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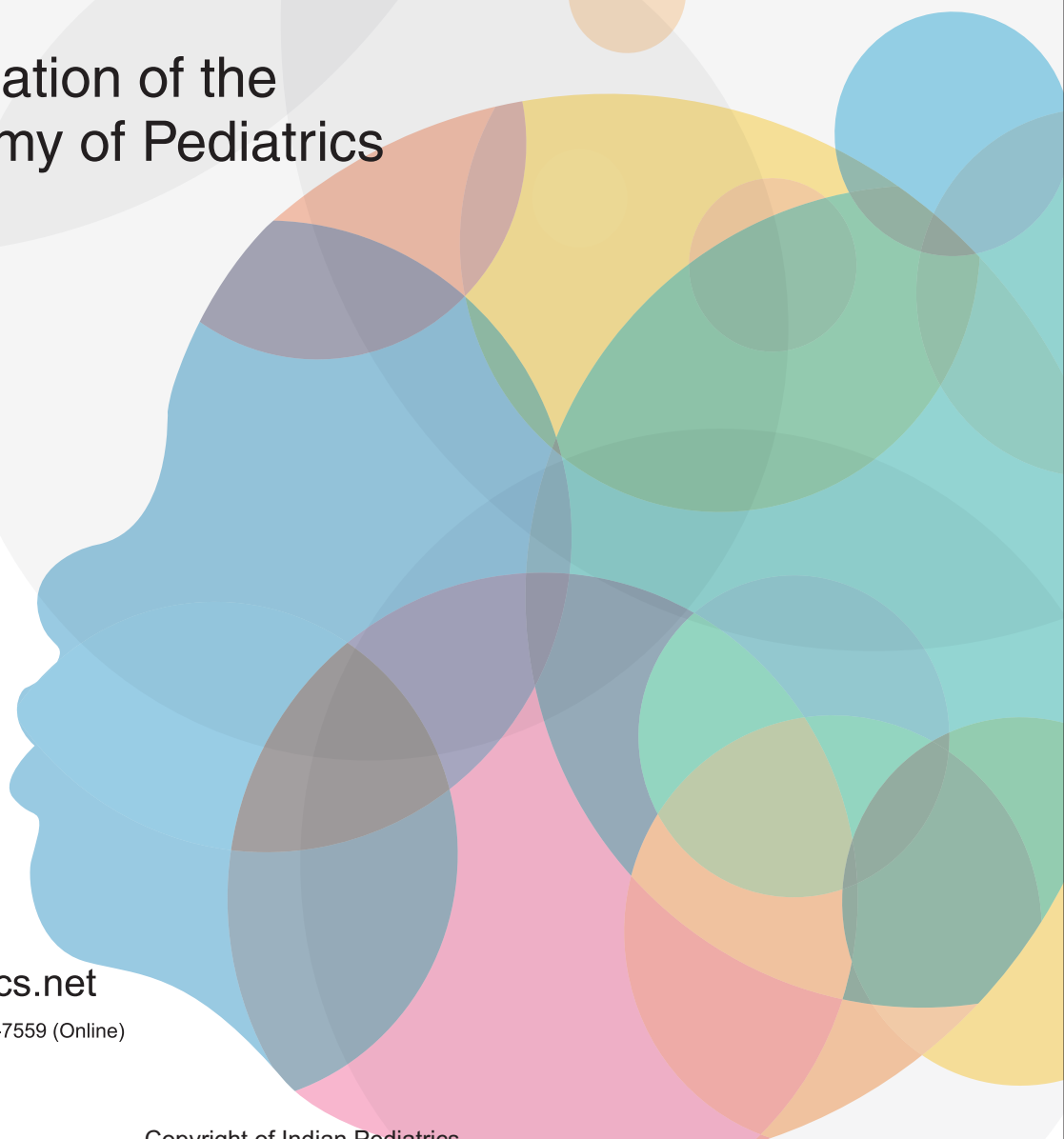

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IAP Guidelines for pediatric skincare

state that the newborn skin undergoes various structural and functional changes[1*]

Use of appropriate evidence-based skincare practices are important[2]

Protect the infant skin barrier function with safe, appropriate, and evidence-based products

Johnson's® CHOOSE gentle™

CLINICALLY mildness PROVEN®

Evidence-based skincare regimen

Cleansing regimen

As mild as pure water to maintain the skin barrier function[3,4]

Helps maintain the skin barrier function[5]

Moisturizing regimen

Improves the skin barrier integrity[6,7]

Helps enhance the skin barrier function for moisture retention[8]

*From birth to the first five years of life

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Examinations Should Test Knowledge, Not Nerve!

