ratio (ACR) (normal, <30 mg/g creatinine) [6], fundus evaluation by indirect ophthalmoscopy, lipid profile after 12 hours of fasting and hypertension (≥ 95 th percentile more than three occasions). Genetic testing for monogenic diabetes (first degree relative with diabetes onset <40 years, autosomal dominant family history, negative antibody, no diabetic ketoacidosis and insulin resistance) performed using targeted next generation gene sequencing for thirteen MODY genes [7]. Comorbidities like obstructive sleep apnea syndrome, fatty liver, polycystic ovaries diagnosed as per standard criteria and Homeostatic model for assessment of insulin resistance calculated as (fasting glucose (in mg/dL) x fasting insulin (in μ U/mL)/405.

Children were managed with fluid therapy, intravenous insulin, lifestyle measures, oral metformin, subcutaneous glargine and multiple daily injection (MDI) regimen using glargine and aspart insulin, as appropriate [6]. Self-monitoring of blood glucose and log book maintenance advised. Subjects were followed up 3-monthly for one year with assessment of adherence of lifestyle measures, medications, anthropometry, hypoglycemic episodes and HbA1C. Management was escalated or deescalated as indicated [6]. Data were entered in excel sheet, and summarized as mean (SD), or numbers (percentages).

We recruited 21 subjects with mean (SD) age of 14.5 (2.1) years (10 boys) and all with Tanner stage ≥ 2 , out of 265 (7.9%) registered in the diabetic clinic (Table I). Monogenic diabetes testing was performed in five subjects: all were negative. Of these, 9 (42.8%), 12 (57.1%) and none had a parent, relative or sibling with T2DM, respectively; 6 (28.5%) had history of gestational diabetes mellitus in the mother. Co-morbidities in our subjects included fatty liver and obstructive sleep apnea syndrome in 5 (23.8%) and 2 (9.5%), respectively. 19.0% had systolic hypertension [mean (SD) systolic blood pressure Z-score 0.9 (0.3)], 14.2% had diastolic hypertension [mean (SD) diastolic blood pressure z-score 0.7 (0.2)] and 47.6% subjects had dyslipidemia as complications. Echocardiographic evaluation was performed in these four children, and two had left ventricular hypertrophy (initiated on enalapril). On screening for microvascular complications, two had diabetic nephropathy (persistent elevation of urine albumin-creatinine ratio) and none had diabetic retinopathy.

Subjects who had life threatening complications were initiated on metformin and MDI regimen (14.2%). Those with ketosis started on metformin with basal insulin (28.5%) and remaining 57.1% of subjects were on metformin monotherapy. On follow-up at 6 months, one, one and 13 subjects were on metformin with MDI, metformin with basal insulin and metformin monotherapy. None, one and 13, of the 14 subjects

Table I Clinical and Laboratory Profile of Adolescents With Type 2 Diabetes Mellitus (N=21)

<i>Study parameters</i>	<i>Value</i>
<i>Clinical presentation, n (%)</i>	
Asymptomatic	6 (28.5)
Classical symptoms ^b	12 (57)
Atypical features ^c	3 (14.2)
Ketosis without acidosis	6 (28.5)
Hyperosmolar non-ketotic syndrome	2 (9.5)
Diabetic ketoacidosis	1 (4.7)
<i>Anthropometry</i>	
Height SD score ^a	0.6 (0.5-0.7)
BMI SD score ^a	3.9 (3.1-4.2)
Waist circumference z-score ^a	2.8 (2.5-3.2)
<i>Biochemical assessment</i>	
C-Peptide (ng/mL) ^a	4.9 (4-5.2)
HbA1C (%)	10.5 (1.1)
HOMA-IR ^a	9.4 (8.1-10.3)
LDL cholesterol (mg/dL)	152.5 (12.3)
HDL cholesterol (mg/dL)	35.5 (8.6)
Triglyceride level (mg/dL)	178 (21.4)

Values in mean (SD) or ^amedian (IQR); ^bpolydipsia, polyuria and polyphagia; ^cfoot ulcer, delayed menarche, pruritus vulvae.

who were followed up at 12 months were on metformin with MDI, metformin with basal insulin and metformin monotherapy, respectively.

During the one year follow-up, the HbA1c was 10.5% (at baseline), 8.5% (at 6 months) and 8.1% (at 1 year). Correspondingly, the BMI z-scores were +3.9 (at baseline), +3.7 (at 6 months) +3.8 (at 12 months). Two episodes of hypoglycemia observed during the study period. Both episodes occurred early morning with autonomic symptoms and both subjects were on insulin therapy). On follow-up, two children with hypertension had normal blood pressure, two adolescents had reduction in LDL levels, and one child with diabetic nephropathy had control of microalbuminuria and no adverse reactions to therapy.

In our series, 28.5% were asymptomatic and 14.2% presented as emergencies. It is very important that pediatricians recognize existence of hyperosmolar non-ketotic coma [8] as a diabetic emergency in obese adolescents requiring aggressive fluid therapy vs DKA where over-hydration results in cerebral edema. We observed significant complications at diagnosis, endorsing ISPAD guidelines which recommend early screening of vascular complications in T2DM [3]. Asymptomatic phase results in prolonged exposure to hyperglycemia and early complications. On follow-up, safety of metformin, good improvement in HbA1C, static BMI z-scores observed. Similar safety profile, reduction in BMI z-score of -0.045 and a reduction of HbA1C of -1.3 has been reported [9,10]. Strengths of our study include management as per ISPAD guidelines and one year follow-up period. Inability to quantify adherence of lifestyle measures and 33.3% drop-out at 12 months are limitations in our study.

Adolescents with T2DM have heterogeneous presentation, significant comorbidities and complications; familial clustering and good biochemical response to metformin therapy observed.

Contributors: The study was conceptualized by HKP, SW and ST; study design was framed by HKP and KN. UG: data collection; HKP, SW, UG: analysis; HKP, KN, SW, ST: clinical management of cases. All authors approve the final manuscript.

Outcome of Covid-19 Positive Newborns Presenting to a Tertiary Care Hospital

Neonatal data regarding SARS-CoV-2 is sparse from India. On review of hospital records from April- August, 2020, 18/423 (4.25%) neonates were SARS-CoV-2 RT-PCR positive. 15 (83.3%) neonates recovered and 3 (16.6%) succumbed. Only 50% of the positive babies had positive mothers/ caretakers, a contact could not be traced in others.

Keywords: Contact tracing, Horizontal transmission, Vertical transmission.

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UMAMAHESWARI GURUNATHAN, HEMCHAND KRISHNA PRASAD,* SHERLIN WHITE, THANGAVELU SANGALALINGAM AND NEDUNCHELIAN KRISHNAMOORTHY

Department of Pediatrics, Mehta Multispeciality Hospitals India Pvt Ltd, Chennai, India.

*pediatricendocrinology.mehta@gmail.com

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The symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive cases are highly variable and within the paediatric population, neonates and infants are more severely affected. Neonates can acquire infection vertically during delivery or horizontally from caregivers. As neonatal data on the disease is limited, we, herein, share our experience.

Medical records of all out-born neonates presenting for admission to the NICU from April 1 to August 31, 2020 were reviewed. Clearance from institutional ethics committee was taken.

For planned referrals and untested neonates in the

emergency ward, mother and baby's SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab was requested. If positive, babies were transferred to the COVID19 positive NICU and managed as per standard NICU protocols. Repeat testing for SARS-CoV-2 infection was carried out as per Indian Council of Medical Research/ Ministry of Health and Family Welfare guidelines every 5-7 days, if baby remained symptomatic or developed new onset symptoms. Expressed breast milk of SARS-CoV-2 negative (RT-PCR of nasopharyngeal/ throat swab) mothers donated to the hospital human milk bank was administered to stable feeding babies. When mothers were available and the baby's clinical condition was satisfactory, direct breastfeeding was allowed. Kangaroo mother care (KMC) was not practiced at the time as guidelines regarding KMC in coronavirus disease (COVID-19) were not clear. Data was entered and analyzed on Microsoft Excel.

Of the 423 outborn neonates; 18 (4.25%) tested positive for SARS-CoV-2 by RT-PCR of nasopharyngeal swabs. These included a pair of dichorionic diamniotic twins. Four babies were preterms (youngest weighing 1000 g), and 9 were delivered by caesarian section, with the most common indication being meconium stained liquor. All positive neonates had symptoms warranting neonatal intensive care unit (NICU) admission. Clinical presentation was varied, with respiratory distress being the most common, which could be attributed to neonatal respiratory or cardiac problems. Six babies required ventilation (**Table I**). Fever was the other common symptom, but a focus could not be elicited in any case.

Of interest to note was case 7, first of a pair of twins admitted for meconium aspiration syndrome and late onset *Pseudomonas aeruginosa* sepsis. Baby had persistent thrombocytopenia despite two weeks of appropriate antibiotics treatment, and clearance of bacteria on repeat blood, cerebrospinal fluid, urine and endotracheal cultures. She developed ascites, cholestasis, elevated lactate dehydrogenase (13,700 U/L), deranged coagulation profile and elevated Interleukin-6 (13.58 pg/ mL). She required invasive mechanical ventilation, inotrope support, intravenous immunoglobulin and low molecular weight heparin. Upon retesting, baby continued to show SARS-CoV-2 positivity till day 21, and died on day 28. Multisystem inflammatory syndrome (MIS-C) was suspected in this case [1,2].

Fifteen neonates survived and were discharged home, and three died after 2-28 days of stay. Median (IQR) duration of hospital stay was 10 (9,16) days. Retesting was done as per protocol for 14 babies (remaining three became asymptomatic, and one died). Eight babies were negative on first retest, one on second retest (one succumbed before second) and four continued to be positive after third retest. Of the four babies who continued to test positive, three were critically sick and required ventilation and intensive care stay for more than 2 weeks.

Upon contact-tracing, 9 mothers and 1 caretaker (paternal aunt) were positive. Three of the positive mothers tested negative prior to delivery but tested positive on re-screen. Only

one mother was symptomatic with fever. No contact was identifiable in 8 babies which may imply low viral load in the caregivers.

We, herein, highlight the clinico-demographic details and outcomes of SARS-CoV-2 positive neonates presenting to the outborn unit of a tertiary care pediatric hospital. All positive neonates in our study were symptomatic and respiratory symptoms were the most common. Fever was seen in one-sixth, unlike children and adults where fever is a predominant symptom [3-6]. Like older children, the overall prognosis of SARS-CoV-2 infection in neonates is better than adults [3-8], unless they have other co-morbidities e.g., total anomalous pulmonary various connection or polycystic kidney disease with renal failure seen in our series. Though systematic reviews attribute neonatal symptoms to COVID-19, most of our cases had symptoms which could be explained by neonatal illnesses [5].

A limitation of our study was that viral titers were not done. Neonates who remained PCR-positive for a long duration may imply a higher viral load. Although the frequency of SARS-CoV-2-positive neonates is extremely low, a significant

Table I Diagnosis, Treatment and Outcome of SARS-CoV-2 Positive Neonates (N=18)

Characteristics	No. (%)
<i>Diagnosis^a</i>	
Respiratory distress	5 (27.8)
Meconium aspiration syndrome	3 (16.7)
Respiratory distress syndrome	1 (5.5)
Aspiration pneumonia	1 (5.5)
Fever	3 (16.7)
Seizures (metabolic)	2 (11.1)
Neonatal jaundice	2 (11.1)
<i>Management^b</i>	
Respiratory management	
Oxygen therapy	1 (5.5)
Non invasive ventilation	2 (11.1)
Invasive ventilation	4 (22.2)
Inotropes	2 (11.1)
Antibiotics	9 (50)
Blood products	3 (16.7)
Intravenous fluids	7 (38.9)
Phototherapy	3 (16.7)
Supportive therapy	4 (22.2)
<i>Outcome</i>	
Length of hospital stay, d ^c	10 (9,16)
Mortality	3 (16.7)

^aFeeding difficulty, Pierre Robin Sequence, Total Anomalous Pulmonary Venous Communication (TAPVC), Hirschsprung's Disease, Polycystic Kidney Disease with Acute Kidney Injury (PKD), Diarrhea; ^bIntravenous immunoglobulin and low molecular weight heparin in one baby. ^cvalues in median (IQR).

proportion of the affected neonates requiring intensive care and mechanical ventilation suggests that the disease in neonates is more severe than older children [3-8], which correlates with our study as well.