REMESH KUMAR R.
President, Indian Academy of Pediatrics 2022
drremesh2006@yahoo.com

In the month of May, a 18-year-old student, who was a resident of Bihar and had come to study in Kota, Rajasthan a month earlier, committed suicide on May 2, 2022 [1]. The reason for his taking the extreme step was suspected to be exam-related stress. This was the second incident of suicide of a coaching student in Kota in ten days, and the fourth in a month. Kota is known as the coaching capital of India, and the private tutorials that thrive there are industries in themselves. Every year, more than 150,000 students throng to this city to prepare themselves for JEE and NEET at its 150-odd coaching centers. Hence, it has become symbolic of the craze for competitive education and its negative impact on young minds, due to its high incidence of teen suicides. As many as 19 students are reported to have committed suicide in Kota in 2017.

Teen suicide, while being extreme and on the rise, is only the tip of the iceberg. Exam-related stress is an all-pervading problem that is little observed and even less understood. Various research studies have revealed that as many as two-thirds of students aged between 14 and 25 experience worrying levels of exam anxiety. As the day of the exam approaches, there will be signs of stress and mental breakdown. The release of various stress hormones in the body to combat situations of stress might lead to edgy and nervous feelings[2]. "*Muscles become tense, breathing faster, mouth dry, while the heart pounds and sweating increases. Early signs of excessive stress are headaches, loss or change in sleep pattern, loss of appetite and temper, tired and sick feeling, loss of concentration and a sense of restlessness. Sometimes the unusually excessive stress may trigger panic attacks, depression, …..or even self-harming behavior like suicide attempts. An adolescent with sleepless nights, troubled thoughts, loss of appetite, rapid pulse, and trembling hands is a typical case of exam fear,*" state the authors [2].

Who Is to Blame?

Modern civilization is highly competitive. It places a high premium on worldly achievement and material success. The entire system has evolved to perpetuate this ideal. Wealthy and glamorous people have replaced men and women of knowledge or talent as our role models. Lifestyle has become urbanized with a high dependency on industry for jobs, and the education system, in turn, has become a feeder of human resources to industry. Parents find their sense of security and emancipation in their children, who can thrive in this system. The systems of governance lack both the vision and motivation to change the status quo. The end victims of this vicious cycle are the innocent children who are pushed into the rat race of 'success' and ill equipped to cope with the stress-inducing situations brought about by the high expectations of both parents and schools.

The education system is particularly flawed in that it does not rely on a child's natural curiosity to learn, but rather it functions in a strictly regimented mode, little respecting the child's need for freedom and inclination to learn through experimentation and experience. Discipline is imposed rather than inspired. A systemic bias in favor of academics rather than all-round development makes it particularly taxing for young and evolving minds. Memorization of information stands in for genuine understanding. Rather than being an empirical measurement of the student's learning and comprehension, exams have become "make or break" situation, and the entire life of the student seems to hinge on them.

Parents, on the other hand, tend to relegate their entire responsibility for education to the school system and invest little or no personal involvement in the educational process. They seem to equate their discharge of duty towards the child's education with the payment of school fees, the purchase of books, and harboring expectations of good performance in exams. Parents rarely engage in meaningful conversations and exchanges with their children regarding their school life. Children too do not trust their parents enough to disclose all that is happening in their lives, partly because they do not know how to express it and more so because they fear how any disclosure they voluntarily make will be received. This disconnect between the parent and the child is a contributory factor for stress in children.

The Larger Issues

The education system itself is subject to state policy. Governments, being bureaucratic by nature, take time to introduce any change. Much of our educational policy appears outdated and, in fact, counterproductive. While there have been commendable reforms to introduce modern educational practices and also to protect the rights of children up to the higher middle school level, there has been no corresponding scaling of reforms to reach the higher strata of schooling. In fact, factors that exert undue pressure on students have intensified greatly from high school onwards, and there is no relief to the individual until he or she gets settled into a well-paying job. The precondition for this is good scores in the exams. The other options are (if parents allow) to opt out of this artificially induced rat race by choosing to pursue his or her dreams on their own, or decide to settle for a substandard life, or, as a few sadly do, to end the torture of existence once and for all.

Thus, there are multiple factors at play which contribute to exam stress. From the points discussed above, it is clear that we live in an ecosystem that is predisposed to it. In fact, it would be reasonable to postulate from our observations that the stresses imminent in the adult world are merely getting transferred to children under the guise of 'preparation' for the rat race that lies ahead in an apparently 'ideal' world. Being relatively recent in occurrence and symptomatic of modern, urbanized culture, there are very few scientific studies to go by to address the issue. However, according to an in-depth study [3], suicides among children and young adults peak at the beginning of exam season, adding to fears that pressure to get good results is harming their mental health. Other causes include bullying and bereavement.

Prevention Better Than Cure

As doctors, what should concern us is how we can respond effectively to mitigate this issue. Safeguarding young lives is our professional responsibility, and we should do all we can to further it. Yet, frankly, can we? The manifestation of stress is psychological in nature and presently not clinically relevant. As things stand, such cases may very rarely come to the attention of a paediatrician, and that too circumstantially. Most of the causative factors concerning this are largely beyond our control. On a pragmatic note, 'prevention is better than cure' has been proposed as the better model for dealing with the issue [2], and the authors state "….. *the best way to prevent exam stress is confidence, ensured by timely preparation for the exam*" [2].

This is basically preemptive in nature, and might not be timely for cases that might get referred to us, which will typically be in the midst of the problem. In such cases, the clinician may advise therapeutic measures like deep breathing, relaxation routine, proper food, physical activity, adequate sleep and alignment with support groups. More than this, an understanding attitude on the part of the clinician will go a long way in providing relief to both the child and the parents. Good understanding is required in order to break the vicious cycle of stress and enable a child to gain a healthy upbringing. Belonging to a specialty concerned with child health, we also have a moral obligation to advocate against the factors that adversely affect children. We can use social platforms and the mass media to convey our concerns and hope that eventually policies will change and society will improve for the sake of better care of children.

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INVITED COMMENTARY

Mysteries of Dosing Vitamin B12 and Much More!

SARITA DEVI,[1] HARSHPAL SINGH SACHDEV,[2] ANURA VISWANATH KURPAD[1*]

From [1]St. John's Medical College, Bengaluru, Karnataka; [2]Sitaram Bhartia Institute of Science and Research, New Delhi.
**a.kurpad@sjri.res.in*

Tandon, et al. [1] studied the relative efficacy of high-dose oral and parenteral vitamin B12 in deficient children with macrocytic anemia, and found that in the short term, parenteral vitamin B12 was more effective in increasing their serum vitamin B12 and hemoglobin concentrations. This is not surprising, given the dosing routes. However, the issue is somewhat muddled by both groups getting a single parenteral vitamin B12 (1000 µg intramuscular) dose at the beginning of the trial [1], such that this was not a pure parenteral-oral dose comparison. Further, higher rates of attrition and concomitant iron therapy in the parenteral group weaken the interpretation. The difference in effect on hemoglobin after three months of treatment was dramatic: the hemoglobin increment in the parenteral group was nearly 2 g/dL greater than the oral group, in spite of other important causes of anemia not being ruled out [1]. The parenteral group possibly had greater baseline deficiency of vitamin B12 and hemoglobin, thereby suggesting regression to the mean as a partial explanation.

The relative benefits of oral vs parental dosing can be better understood through the prism of absorption. This requires effective gastric function: first acidity to release vitamin B12 from salivary haptocorrin and then intrinsic factor (IF) to bind and chaperone free vitamin B12 to the terminal ileum, where it is internalized by binding to finite numbers of Cubam receptors. Recently, a safe, stable isotope (^{13}C)-labelled vitamin B12 test became available, showing an average vitamin B12 bioavailability in normal Indian adults of ~50%, at an oral dose of 2.5 µg; with a 18 µg oral B12 dose, the absorption was 8% [2]. This is not surprising; since the number of transporters is finite, absorption follows zero-order kinetics, with a maximum of about 1 µg vitamin B12 absorption [2]. However, in addition, a passive absorption of about 1-5% of the dose was described, presumably following first-order kinetics. With a 500 µg oral dose, as in this trial, a substantive 5-25 µg could be passively absorbed, which is reflected in the increased serum vitamin B12 concentrations [1].

With effective passive absorption at high doses, the question remains whether oral or parenteral vitamin B12 is better for the treatment of deficiency anemia. Although Tandon, et al. [1] showed that sustained parenteral vitamin B12 resulted in significantly higher concen-trations of serum B12 and hemoglobin in deficient patients, the oral dose had a substantial effect on serum B12 concentrations (nearly 400 µg/mL; about two-third of the effect of the parenteral dose), but the confounding effect of the initial parenteral dose cannot be ruled out [1]. Other studies have also suggested that high oral doses are good enough, given the passive absorption, for pernicious anemia and food cobalamin malabsorption [3]. A Cochrane review has; however, highlighted the need for further clinical trials, as only low-quality evidence was available to suggest that oral doses (1000 µg/day vitamin B12) were as effective as parenteral in replenishing stores in a deficient elderly population [4]. These high resto-rative doses over 1000 µg are recommended because of the wide normal variation in absorption, by nearly four-fold in normal adults [2,5].