Contributors: BS, SR, VD, SP, MB: conceived, designed the study, finalized the manuscript; BS, VD, SR: data collection, data analysis, writing manuscript; BS, VD, SR, SP: data collection, data analysis, managed the babies; BS, VD, SR, SP: Literature search, interpretation of data, writing manuscript.

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**BHAVYA SHAH, VAIDEHI DANDE, SUDHA RAO,*
SANJAY PRABHU AND MINNIE BODHANWALA**
From Department of Pediatrics,
Bai Jerbai Wadia Hospital for Children,
Mumbai, Maharashtra, India
*c_sudha@hotmail.com

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Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Immunity

This is a retrospective analysis of clinical characteristics of children with inborn errors of immunity who underwent hematopoietic stem cell transplant (HSCT). Although the mean age at diagnosis was 24.4 months, it was 51.9 months at HSCT. There is an urgent need to improve awareness, expand donor registries and initiate newborn screening for inborn errors of immunity.

Key words: *Primary immune deficiency disorders.*

Inborn errors of immunity or primary immune deficiency disorders (PIDDs) occur with a frequency of 1 in 5000 to 1 in 1000 [1], and are frequently misdiagnosed resulting in avoidable morbidity and mortality [2]. Diagnostic tests and hematopoietic stem cell transplant (HSCT) are not uniformly accessible [3].

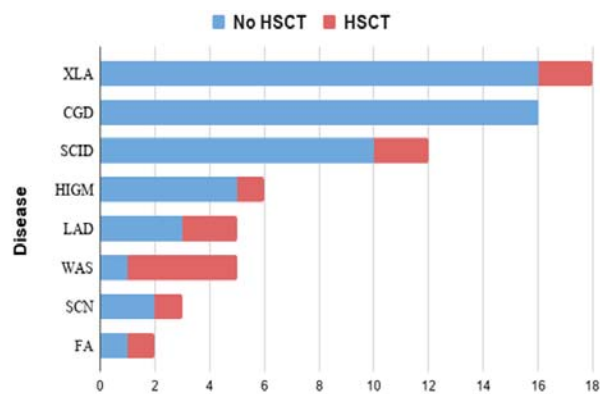
Government Medical College, Kozhikode, a tertiary care hospital in Kerala, and CSIR Institute of Genomics and Integrative Biology, Delhi have been conducting a program on primary immune deficiency disorders over the last five years. Although HSCT is often the only curative option, we are dependent on centers outside the state. The study was designed to document the clinical characteristics of children who underwent HSCT for an inborn error of immunity.

Hospital records of children with PIDDs who attended the immune deficiency clinic from June, 2015 to May, 2020 were

obtained and data of those who underwent HSCT were analyzed. Only children who had completed at least 3 months post-HSCT were included. Variables studied included age at onset diagnosis and at HSCT, gender, relationship with stem cell donor, time since HSCT and diagnostic genetic or phenotypic marker. Quantitative variables were entered on an Excel data sheet and frequency and associations calculated using the statistical package Epi Info (version 7.2.3.1).

HSCT was performed in 13/67 (19.4%, 11 boys). The indications included Wiskott-Aldrich syndrome (4, 30.8%), and leukocyte adhesion deficiency, severe combined immune deficiency, and X-linked agammaglobulinemia in two each (15.4%) congenital neutropenia Fanconi anemia, and hyper IgM syndrome were diagnosed in one child each. The median (IQR) age at diagnosis of children who underwent HSCT was 14 months (first quartile, III quartile). The median (IQR) age at HSCT was 27.5 (first quartile, III quartile) months and the median (IQR) interval between diagnosis and HSCT was 7 (first quartile, III quartile) months. Recurrent pneumonia was the commonest presenting feature in 7 (54%) children, followed by frequent skin and soft tissue infections in 6 (46%) and recurrent otitis media in 4 (30.8%). Frequent abscesses, recurrent diarrhea and bleeding were presenting features in 2 (15%) children each. HSCT was done in an asymptomatic child with Fanconi anemia after his elder sister succumbed to the same disease.

Of the 13 children who underwent HSCT, 9 (69%) children had a matched sibling donor and 2 children each (15%) had matched unrelated donor transplants (MUDs) [4] and haploidentical stem cell transplants. Reduced intensity conditioning (RIC) [5] with treosulfan and fludarabine was



SCN: Severe congenital neutropenia; FA: Fanconi anemia; HIGM: Hyper-IgM syndrome; LAD1: Leukocyte adhesion deficiency; SCID: Severe combined immune deficiency; WAS: Wiskott–Aldrich syndrome; XLA: X-Linked agammaglobulinemia.

Fig. 1 Number of patients with primary immune deficiency disorders who underwent hematopoietic stem cell transplants (HSCT).

used and 12 children had sustained engraftment. There was one graft rejection with autologous reconstitution, and a second HSCT resulted in sustained engraftment. Post-HSCT complications included bacterial sepsis, cytomegaloviral reactivation, steroid-induced hypertension and graft versus host disease. There was no mortality and the mean duration of post-transplant event-free survival was 25.1 months.

HSCT was performed for 2 (15%) children with XLA. Although this is not the standard treatment, but it has been found to be a feasible option where availability and cost of immunoglobulin replacement therapy are limiting factors and parents are not keen on lifelong replacement [6].

The median interval between onset of symptoms to diagnosis was 9 months. This emphasizes the need to improve awareness among pediatricians [2]. The mean interval between diagnosis and HSCT was 40.9 months, accounting for the high mortality. Improved outcomes are described with HSCT before 3.5 months of age before onset of infectious complications [7,8]. The youngest child who underwent HSCT in this series was 5 months.

The outcome of HSCT for children with matched unrelated donors (MUDs) and haploidentical donors has improved globally [4,9] both children in this series had good outcomes. Limitations of the study include the small sample size and the variable time since HSCT with possible recall bias.

The main stumbling blocks to wider use of HSCT remain the cost and non-availability of suitable donors. National rare disease policy addressing the major concerns of affected families would be the way forward. Awareness regarding PIDDs should be rapidly scaled up, donor registries expanded and government funding streamlined. A newborn screening program would help to reduce mortality.

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GEETA M GONVINDARAJ,^{1*} U RAMYA,² TPASHRAF,¹ REVATHI RAJ² AND VINOD SCARIA³

From ¹Departments of Pediatrics, Government Medical College, Kozhikode, Kerala; ²Paediatrics Hematology Oncology, Blood and Marrow Transplantation Apollo Hospitals, Chennai, Tamil Nadu; ³CSIR Institute of Genomics and Integrative Biology (CSIR-IGIB), Delhi, India.

*geetakkumar@gmail.com

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A Novel Cause of Toxic Encephalopathy in an Adolescent Boy

A 12-year-old boy presented to the emergency room with acute onset altered sensorium. His parents gave history of multiple episodes of non-bilious and non-projectile vomiting two hours after returning from school and having lunch. Following which he became drowsy, spoke inappropriately, had history suggestive of visual and auditory hallucinations, and bladder incontinence. There was no history of fever, seizures, weakness in any limb or cranial nerve palsies. There was no past history of altered sensorium or seizures and the child was not on any medications.

The child had a heart rate of 120 per minute, respiratory rate of 32 per minute, blood pressure of 100/60 mm Hg (50th to 90th centile), was febrile with a temperature of 101⁰F and was in a minimally conscious state (Glasgow coma scale 8). Both pupils were mid-dilated and were sluggishly reacting to light. The child had an involuntary pill rolling movement of his fingers which disappeared on sleeping. Rest of the motor examination was normal. There were no cerebellar signs, signs of meningeal irritation or signs of raised intracranial tension.

A provisional diagnosis of acute onset encephalopathy with mydriasis was kept with differential diagnosis of viral encephalitis, metabolic encephalopathies (including uremic and hepatic), intoxication, post-ictal state and snake envenomation. The child was managed empirically with intravenous fluids, injection ceftriaxone (1 g/kg/d) and acyclovir. On investigation, dextrose was 107 mg/dL, hemoglobin 10.5 g/dL, leukocyte count $6.7 \times 10^9/L$, platelet count $260 \times 10^9/L$, sodium 142 mEq/L, potassium 4.2 mEq/L and ionized calcium 4.5 mEq/L. Serum creatinine, bilirubin and alanine transaminase were within normal limits. Blood gas revealed a pH of 7.43, bicarbonate 23 mmol/L and lactate 1.3 mmol/L.

The child's vitals remained stable and with continued supportive care his sensorium improved to normal in the next 36 hours. Urine toxicology screen by qualitative radio immune assay (threshold for detection >50 ng/mL) showed presence of tetrahydrocannabinol (THC), thus supporting toxin ingestion (marijuana) as the cause of encephalopathy. After regaining his sensorium, the child revealed that he had consumed a chocolate-like sweet that had been given to him by a friend on the day of symptom onset.

Cannabis is consumed in different forms such as dried leaves (marijuana), resin (hashish), and concentrated resin extract (hashish oil). Hashish may be easily mistaken for a chocolate by a child, and this may be the reason why hashish is the most common (38%) documented oral ingestion [1]. THC is the main psychoactive ingredient that binds to brain cannabinoid receptors, producing dose- and time-dependent stimulant, hallucinogenic or sedative effects. Effects of cannabis starts from

30 minutes to 3 hours of ingestion and lasts up to 12 hours. With the increased bioavailability of cannabis concentrates and the smaller body mass in children, childhood cannabis ingestion results in high serum THC levels, even if small amounts are consumed [2].

Paediatric cannabis intoxication has a variable presentation, most commonly neurological (confusion, lethargy, coma or agitation) followed by ophthalmological (bilateral reactive mydriasis), cardiovascular (tachycardia, hyper- or hypotension) and respiratory depression needing mechanical ventilation [3]. These symptoms are nonspecific and mimic postictal state, encephalitis, metabolic causes and sympathomimetic agent poisonings which may lead to a delayed diagnosis and unnecessary diagnostic evaluation, particularly in a drowsy child. High index of clinical suspicion and early urine screening can prevent invasive and costly investigations like lumbar puncture and neuroimaging respectively, and may reduce the need for prolonged empirical treatment with intravenous antibiotics and antivirals. Its rare availability in most settings, lack of expertise in testing and high cost limits its widespread use. Initial urine screening is typically performed with enzyme multiplied immunoassay technique, which is then confirmed by gas chromatography-mass spectrometry [4,5]. Results of screening test are available in a few hours (reduced to minutes with point of care testing) whereas the confirmatory test requires a few days.

Examination of the pupils provides a valuable clue to the underlying disease, especially in cases of suspected toxin. Mydriatic pupils are seen in anticholinergic (atropine, antihistaminic, antipsychotic), sympathomimetic (cocaine, amphetamine, lysergic acid diethylamide, etc) toxidromes and cannabis ingestion, whereas miotic pupils are seen in cholinergic (organophosphate, carbamate) and opioid (morphine, heroin, codeine) toxidromes [6]. In this case of unexplained encephalopathy with reactive mydriatic pupils, we narrowed our differentials to the former category of intoxicants.

Clinical recognition of altered mental status by marijuana exposure can be challenging in children. However, increased awareness regarding childhood drug abuse, its clinical effects especially on pupils, as well as utilization of toxicology screen in those with high suspicion facilitates early diagnosis, limits extensive investigations and facilitates implementation of preventative measures, especially in a resource-constrained setting like ours.