One additional finding from the present trial [1], that of the quite dramatic effect of parenteral dosing on hemoglobin, merits mention. The parenteral group started with a lower baseline hemoglobin and serum vitamin B12 (9.4 g/dL and 85 pg/mL) with particularly low hemoglobin values (lower IQR of hemoglobin: 6.5 g/dL) compared to the oral dose group (11.3 g/dL and 112 pg/mL). The 50% higher increase in serum vitamin B12 concentration in the parenteral group might be a reason for their better hemoglobin response, but this is unlikely. A weak but significant relation has been shown between hemoglobin and serum vitamin B12 in the range of <400 pg/mL [6] but this does not explain why a nearly 30% hemoglobin increment was observed in the parenteral group, particularly when the mean corpuscular volume change was similar between groups. A similar study in Turkish children younger than 18 years showed similar increments in serum vitamin B12, but much smaller changes in hemo-globin, similar between groups, one month after treatment [7]. Thus, there are still unanswered questions, and future dosing comparisons should include detailed characteri-

zation of the cause of anemia, sequential measurements of hemoglobin, along with functional biomarkers of vitamin B12 deficiency.

From a public health perspective, vitamin B12 deficiency, and macrocytic anemia should be rampant in India, given dietary habits, and the daily vitamin B12 requirement in 1-5-year-old children, which ranges from 1.2-2.2 µg [8]. However, a recent national survey of under-5 Indian children found only 13.8% prevalence of vitamin B12 deficiency [9], defined by serum vitamin B12 concentrations, with prevalence of macrocytic anemia due to folate or vitamin B12 deficiency of around 19% [10].

Thus, many questions about vitamin B12 remain: what is its daily requirement estimate in Indians; do adaptations in the conservation of vitamin B12 stores occur; why is the prevalence of its deficiency so low in apparently vegetarian populations; and in clinical defi-ciency, what should the appropriate dosing schedules be? We look forward to more studies to address these gaps in the literature.

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INVITED COMMENTARY

Is the Time Ripe to Shift to Oral Vitamin B12 Therapy in Megaloblastic Anemia – Perhaps, Not Yet!

MUKUL AGGARWAL,* AMIYA RANJAN NAYAK, MANORANJAN MAHAPATRA
Department of Hematology, All India Institute of Medical Sciences, New Delhi.
**mukulhemat@gmail.com*

Vitamin B12 (cobalamin) plays a crucial function in cellular metabolism, especially in maturation of blood cell precursors and myelination of the nervous system. It is produced by microbes and is primarily found in foods of animal origin. Intrinsic factor, produced by the stomach parietal cells, and the cubam receptor in the distal ileum are both necessary for intestinal absorption [1]. Clinical spectrum of B12 deficiency may vary from mild anemia to extreme forms of neurological deficits including ataxia, dementia, psychosis, and pancytopenia [2]. Autoimmune pernicious anemia, caused by lack of intrinsic factor production by gastric parietal cells, is the main risk factor for developing B12 insufficiency in higher-income countries. Insufficient dietary intake is the most common cause in low-income countries. In a study done by Yajnik, et al. [3], 67% of the randomly selected men had low vitamin B12 levels, most of them were middle class residents and vegetarians. The prevalence of vitamin B12 deficiency is around 47% amongst north Indian population [4].

Cobalamin deficiency demands early recognition and effective administration of therapy. For treatment of vitamin B12 deficiency, parenteral formulations are preferred due to unpredictable absorption through oral route and are given initially on daily/alternate day basis for 10 doses, then weekly for four doses and sub- sequently once a month. Even in patients with gut disease causing malabsorption, pernicious anemia or gastric resection, oral vitamin B12 therapy can still achieve reaso-nable results due to absorption via passive diffusion (1.2 percent of total absorption of vitamin B12). Though the British guidelines recommend oral supplementation for mild vitamin B12 deficiency, there are no clear recommen-dations for our population [5]. Complete correction of anemia usually takes 6-8 weeks, but reticulocytosis appears within 4-7 days with disappearance of megalo-blastic marrow changes within 48 hours. In this context, the study by Tondon, et al. [6], published in the current issue of the journal, is truly relevant for the low-income population.

In this open labeled randomized controlled study [6], 80 children with clinical and laboratory signs of nutritional macrocytic anemia, aged 2 months to 18 years, were included. All patients received first 1000 µg parenteral dose, after which they were randomly assigned to receive the following doses parenterally (group A) or orally (group B). Post 3 months of treatment, the parenteral therapy group experienced a noticeably greater increase in hemoglobin [2.7 vs 0.5; P=0.001] and vitamin B12 levels [600 vs 399; P=0.016]. This was done after matching the groups for age, sex, diet, nutritional status etc. The study is adequately powered (80%), and recruited required subjects in both arms to justify the results.

The current study [6] has efficiently compared the efficacy of therapy via both oral and parenteral routes in the Indian population but addressing a few shortcomings could have been a bonus. Folic acid and iron deficiency were not identified separately, and iron supplementation was given based on clinical parameters and laboratory evidence of dimorphic anemia. Matching for highly prevalent dual deficiency anemia and proper diagnosis of iron deficiency by serum ferritin could have been done. The reason behind giving first parenteral dose to all participants is not clear. This highlights the ethical dilemma for treating deficient patients with standard of care supplementation. With evaluation for etiology of vitamin B12 deficiency (pernicious anemia/malabsorption/ low intake etc.), the study [6] could have become more robust. This may have an important bearing on response to different therapeutic routes as well. Finally, the study [6] did not include patients with very severe anemia as the mean hemoglobin level of the parenteral group was 9.4 g/dL and the oral group was 11.3 g/dL, and it is well known that rise in hemoglobin is quicker with lower baseline level.

Kuzminski, et al. [7] randomized newly identified vitamin B12 deficient patients to vitamin B12 via intramuscular or daily oral schedule and observed better increase in serum cobalamin levels with oral therapy.

Verma, et al. [8] demonstrated a prompt and adequate biochemical response with only oral therapy in children with isolated vitamin B12 deficiency; however, it took more than a month for the hemoglobin to improve.

Supplementation through oral route is always preferred by the patients solely because of the ease and avoidance of painful injection. Cobalamin injections can be associated with injection site reactions, nausea, gastrointestinal disturbances, and precipitation of hypokalemia. According to a budget impact research, oral vitamin B12 therapy can be more affordable than parenteral preparations [9]. On the other hand, parenteral therapy has its own advantage of producing quick response and efficiency in patients with severe malabsorption problems, and cases where compliance is an issue.

The debate is ongoing regarding the route of cobalamin therapy. More randomized studies like this are needed in future, taking care to include isolated vitamin B12 deficiency cases, different food habits, complete etiological work up as well as a longer follow up.

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INVITED COMMENTARY

Nutraceuticals in Pediatric Headache: Food for Thought

THILINIE RAJAPAKSE,[1,2*] JANETTE MAILO[1,2]

*[1]Department of Pediatrics (Neurology) Faculty of Medicine & Dentistry, College of Health Sciences, University of Alberta, Edmonton, Alberta, Canada; and [2]Stollery Children's Hospital Headache Program, Women & Children's Research Institute, Edmonton, Alberta, Canada, *thilinie.rajapakse@ahs.ca*

Both parents and health care practitioners worldwide seek safe, effective and tolerable treatments for migraine in children. While many evidence-based pharmacologic options exist [1], families often turn to complementary and alternative medicine with a hope that effective and safe therapies can be offered to their children with a more tolerable side effect profile and equivalent efficacy. To that end, nutraceuticals represent "food, or parts of a food, that provide medical or health benefit, including the prevention and treatment of disease" [2]. In varying international markets they represent a variety of agents including functional foods, nutritional supplements, vitamins and herbal remedies, some of which have been used for thousands of years.

In India, the regulatory aspects of herbal medicine falls under the Drug and Cosmetic Act (D and C) of 1940 enforced by the Department of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) which requires manufacturers to acquire a license to manufacture and market herbal medicines. Within this, information regarding the manufacture, registration, sale, license and GMP (good manufacturing practice) certificate from manufacturers are required by various sections of the D and C act, with the recent mandate of product labelling with manufacturing and expiry dates on product labels as of 2017 [3].

In Canada, all natural health products must have a product license before sale in Canada under the provisions of the Natural Health Products Regulations in effect since January, 2004. The license is obtained following submission of information to Health Canada including medicinal ingredients, source, dose, potency, non-medicinal ingredients and recommended use(s). Once Health Canada has assessed a product as safe, effective and of high quality it issues a product license with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) which must by law appear on the label. Good manufacturing practices (GMPs) are also enforced in Canada to ensure safe and high quality products with specific labelling and packaging requirements [4].