AMAN ELWADHI, ABHIJEET SAHA* AND AROHI GUPTA

*Department of Pediatrics,
Lady Hardinge Medical College and
associated Kalawati Saran Children Hospital,
New Delhi, India.*

**drabhijeetsaha@yahoo.com*

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Introduction of Proton Beam Therapy in Intracranial Germ Cell Tumors in India

Intracranial germ cell tumors (ICGCT) represent rare tumors comprising 1-2% of brain tumors and <3% of all neoplasms in children [1]. Optimal management of ICGCT involves multimodal therapy including surgery, radiotherapy (RT) and systemic chemotherapy [2]. Proton beam therapy (PT) has unique features of delivering sharp fall-off of RT dose resulting in significant sparing of normal tissues compared to traditional photon therapy. We describe our initial experience in treatment of these tumors using image-guided intensity modulated proton therapy (IMPT) at our center, the first and only PT facility in South Asia.

An 18-year-old male presented with history of decreased appetite, weight loss, and generalized weakness for six months. Magnetic resonance imaging (MRI) of brain showed lesions in periventricular region and subsequent stereotactic biopsy was suggestive of intracranial germinoma with CD117 and Oct4 positivity. Cerebrospinal fluid (CSF) analysis revealed increased beta human chorionic gonadotrophin (β -HCG) and normal alpha fetoprotein (AFP) with no malignant cells. He received four cycles of etoposide and carboplatin according to ACNS0232 protocol [2], following which, his tumor markers normalized and he was subsequently treated with IMPT to a total dose of 40 GyE in 23 fractions (23.8GyE in 14 fractions craniospinal irradiation (CSI) and 16.2 GyE in 9 fractions boost to gross residual and pre chemotherapy volumes) [3]. He tolerated PT well and subsequent MRIs done 6 weeks, 6 months and 14 months post-PT did not show any residual disease. His tumor markers and endocrine values were within normal limits with his height relatively stable as he has already achieved his growth spurt. He has resumed his socio-academic activities and is on regular follow-up for the past 20 months.

A 16-year-old boy presented with sudden onset diplopia since five months. MRI showed well defined lobulated mass lesion measuring 2.4×2.1×3.1 cm in the region of third ventricle. Tumor marker analysis showed elevated serum β -HCG (1626 mIU/mL) and AFP (2.0 ng/mL). CSF analysis reported increased β -HCG measuring 3589 mIU/mL and AFP measuring 0.47 ng/mL. A diagnosis of NGGCT (choriocarcinoma) was made and he subsequently received four cycles of ifosfamide, cyclophosphamide and carboplatin (ICE), followed by IMPT to a total dose of 54 GyE in 30 fractions (CSI 30.6 GyE in 17 fractions followed by boost of 23.4 GyE in 13 fractions) [3].

Follow-up MRI post-PT after 2 month and 18 months showed interval decrease in residual disease. Post-PT tumor markers were normal and endocrine functions optimal, with the patient's height relatively stable. He has been on regular follow-up since past 20 months and has been continuing his normal socio-academic activities.

A 15-year-old female with amenorrhea, presented with increased thirst, micturition, weight loss, and blurring of vision towards left side over a period of two years. Visual perimetry showed bilateral temporal hemianopia. MRI brain with spine screening revealed a 2.1×2.3×2.3 cm suprasellar lesion compressing the optic chiasm. She underwent a right pterional craniotomy and gross total resection of lesion, reported as intracranial germinoma. Her tumor markers (serum and CSF) showed mild elevation of β -HCG (2.8 mIU/mL). She was on thyroid, cortisol and desmopressin supplements post-surgery because of decreased endocrine functions. Her neurocognitive evaluation before proton therapy showed her in the high average range. She received four cycles of three weekly etoposide and carboplatin followed by IMPT (**Fig.1**) to a total dose of 40 GyE in 25 fractions (24 GyE in 15 fractions to whole ventricular volume and 16 GyE in 10 fractions to tumor bed) [4]. Post-PT tumor markers were within normal limits. Follow up MRI after one, six and twelve months did not show any residual disease. Post proton therapy, her endocrine function did not deteriorate and she was continued on hormone supplements. Subsequent ophthalmic evaluation showed no visual deficits. The patient has been on regular follow up for the past 15 months and has resumed her normal academic activities.

For all these patients, cases were discussed in multidisciplinary tumor boards. Patients, after customized immobilization, underwent a planning CT and MRI. Dedicated PT plans were generated for each case using Monte-Carlo optimization and 3-4 PT fields [3]. Treatments were delivered on a daily basis (5 fractions a week) after carefully laid out quality assurance checks as per institutional protocols. Significant reduction of the radiation dose to critical structures such as hippocampi and cochlea were observed.

RT is an integral part of treatment of ICGCT but can be associated with considerable late effects including neurocognitive disturbances and risk of secondary cancers, and chemotherapy alone is insufficient due to high rates of local and metastatic recurrence. Current standard of care is ventricular radiotherapy in case of localized and CSI in case of disseminated germinomas [4,5]. In comparison with conventional radiotherapy, PT due to its unique physical and biological



Fig. 1 Dose distribution of whole ventricular radiotherapy using Intensity modulated proton therapy.

characteristics results in delivering low entry dose and deposit the majority of their energy at the end of their path, yielding a typical dose energy peak called 'Bragg peak.' This steep fall-off allows for the delivery of high radiation doses to the tumor and sparing of tissue beyond the tumor. All our patients underwent PT as a part of curative management and tolerated the treatment well. One patient treated with CSI had grade III neutropenia managed conservatively, whereas others did not experience more than grade II toxicities. Mean dose to hippocampus for all our patients was less than 30 Gy, below the accepted threshold for intelligence quotient preservation [6]. All patients could resume their normal schooling after the treatment, with no impact so far in their educational activities, and maintained quality of life. However, neurocognitive assessments were not available for two out of the three patients, and could not be planned due to the logistic challenges because of the ongoing COVID-19 pandemic.

Acute Meningoencephalitis in a Child Secondary to SARS-CoV-2 Virus

We report a case of cerebrospinal fluid (CSF)-proven severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in a child with acute meningoencephalitis.

An 11-year-old boy presented with one day history of fever, headache, vomiting and altered sensorium. There was no history of cough, fast breathing, rash or abdominal pain. On examination he was hemodynamically stable with a Glasgow coma scale (GCS) of 9 (E3 V2 M4). There was no cranial nerve paresis and he had signs of meningeal irritation (neck stiffness and positive Kernig's sign). In motor functions, he had increased tone with brisk reflexes and extensor planters in both lower

We have successfully implemented PT in the treatment of ICGCT in India. PT should be considered as a treatment option for optimal management of these curable tumors. Further follow up is required to assess the long-term sequelae of treatment in these patients.

RISHAN THIMMA SUDARSAN,¹ SRINIVAS CHILUKURI,¹
NOUFAL MANTHALA PADANNAYIL,² PANKAJ KUMAR PANDA³
AND RAKESH JALALI^{1*}

From Departments of ¹Radiation Oncology,
²Medical Physics, and ³Clinical Research,
Neuro-Oncology Cancer Management Team,
Apollo Proton Cancer Centre, Taramani,
Chennai, Tamil Nadu, India.
*rjalali@apollohospitals.com

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limbs. Fundus examination was normal. Child was managed in pediatric intensive care unit as per the standard protocol for acute febrile encephalopathy with empirical broad-spectrum antibiotics and acyclovir along with other supportive care. Blood investigation showed severe lymphopenia (absolute lymphocyte counts 700/mm³) and raised inflammatory markers (C-reactive protein-18 mg/dL, lactate dehydrogenase-4000 U/L, ferritin-2400ng/ml, D-dimer-51091 ng/mL) with deranged liver functions. CSF examination showed pleocytosis (75 cells) with lymphocytic predominance (80%), very high protein (696mg/dL) and normal sugar levels. The RT-PCR test for SARS-CoV-2 was done on a nasopharyngeal swab and CSF because of the outbreak situation and was found to be positive in both. CSF was negative for other neurotropic viruses (herpes, varicella and enterovirus). A head contrast enhanced computed tomography (CECT) scan was normal.

Child was managed conservatively and was given pulse dose methyl prednisolone (30 mg/kg/day) for 3 days followed by tapering doses, in view of high inflammatory markers and no evidence of bacterial infection. Antibiotics and acyclovir were stopped after the confirmed diagnosis of SARS-CoV-2 induced meningoencephalitis on day 4 of illness. Injection remdesivir was not given as a unit protocol as growing evidence did not find it beneficial to prevent mortality in SARS-CoV-2 positive patients and there is not much data of its use in children. Child's sensorium gradually improved in next few days along with downward trend in inflammatory markers. His repeat RNA-PCR for SARS-CoV-2 on nasopharyngeal swab was again positive on day 7 of illness and second CSF examination for the same was refused by the parents. In view of clinical improvement, he was subsequently discharged on request on day 10 of illness as per the government's discharge policy with strict home isolation advice. Subsequent RNA-PCR for SARS-CoV-2 on nasopharyngeal swab became negative on day 15 of illness. Child is in close follow up and is doing well so far.

Most coronaviruses (CoVs) share a similar viral structure and infection pathway, therefore the neurotropic mechanisms previously found for other CoVs may also be applicable for SARS-CoV-2 [1-3]. It is associated with a wide spectrum of neurological manifestations, including encephalopathy, Guillain-Barré syndrome (GBS), and perfusion abnormalities in the brain [put Indian GBS, and encephalitis ref]. However, attempts to detect the virus in the CSF of patients with neurological manifestations have not been widely reported. Only two cases in adults around the world has been reported so far out of which one showed the virus using gene sequencing of the CSF and the other one showed RT-PCR positive in CSF (similar to our case), suggesting that the virus has the potential to cross the blood brain barrier [3,4]. The SARS-CoV-2 receptor for cell entry i.e., membrane-bound angiotensin converting enzyme 2 (ACE2) which is also expressed in neurons, as well as endothelial and arterial smooth muscle cells in the brain potentially allowing

SARS-CoV-2 to cross the blood-brain barrier and cause viral meningitis [5]. Panciani, et al. [6] hypothesized a three-step model to explain the neuroinvasive potential of SARS-CoV-2, suggesting that the viral load in CSF progressively increases and it triggers an inflammatory response, but the viral clearance precede the occurrence of indirect SARS-CoV-2 effects on the CNS [6].

This case highlights the neurotropism of SARS-CoV-2 virus, and that meningoencephalitis may be the initial presentation of SARS-CoV-2 even without respiratory symptoms. We feel early use of immunosuppressants like methylprednisolone, especially in the setting of hyperinflammatory syndrome, is crucial for better outcome.

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MUKUL PANDEY

*Department of Pediatrics, St Stephens Hospital,
Delhi, India.*

mukul2k_2000@yahoo.com

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Hepatic Visceral Larva Migrans Causing Hepatic Artery Pseudo-Aneurysm

Visceral Larva Migrans refers to migration of second stage nematode larvae through human viscera most commonly the liver and lungs. This entity usually presents with fever, abdominal pain, hepatomegaly and respiratory symptoms. Here we describe hepatic visceral larva migrans causing hepatic artery pseudoaneurysm and presenting with upper gastrointestinal bleeding and its management.

Parasitic infections of liver are commonly encountered in clinical practice and can have myriad presentations posing a clinical diagnostic challenge. Hepatic visceral larva migrans (VLM) is one such entity presenting with prolonged fever and

liver involvement especially in areas endemic for the parasite. Hepatic artery pseudoaneurysm is a complication described mostly with traumatic liver injury and post-surgery [1]. We describe this complication secondary to hepatic VLM and its successful management.