Options studied in children [5] for the treatment of migraine include vitamins such as vitamin D and B2 (riboflavin), antioxidants such as coenzyme Q10, minerals including magnesium, phytomedicines such as butterbur and dietary sources of polyunsaturated fatty acids (PUFAs) such as omega-3 fatty acids. A recent review [5] concluded that due to low quality evidence and limited studies, no definite conclusions could be drawn upon the efficacy of nutraceuticals for the treatment of pediatric migraine. However further study was encouraged due to preliminary efficacy signals, favorable safety profiles and plausible mechanism of action in migraine for both coenzyme Q10 and magnesium. A particular recommendation of the review was to consider stratifying patients based on pre-treatment level if the nutraceutical under investigation is measurable.

The study by Bhurat, et al. [6] in *Indian Pediatrics* highlights this important gap in the literature in the case of the mineral magnesium. In particular, magne-sium plays an important role in in nerve transmission and a protective role against excessive excitation. The study by Bhurat, et al. [6] adds further evidence to the body of knowledge that adolescents with migraine are deficient in magnesium [7,8] and therefore a role for magnesium supplementation may contribute to the management of migraine in children. This particular cross sectional study of age and sex matched children found that in an adolescent (10-18 year old) subgroup serum magnesium levels were signifi-cantly lower in children with migraine compared to those without a headache disorder. While the sample sizes were small, the study adds important evidence to the consi-deration that magnesium replacement may be a useful migraine therapy in magnesium deficient adolescents with migraine. This requires further study, with previous evidence suggesting potential efficacy of magnesium in the prevention of pediatric migraine [9].

In regions where access to prescription medication for migraine may be limited due to access or finances,

nutraceuticals may represent an alternative source of therapy for migraine in children. However, great care must be taken with children as regulatory bodies internationally differ with respect product testing and safety regulations and practitioners should be well aware of local licensing policies and products prior to recommen-dation for their use of children. With further rigorous study ideally through randomized controlled trials, if produced safely and dosed appropriately for weight and age, nutraceuticals may represent a path of accessible and effective migraine therapy for children worldwide.

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RESEARCH PAPER

Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: *A Randomized Controlled Trial*

RAHUL TANDON,[1] JIGAR THACKER,[1] UTKARSH PANDYA,[2] MAMTA PATEL,[3] KRUTIKA TANDON[1]

From Department of Pediatrics, [1]Pramukhswami Medical College, Bhaikaka University, Karamsad, Gujarat; [2]Department of Pediatrics, Guru Gobind Singh Hospital, Jamnagar, Gujarat; [3]Department of Biostatistics, Central Research Service, Bhaikaka University, Karamsad, Gujarat.

Correspondence to: Dr Krutika Rahul Tandon, Professor and Head, Department of Pediatrics, Pramukhswami Medical College, Bhaikaka University, Karamsad 388 325, District Anand, Gujarat. tandonkrutika72@gmail.com

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Background: There is limited literature in children on efficacy of different routes of vitamin B12 administration for vitamin B12 deficiency macrocytic-megaloblastic anemia.

Objective: To compare parenteral with oral vitamin B12 therapy in children with macrocytic-megaloblastic anemia.

Study design: Single-center, open-label randomized controlled trial.

Participant: 80 children aged 2 month-18 year with clinical and laboratory features of nutritional macrocytic anemia.

Intervention: All children received an initial single parenteral dose of 1000 µg vitamin B12 followed by randomization to either parenteral or oral vitamin B12 for subsequent doses. Group A was given 1000 µg intramuscular (IM) vitamin B12 (3 doses on alternate days for those aged <10 year, five doses for age >10 year), followed by monthly 1000 µg IM for the subsequent two doses. Group B was given daily oral vitamin B12 1500 µg (500 µg in <2 years age) for three months. Folic acid and iron supplementation, and relevant dietary advice were given to both groups in a similar fashion.

Outcome: Improvement in serum vitamin B12 levels and total hemoglobin was compared three months post-treatment.

Result: The median(IQR) increase in serum vitamin B12 level was significantly higher in group A [600 (389,775) vs 399 (313, 606) pg/mL; *P*= 0.016]. The median (IQR) rise of hemoglobin was also more in group A [2.7 (0.4,4.6) vs 0.5 (-0.1,1.2) g/dL; *P*=0.001].