A 12-year-old girl presented with high grade fever, jaundice and right upper abdominal pain with progressive abdominal distension associated with weight loss for four months and a history of recurrent black tarry stools requiring blood transfusions. She was resident of a rural area and her family of seven lived in an overcrowded house, belonged to lower socioeconomic status with poor hygiene practices, consumed vegetarian diet and had exposure to pet animals in neighborhood. On examination she was underweight (BMI 12.5 kg/m²), febrile and tachypneic, had severe pallor with pedal edema and no skin lesions. Systemic examination revealed firm tender

hepatomegaly (liver span:17 cm) without ascites or splenomegaly and crepitations on right side of chest. Ophthalmoscopic examination was unremarkable. Investigations revealed anemia (hemoglobin 5.7g/dL), and leukocytosis ($16 \times 10^3/L$) with eosinophilia ($1.4 \times 10^3/L$). Liver function tests were alanine aminotransferase 23 U/L, aspartate aminotransferase 19 U/L, alkaline phosphatase 590 U/L, total bilirubin 1.5 mg/dL with direct fraction 1.2 mg/dL, serum albumin 1.9 g/dL with albumin:globulin ratio of 0.4. As the child was sick at arrival, she was started on broad spectrum antimicrobials and supportive treatment (blood transfusion and albumin). Ultrasonography showed hepatomegaly with diffuse hypoechoic cystic lesions in both lobes of the liver. MRI abdomen showed lesions in the liver appearing hypointense on T1-weighted and hyperintense on T2-weighted images (**Fig.1a**) with mildly dilated common bile duct and normal intrahepatic biliary radicles. Dual phase CT scan of abdomen revealed multiple discrete and confluent hypodense lesions in both lobes of liver along with a 1.5 cm pseudoaneurysm (arrow) arising from the posterior branch of the right hepatic artery (**Fig.1b**). Based on clinical and radiological findings, a differential diagnosis of visceral larva migrans, cat scratch disease, Fascioliasis, disseminated tuberculosis and invasive candidiasis with underlying immunodeficiency along with pseudoaneurysm with suspected hemobilia was kept. The patient underwent digital subtraction angiography (DSA) and successful embolization of the pseudoaneurysm with n-butyl cyanoacrylate glue. Subsequent investigations revealed normal stool examination and negative Toxocara IgG serology, Echinococcus IgG serology, procalcitonin, Mantoux test, gastric aspirate genexpert for Tuberculosis, and HIV serology. Bacterial and fungal blood culture was sterile and upper GI endoscopy was normal. Percutaneous liver biopsy demonstrated ill-defined eosinophilic granulomas suggesting parasitic infiltration. Special stains and tissue culture were negative for acid fast bacilli (AFB), Bartonella and fungal elements. Based on clinical, radiological and histopathological findings, diagnosis of visceral larva migrans was made and child was started on albendazole (10mg/kg/day), diethylcarbamazine (4mg/kg/day) and oral steroids (1mg/kg/day) in 3 cycles of 3 weeks each with gradual tapering of steroids over next one month. Follow up imaging at six months showed resolution of hepatic lesions.

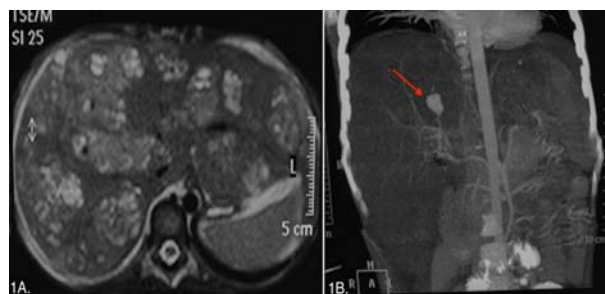


Fig. 1 (a) Axial T2 weighted MR image shows multiple conglomerate heterogeneous lesions in both lobes of liver, (b) Coronal CT angiography image shows a pseudoaneurysm (arrow) arising from the posterior branch of right hepatic artery.

Visceral larva migrans (VLM) refers to migration of second stage nematode larvae through human viscera most commonly liver and lungs. The etiological agents include *Toxocaracanis*, *Toxocaracati*, *Baylisascarisprocyonis*, *Cappilaria hepatica*, and *Ascarissuum* [2]. Humans are accidental hosts and acquire infection by ingestion of food contaminated with infective eggs. The clinical manifestations are fever, hepatomegaly, weight loss and respiratory symptoms mimicking asthma. An IgG ELISA based on 30 kDa recombinant Toxocara excretory–secretory antigen has 92% sensitivity and 89% specificity [3]. Features suggestive of VLM on CT are presence of multiple confluent peripheral and periportal ill-defined hypodense, oval or elongated nodular lesions scattered throughout liver parenchyma with peripheral rim enhancement and MRI shows T2 hyperintense/T1 hypointense lesions with restriction on diffusion weighted sequences [4]. Confirmation is by histopathological examination which shows presence of eosinophilic granuloma, palisading histiocytes and very rarely larva may be visualized. The slow migration of larva through the tissue incites a host inflammatory response along with eosinophilic infiltration and destruction of liver parenchyma. The cytotoxic eosinophil derived proteins may damage the endothelium causing vascular complications [5]. Hepatic artery pseudoaneurysm, a rare complication has not been previously described with VLM. Pseudoaneurysm develops due to the erosion of the eosinophilic abscesses into the hepatic artery. Rupture of the aneurysm results in hemobilia and the patients may present with hematemesis or melena or both. In cases of rupture of the aneurysm, early intervention by angio-embolisation of feeding artery should be considered. The embolizing agents used include coils, n-butyl cyanoacrylate glue and thrombin [1]. Medical therapy includes diethyl-carbamazine, mebendazole or albendazole for 2-3 weeks. Steroids are indicated in cases of ocular and neurological toxo-cariasis and in acute inflammatory manifestations of VLM [6].

We conclude that hepatic VLM can be a rare cause of hepatic artery pseudoaneurysm resulting in upper gastrointestinal bleeding. Early recognition and comprehensive management is of utmost importance.

RITU,¹KUMBLE S MADHUSUDHAN² AND ROHAN MALIK^{3*}

Departments of ¹Pediatrics, ²Radiodiagnosis, and
³Hepatology and Clinical Nutrition,
All India Institute of Medical Sciences,
New Delhi, India.

*dr.rohanmalik@gmail.com

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Tocilizumab Use in Children with Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a constellation of symptoms arising as a result of sudden and rapid release of cytokines into the blood from immune cells. CRS is characterized by high fever, hypotension, hypoxia, and/or multiorgan toxicity. Elevated liver enzymes and renal impairment are also noted and severe CRS can lead to life-threatening cardiorespiratory compromise [1]. CRS is increasingly seen as a medical emergency in children with blood disorders, and this could either be a presenting feature of their underlying disorder or a therapy-related event. Early recognition and therapy are essential, especially in severe cases. Scant data is available on the use of interleukin 6 (IL-6) inhibitor tocilizumab in very young children. We present a series of clinical situations in which we had used the CRS grading criteria to make a diagnosis and plan risk-based use of tocilizumab.

A 15-month-old girl presented with failure to thrive, generalized hypotonia, oral thrush and recurrent respiratory infections. She was diagnosed to have severe combined immune deficiency with *ORAI1* mutation. She underwent haploidentical stem cell transplantation with post-transplant cyclophosphamide and conditioning including fludarabine/treosulphan. After infusion of stem cells, she developed progressive symptoms suggestive of CRS including fever, tachycardia, and hypertension with one episode of posterior reversible encephalopathy syndrome, elevated liver enzymes and respiratory distress (requiring oxygen supplementation with high flow nasal cannula). Hypertension was noted, which was most likely secondary to the underlying calcium channelopathy associated with the mutation. CRS progressed to grade IV 11 days post-infusion. Serum ferritin, when elevated, suggests a cytokine surge in response to inflammation. The serum ferritin measured was 73000 mg/L. She was treated with 4 mg/kg of tocilizumab and made a dramatic recovery with a serial drop in serum ferritin within 48 hours.

An 8-year-old boy presented with fever, tachycardia, hypotension, cervical and axillary lymphadenopathy, hepatosplenomegaly, elevated liver enzymes and pancytopenia. Ferritin was elevated with levels up to 98000 mg/L. He has respiratory distress and required inotropes and oxygen supplementation. In view of features suggestive of grade 4 CRS, he was treated with one dose of tocilizumab in the intensive care unit. His symptoms recovered dramatically and serum ferritin dropped to 2700 mg/L in 72 hours. Bone marrow aspiration

cytology was unremarkable. Axillary lymph node biopsy and immunohistochemistry confirmed the diagnosis of classical Hodgkin lymphoma. We could commence chemo-therapy for Hodgkin lymphoma five days later, which was complicated by *E.coli* sepsis. He remains in remission over a year from diagnosis.

A 12-year-old boy presented with fever, tachycardia, tender hepatomegaly, and elevated liver enzymes (serum glutamic pyruvic transaminase, of 2500 IU/L and serum glutamic oxaloacetic transaminase, 2500 IU/L). He subsequently developed features of grade 3 CRS with respiratory distress and hypotension. Investigations revealed a serum ferritin of 69,000 mg/L, and Hepatitis A infection. He received one dose of tocilizumab at 4 mg/kg. The neutropenic phase following the drug was complicated by candida sepsis. He showed a complete recovery with normal blood counts, and remains on tapering steroids and cyclosporin.

There are several grading systems for CRS, where it is graded as grade I, II, III, IV, with grade I including fever without constitutional symptoms, grade II including hypotension responding to fluids and/or hypoxia responsive to <40% FiO₂, grade III including hypotension requiring pressor and/or hypoxia requiring oxygen >40% FiO₂ and grade IV consisting of life-threatening complications [2]. Several mouse-models have demonstrated the elaboration of cytokines namely IL2, IL3, IL6, interferon-gamma and GM-CSF in CRS with macrophages and monocytes being direct mediators of CRS [3]. Serum ferritin is an easily accessible diagnostic tool in these children and serial values help guide therapeutic interventions. CRS needs to be carefully distinguished from sepsis, and the clinical background and active surveillance for infections is crucial to prevent immediate mortality from sepsis.

Cytokine release syndrome has been reported by several groups in recent years post T cell replete peripheral blood haploidentical stem cell transplantation with post-transplant cyclophosphamide, with IL-6 being the most prominent biomarker. CRS also has an impact on increased risk of graft versus host disease [4]. Tocilizumab has been shown to be safe and effective in curbing the adverse effects associated with severe CRS [3,5] in especially post-transplant and rheumatological conditions. There is an ongoing clinical trial (NCT03533101) where tocilizumab will be administered pre-emptively prior to transplantation in the above group of patients.

We report that tocilizumab can be used safely even in the very young children at a dose of 4 mg/kg intravenously to provide immediate relief in life-threatening situations. The use of high dose steroids in these critically ill children with profound

neutropenia increases the risk of infection. Tocilizumab, in our experience, is a safer option even in infants and it provides immediate relief to the dramatic symptoms.

**DR REVATHI RAJ, DR RAMYA UPPULURI* AND
DR VENKATESWARAN VS**

*From Department of Pediatric Hematology, Oncology,
Blood and Marrow Transplantation,
Apollo Hospitals, Anna Salai, Teynampet,
Chennai, Tamil Nadu, India
ramya.december@gmail.com

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Eosinophilic Meningitis in a Toddler

Eosinophilic meningitis (EM) is a chronic aseptic meningitis often caused by helminthic infestation. EM is defined as eosinophils >10 per mm³ in CSF or >10% of total CSF leukocyte [1,2]. The most common infectious cause of EM worldwide are *Angiostrongylus cantonensis*, *Gnathostoma spinigerum* and *Basyliascaris procyonis* [1,2]. Non-infectious causes include malignancy like non Hodgkin lymphoma, multiple sclerosis, hypereosinophilic syndromes, malfunctioning ventriculo-peritoneal shunt and adverse drug reactions [2]. Even though EM has been reported in adults and children from India, parasitic etiology has not been confirmed in those cases [4]. We report a one year old child, resident of South Kerala, India, who reported with prolonged fever due to confirmed helminthic infestation.

A 1-year-old female child presented with 3 weeks history of irregular fever, irritability and poor oral intake. Child was started on oral cefixime from suspecting UTI. On admission, she had continuous fever for 5 days with irritability and episodes of inconsolable cry for 3 days. No history of vomiting or seizure, ear infection, head trauma, recent vaccination or contact with Tuberculosis, or exposure to any drugs or allergens. On examination, vitals were stable with no features of raised intracranial pressure or signs of meningeal irritation and with a normal CNS examination. On investigation, white blood cell count was $14.8 \times 10^9/L$ (36% neutrophils, 42% lymphocytes, 22% eosinophils) with peripheral smear showing eosinophilia and no parasites or abnormal cells. C-reactive protein was negative. Stool and urine examination did not reveal ova or cysts. In view of non remission of prolonged fever and history of irritability and headache, CSF study was done on second day of admission which revealed increased CSF pressure of clear fluid with 1150 whole blood cells, (30% neutrophils, 70% lymphocytes) with a protein 115 mg/dL and sugar 30 mg/dL (blood sugar- 89 mg/dL) suggestive of meningitis. Cultures of blood, CSF and urine were sterile.

Tuberculosis PCR, CSF biofilm for bacterial and viral panel were negative. India Ink and CSF biofilm were negative for Cryptococcus, KOH wet mount did not reveal any fungal elements. Mantoux test and HIV ELISA were negative and Chest Roentgenogram was normal. MRI contrast study of brain showed multiple cortical infarcts with sub cortical and cortical hyper intensities in T2W/FLAIR, leptomeningeal enhancement suggestive of meningitis. In view of meningitis, she was initially treated with ceftriaxone, then upgraded to vancomycin, meropenem and acyclovir. Since fever and irritability persisted even after 7 days of antibiotics, repeat sepsis screen was done, which was negative, and had similar findings on repeat MRI. Therefore, correlating the peripheral eosinophilia with this history, EM was suspected. On revisiting the history, mother gave history of a pet dog at home with rat and snail infestation in the locality. Absolute eosinophil count was 3080/mm³ on day 1, 5500/mm³ on day 7, 2880/mm³ on day12, 3102/mm³ on day 17. Repeat CSF study revealed 295 white blood cell/mm³ (5% neutrophils, 85% lymphocytes, 25% eosinophils) with protein 104 mg/dL, sugar 34 mg/dL (blood sugar-103mg/dL). Real Time PCR was

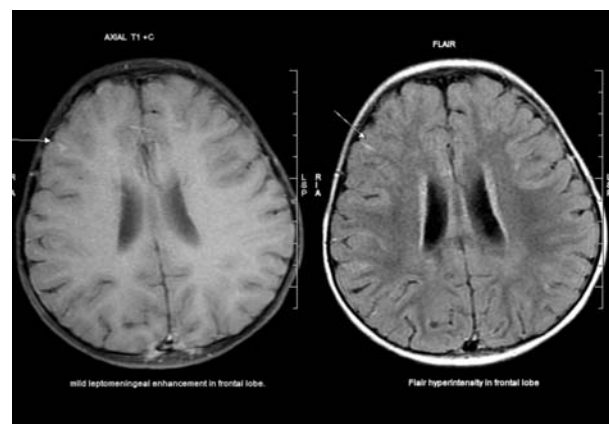


Fig.1 T1W/FLAIR images showing leptomeningeal enhancement/hyperintensity in frontal lobe.

done in CSF, which came positive *A. cantonensis*. She was started on prednisolone 2 mg/kg/day along with Albendazole 15 mg/kg/day for 2 weeks. Within 48 hours of treatment she became afebrile, her sensorium improved with improvement in activity and appetite. After 2 weeks of hospital stay she was discharged in a stable condition with an absolute eosinophil count of 625/mm³ on day 20.

Peripheral eosinophilia is an immunologically mediated response to various conditions like allergic (atopy, medications), neoplasms (leukemia, lymphoma, tumor associated) drug induced hypersensitivity and infectious diseases (parasite, fungal). It is essential to look for non infectious causes of hyper-eosinophilia symptoms, before looking for parasitic infection.

Overall parasitic meningitis is rare, but exact incidence and prevalence is not reported. Among the three major helminths that cause EM [1,2], *A. cantonensis* is the most common. Neurocysticercosis, although rare, also is known to cause EM in endemic areas.

Similar infections have been described in Southeast Asia, South Pacific, Taiwan, Africa, Caribbean, Australia and North America [1]. Shipboard travel of rats is the most common cause for the spread of parasite to other continents as rats are the definitive host. [2,3] and human beings are the accidental hosts. Infection occurs due to ingestion of third stage larvae in raw or undercooked snails or fish and children who play in the dirt in endemic areas are prone for infection. Eosinophilic meningitis is diagnosed presumptively based on travel or exposure history with CSF analysis showing >10% eosinophils, mildly elevated protein and normal glucose or hypoglycorrhachia [5]. Peripheral eosinophilia peaks about 5 weeks after exposure. MRI brain demonstrates high signal intensities, leptomeningeal enhancement, hyper intense signals on T2W image. For detection of parasite in CSF, ELISA is sensitive and specific but is limited by commercial non availability and cross reactivity between helminthic parasites. PCR based studies are sensitive in detecting the parasite DNA.

Treatment is mainly supportive with analgesics, corticosteroids and anthelmintic drugs [6,2]. There is higher

incidence of neurological sequelae among children and prognosis is good with 70% improvement within 1-2 weeks and mortality is <1%.

This case is presented to sensitize the clinician, the rarity of EM, caused by helminthic infection. The possibility of eosinophilic meningitis/parasitic meningitis must be considered in a patient with fever, peripheral eosinophilia, headache with or without meningeal signs. In such patients, CSF eosinophil staining is recommended along with demonstration of parasite antigen through real time PCR will help to establish parasitic etiology and also in prognostication and appropriate follow up.

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ABINAYA GEETHA RAVEENDRAKUMAR,¹ GOPIKA SEKHAR REMADEVI,¹ ELIZABETH KANDATHIL EAPEN,¹ ANILKUMAR THANGAPPAKURUPPU VIJAYAMMA² AND ANJANA³

Departments of¹Pediatrics, ²Neurology and³Pathology, Ananthapuri Hospitals and Research Institute, Thiruvananthapuram, Kerala, India. *grabinaya91@gmail.com

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Undifferentiated Nasopharyngeal Carcinoma and Paraneoplastic Leukemoid Reaction

Nasopharyngeal carcinoma is a rare pediatric malignancy [1]. In this report, we describe a nasopharyngeal carcinoma in child presenting with paraneoplastic leukemoid reaction (PLR). Adult patients with solid tumors presenting with PLR have been reported in the past, but very few pediatric cases have been described [1].

A 11-year-old boy, with a history of global developmental delay, presented with bilateral neck swelling that progressively increased over two months, associated with loss of weight, increased frequency of fever spikes, tiredness and difficulty in swallowing solid feeds. There was no history of contact with tuberculosis. Developmental age was 4 years and his antenatal, natal and post-natal history was uneventful. On examination, he was awake, alert, cooperative, and responded to verbal commands. He was pale, febrile, and had bilateral cervical lymphadenopathy of 15x10x3 cm on the right side and 12x10x3 cm on the left side, non-tender, immobile and firm to hard in consistency. The child was underweight and stunted and head circumference was below 2 SD when compared to age- and sex-matched controls. At presentation, the child was febrile with

tachycardia (rate 110/min), temperature 101⁰F, respiratory rate of 26/min and blood pressure 100/70 mm Hg. Peripheries were warm and well perfused. CNS examination revealed decreased muscle bulk in all 4 limbs with normal tone and reflexes. Other systems were unremarkable.

He was initially treated with an empirical 5-day course of amoxicillin for lymphadenitis. As the swelling did not subside, an excision biopsy of the left lymph node was done, which revealed granulomatous caseous necrosis suggestive of tuberculosis. In view of no response to anti tubercular treatment (ATT) after 3 weeks of therapy, and his total lymphocyte count showing neutrophilic predominance, a repeat excision biopsy of his right cervical node was done for further evaluation. His complete blood count revealed a total Hemoglobin of 7 g/dL, leucocyte count of 30,000 cells/mm³ (86% polymorphs, 9% lymphocytes, and 5% mixed cells) and platelets were 607,000 cells/mm³. Peripheral smear showed severe hypochromic anisopoikilocytosis and neutrophilic leukocytosis. Basic metabolic panel, liver function test, serum calcium, serum uric acid were normal and LDH of 430 U/L. Retroviral screening, urine, and blood cultures were negative. EBV serology was indicative of past infection. Repeat biopsy from a cervical lymph node showed atypical cellular infiltrate with surrounding fibrosis and inflammation. Immunohistochemistry staining of the biopsy specimen was positive for pan-cytokeratin (pan-CK) but negative for CK5/6, CK7, CK19 (A), CD15, CD30, placental alkaline phosphatase, and CD45 suggestive of metastatic carcinoma. Diagnostic nasal endoscopy (DNE) revealed a polyp in the nasopharynx biopsy which was sent for histopathological examination. CT scan of the neck revealed bilateral II, III, IV, and V cervical lymphadenopathy, enlarged retropharyngeal nodes of 2.6×2.0 cm with multiple necrotic areas. Subsequently, his WBC count on day 10 and 11 of hospital stay increased to 56,000 and 68,200 cells/mm³, respectively (96% neutrophils, 3% lymphocytes and 1% mixed cells), suggesting a hematological of malignancy. Biopsy from the DNE specimen, however, revealed ill-defined sheets of tumor cells (Schmincke pattern [2]), and vesicular nuclear chromatin with prominent nucleoli and a high nuclear to cytoplasmic ratio with strong and diffuse positivity for pan-CK. Peripheral smear during this phase of hyperleukocytosis showed neutrophilic leukocytosis with predominantly mature forms of neutrophils, thrombocytosis and no evidence of blast cells. C-reactive protein level was 4 mg/dL and blood and urine cultures for bacteria and fungi were negative. The cervical lymph node biopsy and the nasopharyngeal specimen stained positive for

pan-CK favored the diagnosis of advanced undifferentiated carcinoma of the nasopharyngeal type T_xN_{3a}M₀ – stage IVB. The hyper-leukocytosis was explained by a paraneoplastic leukemoid reaction after ruling out other common causes of hyper-leukocytosis. The child was treated with cisplatin and 5-fluorouracil, and subsequently treated with radiation therapy. On treatment the white cell count reduced thereby confirming paraneoplastic leukemoid reaction. His symptoms improved during the first 6 months of therapy, but he subsequently developed bone metastasis and died after 19 months of initial diagnosis.

The most common variant of nasopharyngeal carcinoma in children is the undifferentiated non-keratinizing carcinoma most commonly presenting as a neck mass [1]. Granulomatous response to the tumor may be dominant in a few cases of nasopharyngeal carcinoma [2], which probably led to the misdiagnosis of tuberculosis in the first place. A marked rise in leukocyte count suggested a hematological malignancy but the staining of the DNE specimen with pan-cytokeratin confirmed an epithelial tumor. Paraneoplastic leukemoid reaction (PLR) in this case was diagnosed after ruling out infections, new malignancy, hemorrhage, and use of drugs like corticosteroids, G-CSF, and minocycline [3]. PLR is thought to be caused due to overproduction of cytokines like IL-10, IL-6, and GM-CSF, which stimulate the bone marrow to produce a large number of leukocytes [4]. In children presenting with solid tumors, PLR should be considered after ruling out more common causes of hyperleukocytosis like a hematological malignancy.

SUMITHA UDAYASHANKAR TARUR* AND
SUDHAKAR PRASANNA

*Institute of Child Health and Hospital for Children,
Madras Medical College, Chennai, India
udayashankar@gmail.com

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Position Paper on Kawasaki Disease in India: Pertinent Issues

National University of Science and Technology,
Muscat; and ²Sohar Regional Teaching Hospital,
Sohar; Sultanate of Oman.
**prashanth_lucknow@rediffmail.com*

We read with interest the recently published IAP position paper on Kawasaki disease (KD) [1]. We would like to highlight the following issues that require further consideration.

Under laboratory investigations, it is noted that serum levels of NT-pro-BNP (N-terminal pro-brain natriuretic peptide) >225 pg/mL can assist in the diagnosis of KD (86.5% sensitivity and 94.8% specificity to suggest myocardial dysfunction). However, in the subsequent section, authors mention that cut-off values for NT-Pro-BNP indicative of myocardial involvement are yet to be clearly defined. The AHA statement [2] also states that this biomarker may not have sufficient discriminative ability. It is notable that during childhood, NT-Pro-BNP is known to vary with age and therefore, it has been suggested that a single cut-off value based on ROC analysis would be inappropriate [3,4].