Conclusion: Increase in serum vitamin B12 levels and hemoglobin was better in children with nutritional macrocytic anemia receiving parenteral as compared to oral vitamin B12.

Keywords: *Knuckle pigmentation, Management, Methylcobalamin*.

Trial Registration: CTRI/2017/07/009124 ***Published online*:** May 31, 2022; ***PII***: S097475591600427

Vitamin B12/folate deficiency is reported to contribute to more than one-third of anemia prevalence in India, and it is next to iron deficiency anemia among children aged 5-9 year, and adolescents [1]. Effective parenteral and oral therapy is available to treat vitamin B12 deficiency, but clear guidelines are lacking for children with predominant hematological manifestations, especially from our region [2,3]. Taking an injection is painful for children, costlier [4], and trained staff is needed for administration. Treatment with an oral form of vitamin B12 was reported to be as effective as parenteral therapy in adults [5]. However, vitamin B12 is rarely prescribed in the oral form, mainly because of concerns about absorption [6].

This study was done to compare the efficacy of oral vitamin B12 therapy with the standard parenteral vitamin B12 therapy in improving viamin B12 levels in children with nutritional macrocytic (megaloblastic and dimorphic) anemia, after three months of treatment.

METHODS

It was a single-center, open-label randomized control trial from March, 2015 to June, 2016, conducted at a rural tertiary care teaching hospital. Approval was obtained from the institutional ethics committee, and the trial was registered retrospecitively with the Clinical Trials Registry of India.

Invited Commentaries: Pages 677-80.

In a previous study among adults [7], the standard deviation of vitamin B12 levels after four months of treatment was 165 pg/mL in parenteral and 595 pg/mL in the oral route groups. Assuming the minimum expected mean difference of vitamin B12 levels between both the groups as 250 pg/mL and considering 5% level of significance, with a power of 80% and drop out of 10%, the required sample size was calculated as 40 in each group.

Randomization of the participants was done into the two groups using WINPEPI software. Sealed opaque

brown envelopes containing the randomization code were prepared by the biostatistician. It was opened by the investigator serially, just before the treatment, once the patient was enrolled after informed written consent from parents or caregivers. We screened 100 children between 2 month to 18 year of age for their eligibility for enrolment. Inclusion criteria were clinical features of pallor, hyperpigmentation of knuckles, infantile tremor syndrome (ITS), mild icterus or giddiness with at least one of the laboratory parameters from the following: peripheral smear showing all three - macrocytic red blood cells, hypersegmented neutrophils, and thrombocytopenia; mean corpuscular volume (MCV) >110 fL [8,9]; and, vitamin B12 level (by ADVIA Centaur VB12 Assay, Seimens) <150 pg/mL [10,11]. Those patients who had received a blood transfusion or vitamin B12 therapy upto one month prior; or were found to have other diseases than nutritional anemia, were excluded. Neurological conditions other than ITS were also an exclusion criteria. Demographic details, clinical presentation, nutritional assessment, anthropometry, and baseline laboratory values of anemia workup at the time of enrolment were recorded.

After enrollment in the study, all children received an initial intramuscular or intravenous single dose of 1000 µg followed by randomization to either parenteral (group A) or oral (group B) for subsequent doses. A total of 80 patients were randomized. In parenteral group, 1000 µg of vitamin B12 were given IM (or intravenous if platelet count < 50×10^9/L) for three doses in children less than ten years of age, whereas a total of five doses were given to those between 10-18 year of age. Subsequently, two more doses of similar strength were repeated at the end of the first and second months of follow-up. In group B, Nurokind OD (Mankind Pharma Ltd; containing methylcobalamin 1500 µg), half tablet under two years of age and one tablet to those aged 2-18 years, was given daily for a total of 12 weeks. In both groups, the investigator gave age-appropriate dietary and nutritional advice. Tablet folic acid (5 mg) was also supplemented to all children in both the groups.

All children were followed up in pediatric outpatient department weekly for the initial 3-4 weeks, and then monthly till completing three months of treatment. After three months of the intervention, all laboratory investigations were repeated, and clinical parameters like pallor, knuckle pigmentation, tingling sensation, general well-being, mood changes, and any adverse drug reactions were assessed.

Statistical analysis: Analysis of the data was performed using STATA 14.2. We used Student *t* test for comparison of normally distributed variables and Mann Whitney *U* test for non-normally distributed variabls. A *P* value <0.05 was considered statistically significant. For the primary outcomes, we conducted a per protocol analysis.