It is mentioned that it may take 36-48 hours for the fever to subside in IVIG-responsive patients [1]. However, both this position paper and the AHA statement define IVIG resistance as persistence or recurrence of fever 36 hours after the end of IVIG infusion. Several recent studies and the Japanese Society of Pediatric Cardiology and Cardiac Surgery guidelines suggest a 48-hour time frame for the same [5]. The 36-hour cut-off, when applied strictly, could potentially lead to over-diagnosis of IVIG resistance. This is a pertinent issue that needs further exploration, considering that the time taken for IVIG infusion itself can be variable (typically 12 hours in North America and 20-24 hours in Japan) [5]. AHA recommends IVIG infusion over 10-12 hours (as opposed to 12-24 hours recommended by the authors) [1,2].

There are certain variations in the definition of recurrence. Recurrent KD is defined as a repeat episode of KD after complete resolution of the first episode [1,2]. Acute illness in KD usually lasts for 4 to 6 weeks and several Japanese surveys have classified KD as recurrent if there is an interval of at least two months from the onset of the first illness to onset of the new episode [6].

In the paper, the available Indian data has not been critically evaluated. It is imperative to consider relevant local data to bring in the much needed Indian perspective. In the process, lack of good quality data on the disease epidemiology and the importance of a national registry could have been highlighted. Finally, a conflict of interest statement by the authors is missing.

GOWDA PARAMESHWARA PRASHANTH^{1*} AND
ANITA TANDON²

*Departments of Pediatrics,
¹College of Medicine and Health Sciences,*

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AUTHORS' REPLY

We are in agreement with the author that NT-pro-BNP is not a well established tool for the diagnosis of KD. As rightly pointed out, NT-pro-BNP varies with age and the values provided in the paper are from the study by Dahdah, et al. [1]. It must be said that one should refer to age related upper limits of normal and it is also useful to keep in mind to avoid making diagnosis of Kawasaki disease just on the basis of NT-pro-BNP alone. Though there has been a global effort to identify a suitable biomarker for KD diagnosis, but that still remains elusive. NT-pro-BNP is presently an accessible tool in many centers and the facts relating to this tool has been added as an addendum in the paper.

Regarding the 36 hours (post intravenous immunoglobulin infusion) being the cut-off for the diagnosis of IVIg resistance, it was more of an adaptation from the American Heart Association (AHA) guidelines [2]. It is important to keep in mind that this period is after the completion of IVIg infusion and the duration of the IVIg infusion (10-12 hours vs 12-24 hours) does not matter much. The longer infusion period would specially apply to the context of school-going children with the disease when a higher total dose of IVIg needs to be infused. It needs to be emphasized that in a disease like KD, it might be useful to

overtreat rather than undertreat to prevent lifelong complications due to coronary aneurysms.

The definition of recurrent KD would essentially mean a recurrence after documented remission of the first episode of KD (clinically, echocardiography and laboratory). It goes without saying that this period would be at least for about 4 to 6 weeks.

This is a position paper on KD providing diagnostic and

therapeutic guidelines for practising pediatricians across the country. We did not intend to highlight or analyze Indian data. Moreover, data on KD in India is predominantly emerging from few centres and not representative of the scenario in the whole country.

BHASKAR SHENOY

*Department of Pediatrics, Manipal Hospitals,
Bangalore, Karnataka, India.
bshenoy@gmail.com*

Inclusion of Multisystem Inflammatory Syndrome in Children and Adolescents Temporally Related to COVID-19 in the Differential Diagnosis of Kawasaki Disease

It was an interesting and informative read to go through the IAP position paper on Kawasaki disease (KD) published recently [1]. It was indeed necessary to have a nation-wide consensus, which is suitable for India where the distribution of health resources is unequal and constrained. KD has become one of the leading causes of acquired heart disease in many developed countries of the world [1]. With almost a year of coronavirus disease 19 (COVID-19) pandemic, a new hyper-inflammatory syndrome affecting children has been observed, and variously labeled as Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 or Pediatric inflammatory multi-system syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) [2,3]. This condition has clinical features which overlap with other inflammatory diseases in childhood like Kawasaki disease (KD) and toxic shock syndrome (TSS) [2].

The position paper [1] mentions various differential diagnosis of KD, but does not mention PIMS-TS or MIS-C. It is important that this entity should be considered in the differential diagnosis of KD, as the clinical presentation is very much overlapping, though the underlying mechanism for hyperinflammation is different. In KD inflammation of the coronary arteries is due to IL-1, the myocardial dysfunction and higher severity of the 2019-nCoV infection is predominantly driven by IL-6 and IL-10 in MIS-C [4]. Three different phenotypes of hyperinflammation in children has been speculated as classic KD, PIMS-TS and macrophage activation syndrome [4]. Though IVIG and steroids are the mainstay of therapy in these conditions and aspirin also important in KD, the prognosis and long term follow up are different. Hence the authors would like to suggest that this evolving inflammatory disease should be included in the position paper as one of the differentials for KD.

TUSHAR JAGZAPE* AND ANIL KUMAR GOEL

*Department of Pediatrics, AIIMS, Raipur, Chattisgarh, India.
tusharjagzape@aiimsraipur.edu.in

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AUTHORS' REPLY

We thank the authors for raising this pertinent point. We are in total agreement that MISC (PIMS) is one of the differential diagnoses of Kawasaki disease. The draft of this article; however, was prepared prior to the onset of COVID-19 pandemic, and thus it was missed out in the list of differential diagnosis of KD in the consensus statement. The committee has modified the differential diagnosis as follows:

Differential Diagnosis of Kawasaki Disease

1. Infections – Bacterial (streptococcal, leptospirosis, rickettsia), Viral (measles, adenovirus, Epstein Barr virus).
2. Toxin related – Staphylococcal scalded skin syndrome, toxic epidermal necrolysis
3. Inflammatory – Systemic juvenile idiopathic arthritis
4. Drug hypersensitivity – Steven-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), mercury hypersensitivity.
5. Multisystem inflammatory disease of childhood temporally related to COVID-19 (MISC-C): A condition recognized and described during the COVID-19 pandemic. This occurs largely in children, usually above 5 years of age, as a short term illness with high grade fever and often with shock with multisystem inflammation. One of the phenotypes can

resemble incomplete Kawasaki disease. This is considered to be secondary to immune dysregulation triggered after or in the later phase of the infection by severe acute respiratory syndrome coronavirus (SARS-CoV-2).

BHASKAR SHENOY

*Department of Pediatrics, Manipal Hospitals,
Bangalore, Karnataka, India.
bshenoy@gmail.com*

Prehospital Management of Children with Dengue Fever Admitted in a Tertiary-Care Center

Initial management of most children with dengue is done by local practitioners initially, and they are subsequently referred in the event of worsening of clinical condition. In the present study, we reviewed the initial management of dengue prior to being referred to our hospital, with special reference to the timing of the laboratory investigations, fluid management and use of platelet concentrates

A chart review of children referred as dengue to our hospital between September and November, 2019 was done after getting approval from the institutional ethics committee of our hospital. The data on pre-hospital management of these children recorded included: whether importance was given to packed cell volume (PCV) or platelet count; timing of dengue NS1 antigen testing, dengue IgM and IgG testing (card versus ELISA method); and treatment (fluid management, use of NSAIDs, antibiotics, and platelet transfusion). PCV is normally done at the time of presentation and repeated when clinically indicated (appearance of warning signs, progression to shock). When PCV is used for fluid titration, it is usually done once in 4 hours.

Among the 643 patients hospitalized for dengue during the study period, 129 (20%) came by self-referral for fever because of their awareness regarding dengue. Most of the children who were brought by parents had dengue fever with no warning symptoms. 514 (80%) were referred by physicians, of which a large proportion were not managed as per protocol [1]. Of the 514, 385 children had dengue fever without warning symptoms, 103 children had dengue fever with warning symptoms, and 26 children had severe dengue.

Among the 80% of children who were referred from outside, in 20% of patients, PCV values were not given importance as fluids were not titrated based on PCV. On the other hand, in 30% of patients, platelet counts were monitored thrice-a-day. Intravenous fluids were not given as per guidelines in 10% of patients, and they had received large volume of hypotonic fluids leading to signs of fluid overload, which was managed with fluid restriction and diuretics.

The timing of investigating NS1 antigen and IgM or IgG were not as per WHO guidelines [1], and card test was done in about 15% of patients. Despite there being no indication for platelet transfusion, 3% of patients had received platelet concentrates. Though the diagnosis of dengue was made, antibiotics were given in view of high spiking fever in 2% children. Mefenamic acid induced gastritis was seen in around 4% children. These children had normal PCV, no physical warning signs, and hence the vomiting was not considered as warning symptom and was attributed to mefenamic acid.

The children referred without warning symptoms needed just a day of observation while the ones with warning symptoms and severe dengue required four days of hospitalization. All the children in the study group improved and there was no mortality.

In a survey done in Singapore [2], where they tested the knowledge on diagnostic methods and clinical management of dengue using a questionnaire, there were significant issues in the understanding and diagnosis of dengue, particularly on the importance of using a diagnostic kit. There were also significant increase in awareness and practices of the best practices of dengue clinical management (choice of fluids and use of platelet concentrates) [2].

It is important to make sure that the protocols are uniformly followed by practitioners to ensure timely referral which in turn improves the outcome and reduces mortality. The present study underscores the gaps in knowledge about dengue management among practitioners, and we plan to conduct training activities for the same.

JANANI SANKAR* AND NITHYA SARAVANAN

*Kanchi Kamakoti Childs Trust Hospital
Chennai, India.*

**janani.sankar@yahoo.com*

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Rooming in, KMC and Exclusive Breastfeeding in COVID Era—A Pediatrician's Dilemma

We read with interest the recent article on ensuring exclusive human milk diet in COVID-19 times [1], which covers practical aspects of newborn care and breastfeeding during the pandemic. However, it does not fully answer the pediatrician's query whether to practice rooming in, kangaroo mother care (KMC) and exclusive breastfeeding, when baby is positive/negative and when mother is positive and symptomatic/asymptomatic.

In general, COVID-19 pandemic has shown adverse effects on newborn nutrition and KMC. Many facilities consider separating neonates and mothers for unspecified periods, until the mother is non-contagious. It is known that temporary early separation and disruption of newborn physiology can affect immunity and increase the risk of infant hospitalization and double the burden on the health system [2]. Practicing KMC has been documented to improve breastfeeding rates compared to conventional neonatal care in COVID-19 [3]. The World Health Organization (WHO) recommends that infants and mothers with suspected/confirmed COVID-19 should be enabled to practice rooming-in and give skin-to-skin contact throughout day and night [4].

In a study on 46 mother-infant dyads, three breastmilk samples tested positive for COVID-19 by RT-PCR and one out of three babies tested positive. This was not concluded as transfer through breastmilk, as there was also close contact with positive mother [4]. As there is no clear evidence of transfer of the virus through breastmilk, the general agreement is that stable neonates exposed to COVID-19 infection can be roomed-in with exclusive breastfeeding [5]. The mother-baby dyad must be isolated from other mothers. The neonate and the mother may be managed in separate isolation facility, if sick/symptomatic [5]. The La Leche League International (LLI) stands firm in giving breastfeeding after observing good hygiene practices to reduce viral transfer. This will offer immunological protections to the breastfed baby, as mothers who become infected shortly before giving birth and those who become infected while breastfeeding, will produce specific secretory IgA antibodies and many other critical immune factors to protect

their neonates. According to LLI, if someone who is breastfeeding becomes ill, it is important not to interrupt direct breastfeeding. The baby has already been exposed to the virus by the mother and/or the family and will benefit most from continued direct breastfeeding [6].

Therefore, rooming in, giving KMC and exclusive direct breastfeeding are recommended in newborns of COVID 19 suspected or confirmed mothers after taking adequate precautions like wearing mask and with strict hand hygiene practices and cough etiquette. Separation, KMC by another family member and giving expressed/donor milk may be practiced only if that is medically indicated, the mother or baby being critically ill.

BETSY MATHEW^{1*} AND KE ELIZABETH²

¹GG Hospital, Trivandrum, Kerala; and
Department of Pediatrics, Sree Mookambika
Institute of Medical Sciences, Kulasekharam,
Kanyakumari, Tamil Nadu, India.
*betsymathew001@gmail.com

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A Tale of COVID-19: Beyond Physical Ailment

Since the initial days of the coronavirus disease 2019 (COVID-19) outbreak, there is increase in fear and anxiety in general population which is palpable worldwide [1]. Pandemics are known to cause short- and long-term mental health issues, particularly in children and adolescents [2].

A 9-year-4-month-old girl was referred to our child development clinic with complaints of on-and-off shortness of breath, crying episodes and excessive fear of the COVID-19 to herself and family members. These symptoms were present since a week. She was developmentally normal. She was reported as a bright and friendly child. No psychiatric illness was reported in any family members. The screen usage of family was increased significantly mainly related to news on the outbreak. Ten days back, her neighbours, including her close

friend, were moved to a hospital due to COVID-19. Parents reported that she had excessive fear thereafter of COVID-19. Her daily routine including appetite, sleep, play and class work was also affected.

While conversing with the child she had moist eyes with mainly short answers to any questions asked. On probing further, she reported about the incident and her fear of separation from the parents if either of them got infected. She had nightmares of being infected with COVID-19. On asking her what she knows about COVID-19, she replied “*it is a deadly virus which spreads from one person to another – once infected the person dies within a short time.*” Her vitals were stable and systemic examination revealed no significant findings. Looking at the clinical scenario, the child was diagnosed to have acute stress disorder with panic symptoms [3].

Cognitive behavioural therapy (CBT) (3-4 sessions in a week) was initiated with a clinical psychologist, focused on restructuring her thoughts and cognition. Due to significant impairment of daily activities and sleep, clonazepam was started at the dosage of 0.5 mg/day in 2 divided doses. Relaxation techniques were advised at home. Parents were asked to decrease screen usage focussing on COVID-19 and to divert her in activities she relished.

Panic disorder, generalized anxiety disorder (GAD), specific phobia, and post-traumatic stress disorder were also considered in differential diagnosis. However, presence of triggering factor and duration of illness helped to rule out the differentials [3]. After one week, overall improvement was observed in the child, and parents reported her improved well-being. Medications were stopped and she was asked to follow up for CBT. The child is on follow-up and symptom free since 4 weeks.

Children are having an increased exposure to media and inadequate knowledge about pandemic. Some individuals can

cope up with it. However, fear of the unknown raises anxiety levels in many children, especially the one with preexisting mental health conditions or neurodevelopmental disorders [2]. They may experience a broad range of concerns, including various internalizing and/or externalizing behavioral issues, increased substance abuse, social isolation, mental health disorders and lowered perceived good health [4].

Proactive and empathetic approach not only to the exposed but also with the unexposed is required. Early pick up with comprehensive history and observation is crucial for diagnosis. Appropriate intervention and meticulous follow up can benefit such children to build resilience during these difficult times.

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NIRALI LOHIYA,^{1*} NIKHIL LOHIYA,² SMITA KARVE³ AND SHARAD AGARKHEDKAR⁴

Division of¹Developmental & Behavioral Pediatrics, Departments of³Psychiatry and⁴Pediatrics, Dr DY Patil Medical College and Hospital; and Department of²Endocrinology, Jupiter Hospital; Pune, India.

*ntmralithakker@gmail.com

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COVID-19 Vaccine in Children: Where Do We Stand?

We welcome the recommendations of the Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (IAP-ACVIP) during the COVID-19 pandemic [1]. These recommendations are likely to assuage the doubts of pediatricians as well as parents. The Government of India is planning to layout the distribution of COVID-19 vaccine soon. In such times, the guidance from IAP-ACVIP regarding immunization of children with the COVID-19 vaccine is much desirable.

Recently a few vaccines have completed phase 3 trials and are likely to be available for the general population very shortly (Phase 4) [2]. Though the efficacy of these vaccines is impressive in trials among adults, there is apprehension for their

safety and efficacy in children. Recently a group of experts stated that the wait shall be prolonged for the pediatric age group due to the lack of clinical trials of COVID-19 vaccine in children and their vulnerable status [3]. However, explicit guidance from the Government of India on this aspect is not yet available. It is high time that the panel considers it as an urgent public health issue and advocates the right decision for children that is based upon robust scientific evidence and strong ethical aspects.

In a scientific view, the decision for vaccination should depend upon the overall disease prevalence and associated mortality and morbidity. For COVID-19, all these three aspects are relatively less severe in children, though due to the unknown status of the long-term implications, the situation remains grave. Another scientific aspect is the efficacy and safety of the vaccine in a given population. Unfortunately, similar to other therapeutic trials for COVID-19, the children are ostracized from vaccine trials too. Hence, this data is lacking at present and

is unlikely to be available in the next few months.

The ethical view advocates that the decision must be coherent with the principles of medical ethics (non-maleficence and beneficence, equity, justice, fairness, and transparency) [4]. All of the principles except non-maleficence and beneficence advocate for the equal share of children among COVID-19 vaccine recipients. In ethics, non-maleficence and beneficence supersede others therefore; vaccinating children cannot be advised unless it has been proven safe.

Since we have a large amount of short-term data on the implications of COVID in children, there is a need to analyze it properly to make an informed decision. Once, phase 4 vaccination trials begin, and we have sufficient data about its safety and efficacy in the general population, children should be enrolled in the ongoing vaccine trials. The results of the phase 3 trial done in children will serve as the best guide for further decision making.

The role of IAP has always been instrumental in all national policies about children. Now it's time to continue that advocacy by giving its representation to the national steering committee for the COVID vaccine so that the children are not ostracized again.

JOGENDER KUMAR* AND JITENDRA MEENA

*Department of Pediatrics,
Post Graduate Institute of Medical Education and Research,
Chandigarh, India.
jogendrayadv@gmail.com

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AUTHORS' REPLY

We appreciate the positive comments of the author regarding the recommendations of the Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (IAP ACVIP) on the subject of vaccination during the COVID-19 pandemic [1]. We would like to allay the apprehension of the author about immunization of children with the COVID-19 vaccine.

In certain situations, as in the present COVID-19 times, with limited availability of vaccines, the priority at this stage is to protect those at highest risk. There is unanimity in the view,

that the priority groups for vaccination are the frontline healthcare workers, to ensure the optimal functioning of the health care system, followed by those over 65 years of age and those with co-morbid medical conditions [2,3].

As of now, studies have shown that COVID-19 is relatively uncommon in children and when infected, typically have milder symptoms and the rate of complications are lower [4,5]. The role of children in transmission of the disease is uncertain and contact tracing studies have shown that children are rarely the index case in family outbreaks [6]. Nevertheless, outbreaks of COVID-19 have been reported in schools and school camps [7]. The temporal association of a novel Kawasaki disease-like multisystem inflammatory syndrome in children with past COVID-19 infection, underlines the need for continued surveillance in pediatric patients [8].

ACVIP is a sub-committee of the IAP, which has the mandate to evaluate evidence on available vaccines and make recommendations primarily for members of IAP. In the case of COVID-19 vaccines, we do not have a vaccine licensed for use in India nor are we expecting a COVID-19 vaccine for children in the very near future. None of the COVID-19 vaccines in phase 3 trials have included young children. The BNT162b2 mRNA COVID-19 vaccine trial has included adolescents 16 years and older and studies in the 12-15 year olds and subsequently the younger age groups are planned [9].

The ACVIP is following the developments very closely and will make recommendations, at the appropriate time, when more robust data is available about the efficacy, safety and availability of Covid-19 vaccines in children.

SRINIVAS G KASI* AND DR ABHAY SHAH

**sgkasi@gmail.com*

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Heme Oxygenase-1 Deficiency

The oxidation of heme to biliverdin is facilitated by a stress-induced enzyme, heme oxygenase-1. This enzyme has antioxidant properties and plays an important role against inflammation. First case of heme oxygenase-1 deficiency was reported in 1999 [1]. The key features of heme oxygenase-1 deficiency, a recently described disorder, are hemolysis, generalized inflammation, bleeding diathesis, nephropathy and asplenia [1,2].

An 8-month old child presented with fever for 1-month. He was first of nonconcordant twins, and the sibling was healthy. On examination, he had dysmorphic facies, frontal bossing, depressed nasal bridge and large ears. General examination revealed pallor, and on systemic examination he had hepatomegaly. Investigation revealed increased inflammatory markers [raised CRP (84 mg/L) and ferritin (3503 ng/mL)], features of hemolysis [raised LDH (5253 U/L), SGOT (210 units/L) and SGPT (114 units/L)], anemia and thrombocytopenia. He was worked up for bicytopenia (EBV, Parvo virus and CMV work up was negative). Other infections like tuberculosis and HIV were also ruled out. Bone marrow examination revealed few hemophagocytes. His initial USG abdomen revealed a normal spleen but on repeat CT abdomen after 6 months, spleen was not seen and only a small focal nodular calcified area within splenic fossa was seen. In view of the unclear primary diagnosis, hemophagocytes on marrow, increased liver enzymes and bicytopenia, he was started on oral steroids, pending further investigations. He improved, fever disappeared and liver enzymes returned to normal, but he needed transfusion once in 2-3 months. However, on tapering steroids, fever reappeared and he became pale again. He was readmitted for investigations. USG showed absent spleen. Hemoglobin electrophoresis showed sickle cell trait.

In view of features suggestive of autoinflammatory disorder, transfusion dependent anemia, and auto-splenectomy, clinical exome sequencing was done, which revealed homozygous nonsense variation in exon 3 of *HMOX1* gene (OMIM*141250) which causes human heme hemoxygenase-1 deficiency, confirmed by Sanger sequencing. Both parents were asymptomatic heterozygous carriers of the pathogenic variation detected in our patient.

When comparing our case with previous cases published in literature, we found our child had delayed development, growth retardation and dysmorphic features as reported earlier. He presented with fever but did not have lymphadenopathy or rash

as seen in earlier cases. Also, he did not have asplenia from the beginning but had autospplenectomy during the course of treatment. Laboratory features similar in our case to the previous cases were, features of hemolysis (raised LDH and SGOT), raised inflammatory markers (raised CRP, ferritin). Our case is different from previously reported cases as he did not have coagulation abnormalities, features of nephritis or abnormal lipid profile [1-3]. Subsequently our patient developed acute arterial stroke confirmed on MRI and later was transfusion dependent. He succumbed to his illness at the age of 3½ years at a peripheral hospital.

Human heme oxygenase-1 deficiency is a disease which is known to be associated with impaired stress hematopoiesis. This results in marked red blood cell fragmentation, intravascular hemolysis, coagulation abnormalities and endothelial damage. This leads to deposits in the kidney and liver. Clinical features include persistent hemolytic anemia, asplenia, nephritis, generalized erythematous rash, growth retardation and hepatomegaly. There is one case report of successful HLA matched stem cell transplantation in the literature.

Though a rare disorder, if a patient presents with features of hemolysis, generalized inflammation, bleeding diathesis, nephropathy and asplenia, diagnosis of human heme oxygenase-1 deficiency should be considered. All the features may not be present as our patient did not have coagulation abnormalities, features of nephritis or abnormal lipid profile. From our case, it is evident that the child had autospplenectomy, whereas literature suggests congenital asplenia.

SOUMYA RENJI,^{1*} NITIN SHAH¹ AND
MANISHA MADKAIKAR²

¹Department of Pediatrics,
PD Hinduja National Hospital and
Medical Research Centre; and

²ICMR- National Institute of Immunohematology;
Mumbai, Maharashtra, India.

*soumya1577@gmail.com

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Optimal COVID-19 vaccination strategy: Single dose versus two doses

Over the last few months, there has been exhilarating news of several vaccines against COVID-19 (Moderna, Pfizer and AstraZeneca) with efficacy ranging between 70-95%. India too has recently approved Covishield (based on the Oxford AstraZeneca vaccine) and Covaxin (by Bharat Biotech) for emergency use. All these have stirred hopes in our minds that a return to normal living could soon be possible.

Most of these vaccines are given in two doses 3-4 weeks apart. Since the target would be vaccinating a majority of the global population, vaccine shortage would be inexorable. Furthermore, it is difficult to assure that those receiving the first dose would turn up for the second. Vaccinating twice as many people with a single vaccine dose would mean a better use of the available resources. Single-dose vaccination seems more alluring as it is easy, less costly, and would probably help in faster achievement of herd immunity. However, its success would highly depend on the protection rendered by one dose of the vaccine, termed single dose efficacy (SDE).

A recent study, using an age-stratified mathematical model combined with optimization algorithms, ascertained the optimal vaccine allocation with one and two doses of vaccine to reduce five key metrics of disease burden (total infections, symptomatic infections, deaths, peak non-ICU and ICU hospitalizations) under a varying assumptions (different levels of social distancing, vaccine availability, vaccine's mode of action, vaccination rate). The results suggest that optimal vaccination strategy critically depends on the SDE. If the SDE is high, single-dose vaccination would prevent up to 48% more deaths than a strategy of vaccinating the high-risk group first. If the SDE is low or medium, mixed vaccination campaigns with one and two doses of vaccine would be better.

At a time when we are unsure of the efficacy of vaccines available, this study suggests that it is an absolute necessity to promptly determine the efficacy of a single dose of vaccine to use it optimally to end the pandemic and resume our routine activities as quickly as possible.
(*MedRxiv preprint 5 Jan 2021*)

Increased cooked meat intake linked to childhood wheezing

Prevalence of childhood asthma has been on the rise over the last few years. It has been found that dietary habits established in early childhood may be associated with wheezing and potentially the future development of asthma.

A study has suggested that certain substances in cooked

meats might predispose to increased wheezing in children. It included 4,388 children aged 2-17 years from the National Health and Nutrition Examination Survey (NHANES) survey data. It was found that higher intake of non-seafood meats and advanced glycation end products, generated during high-temperature cooking of meat, was significantly associated with wheezing, wheeze-disrupted sleep and exercise, and wheezing requiring medication.

Although further studies would be needed to confirm this finding, the study highlights these pro-inflammatory compounds as early dietary risk factors for asthma. These risks are potentially modifiable. This may have broad clinical and public health implications for the prevention of childhood asthma.
(*Thorax 21 Dec 2020*)

Novel imaging unveils if antibiotics reach cellular targets

Antibiotics form the cornerstone of management of infectious diseases. An effective therapy must incorporate drugs with the propensity to invade all infected environments. This is particularly important in cases where antibiotics have to attack intracellular organisms. A thorough understanding of how effectively antibiotics concentrate in various subcellular environments, and consequently target the pathogen, is critical in the selection of the antibiotic of choice.

Researchers at the Francis Crick Institute, UK, have developed a novel imaging method – correlative light electron and ion microscopy in tissue (CLEIMiT) – to know if antibiotics have reached bacteria within tissues. This was done by combining a variety of imaging methods – confocal laser scanning microscopy, 3D fluorescence microscopy, electron microscopy and nanoscale secondary ion mass spectrometry. They analyzed lung tissue of mice infected with *Mycobacterium tuberculosis* and treated with bedaquiline, and found that the drug accumulated not only in foamy macrophages of the lung but also in polymorphonuclear cells. This new approach elucidates the subcellular localization of antibiotics and is a powerful methodological advance to investigate if drugs reach their intracellular targets.

CLEIMiT is applicable to other drugs also, and the researchers have continued their work on the technique, adapting it for other categories of antibiotics. If we could select or develop more effective antibiotics based on where they reach, it might help in more effective antibiotic treatment, thereby reducing the duration of treatment and the risk of antibiotic resistance.
(*PLoS Biology 31 Dec 2020*)

JERIN SEKHAR
drjerincsekar@gmail.com

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INDIAN PEDIATRICS
Volume 57, January – December, 2020

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IMAGE

Dupuytren Subungual Exostosis

An 8-year-old, otherwise healthy boy presented with a 4-month history of a growing mass under the nail of his right fifth toe, painful on palpation, which caused onycholysis. The patient denied recent trauma or occurrence of similar lesions in the past. Family history was unremarkable. X-Ray showed a dorsomedial exostosis, of approximately 4×3 mm, on the right fifth toe.

Dupuytren's subungual exostosis (SE) is a rare heterotopic ossification that commonly involves the first toe or, more rarely, other toes or fingers. It usually presents with a solitary, fixed, painful, sometimes ulcerated or infected dorsomedial mass on the distal phalanx of toes or fingers, associated with elevation and dystrophy of the nail plate. The majority of patients are younger than 18 years. Triggers may be trauma or infections. The diagnosis is confirmed by radiography or histology.

Differential diagnosis includes viral warts, pyogenic granuloma and osteochondroma. Papillomavirus periungual warts are firm, keratotic papules which are located around the nail. They can be painful and cause onycholysis and hyperkeratosis. Pyogenic granuloma, an acquired benign vascular tumor, appears as a rapidly growing erythematous, soft, friable nodule with erosive surface and tendency to bleed under pressure, commonly located on fingers and toes but also in the head and neck region and oral mucosa. Osteochondroma is clinically similar to Dupuytren's SE but radiographically and histologically different – unlike the latter, in the majority of the cases, osteochondroma has continuity with the underlying bone and is covered by hyaline cartilage.

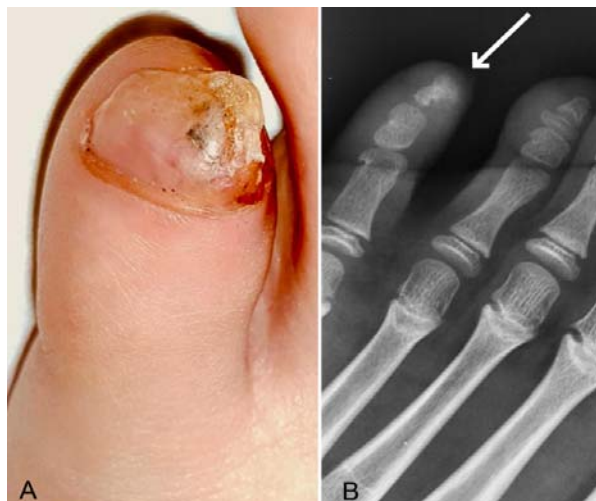


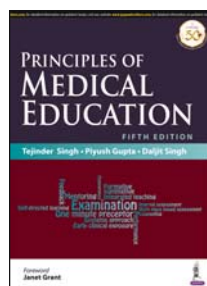
Fig. 1 Dupuytren's subungual exostosis; (a) mass under the nail of fifth toe causing onycholysis, and (b) radiograph showing dorsomedial exostosis (arrow).

Surgical treatment should aim to preserve the nail plate; nevertheless, an incomplete excision may lead to recurrence.

MARIO VACCARO,^{1*} LUCA DI BARTOLOMEO,² AND SERAFINELLA P CANNANO¹

¹Department of Clinical and Experimental Medicine – Dermatology and ²School and Operative Unit of Dermatology and Venereology - University of Messina, Italy.
*mario.vaccaro@unime.it

BOOK REVIEW



Principles of Medical Education (5th Edition, 2021)

ED. TEJINDER SINGH, PIYUSH GUPTA, DALJIT SINGH

Jaypee Brothers Medical Publishers (P) Ltd, Pages: 248

Medical education has to be dynamic, to keep pace with not only the changing health care needs but also the newer teaching-learning methods. India has recently witnessed a major shift in its undergraduate curriculum with focus on competencies, skills, and integration (both horizontal and vertical). The publication of the new edition of this book by authors who have played a key role in shaping the medical education curriculum in the country, is therefore, timely.

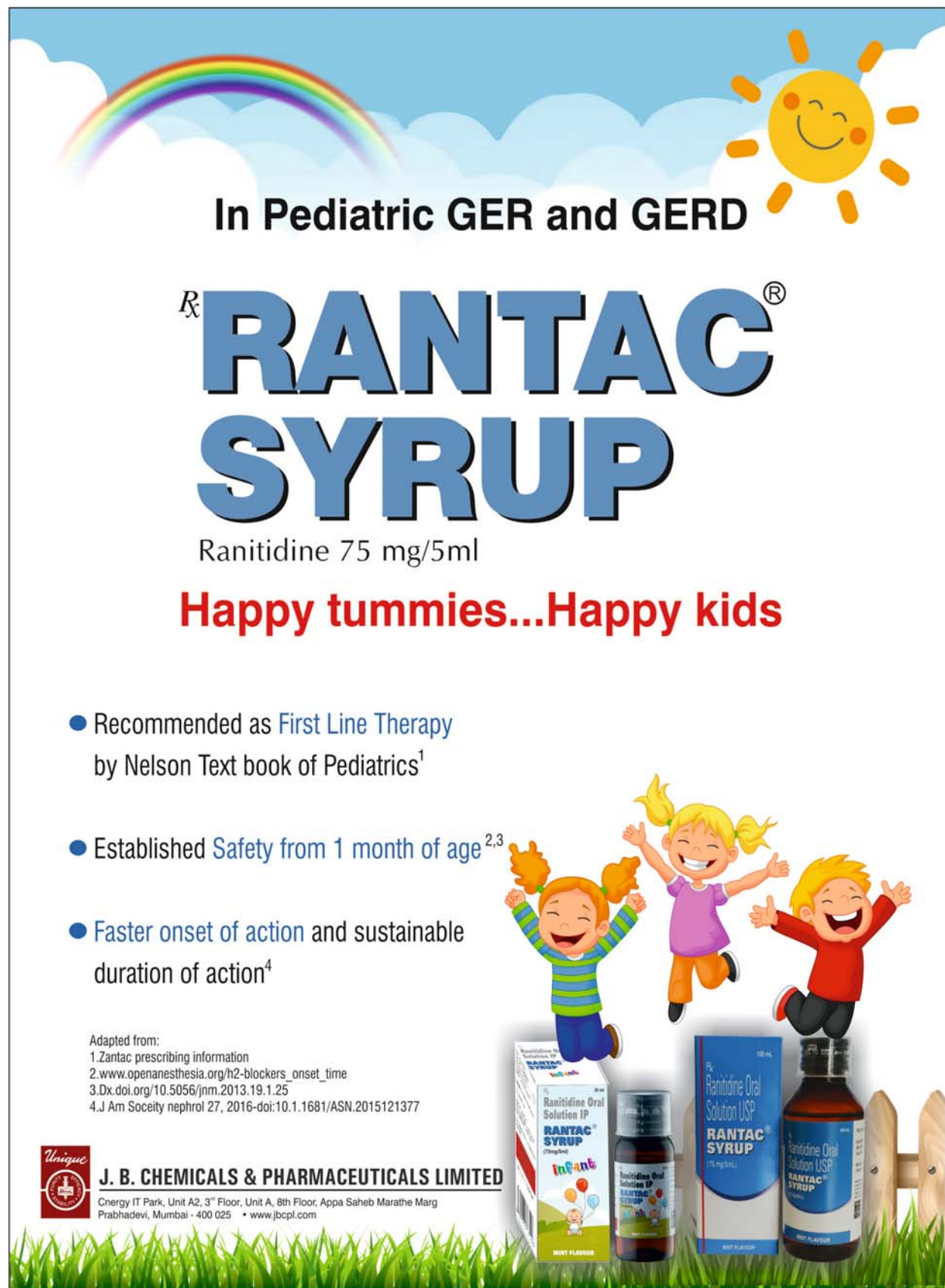
This handbook covers almost all the key themes which every medical teacher must be aware of. The initial chapters of the book cover the principles underlying teaching and learning and shift in

medical teaching, in particular the curriculum and integrated teaching the subsequent sections deal with various teaching methods. A greater part of the handbook is devoted to student assessment in medical education – essay, short answers and objective questions, assessment of practical and clinical skills, and at the workplace. The sections on assessing non-cognitive skills, mentoring, teacher evaluation and faculty development are particularly important.

The book is easy to read with its large well-spaced fonts, boxes with key information and easy to understand illustrations. It is a handbook that every medical teacher should have to help them in planning each day of their teaching. It should also hopefully enthruse them to innovate and make teaching-learning an enjoyable experience for both the preceptor and the student.

SIDDARTH RAMJI

*Department of Neonatology
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3. Dx.doi.org/10.5056/jnm.2013.19.1.25
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