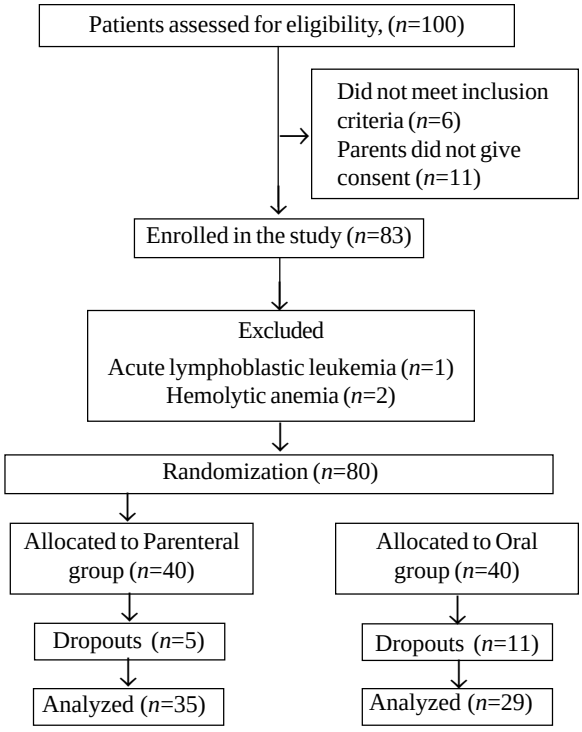

Fig. 1 Study flow diagram.

Table I Baseline Clinical Characteristics of Children With Nutritional Megaloblastic Anemia Enrolled in the Study

Characteristics	*Parenteral group (n=40)*	*Oral group (n=40)*
Age (y)[a]	11 (2.3,15)	13 (8,16)
Girls	30 (75)	21 (52.5)
Diet type		
Vegetarian	26 (65)	28 (70)
Mixed diet	6 (15)	5 (12.5)
Only breastfeeding	8 (20)	7 (17.5)
Iron therapy[b]	25 (62.5)	30 (75)
Nutritional status		
Normal	21 (52.5)	23 (57.5)
Undernutrition	16 (40)	11 (27.5)
Overweight	3 (7.5)	6 (15)
Pallor	24 (60)	26 (65)
Mental changes		
Irritable	7 (17.5)	6 (15)
Apathetic	2 (5)	1 (2.5)
Tremors	9 (22.5)	3 (7.5)
Knuckle pigmentation	37 (92.5)	38 (95)
Jaundice	6 (15)	7 (17.5)

Values in no (%) or [a]median (IQR). [b]in the preceding 3 mo. All P>0.05.

RESULTS

Out of the 80 participants (63.7% girls), 55 (68.7%) were between 10 and 18 years of age, and 8 (10%) were infants. The flow of study participants is shown in **Fig. 1**. **Table I** shows the demographic details and baseline clinical characteristics of the participants. Majority had kunckle hyperpigmentation (75, 93.5%) and followed a vegetarian diet (54, 67.5%).

Table II compares the difference in laboratory values three months post-treatment in both the groups. There was a significantly higher rise in vitamin B12 level [600 (389,775) vs 399 (313,606); *P*= 0.016] and hemoglobin [2.7 (0.4,4.6) vs 0.5 (-0.1,1.2); *P*=0.001] in the parenteral treatment group (**Fig. 2**). The change in additional laboratory parameters after three months is shown in **Web Table I.**

Iron status was not studied for all the participants. However, 25 (62.5%) of patients in the parenteral treatment group and 11 (27.5%) patients in oral therapy group received additional therapeutic iron, either based on a clinical parameter or dimorphic anemia seen in the peripheral smear, which was present in 36 (45%) of the participants.

DISCUSSION

In this single-center randomized control trial comparing oral and parenteral vitamin B12 for vitamin B12-deficiency anemia, the rise in serum vitamin B12 levels and hemoglobin was higher in the parenteral group. However, there was a statistically significant increase in serum vitamin B12 level and hemoglobin concentration after three months in both groups, suggesting that both the parenteral and oral routes effectively treat nutritional macrocytic-megaloblastic anemia in children.

A Cochrane review in 2018 [12] suggested that the oral route of vitamin B12 therapy is as effective as the parenteral group, but it had included only studies conducted in adults [7,13,14]. Only three studies were published subsequently comparing oral vitamin B12

Table II Comparison of Pre- and Post-treatment Difference in Laboratory Values After Vitamin B12 in Children With Nutritional Megaloblastic Anemia

Laboratory parameters	*Parenteral group (n=35)*	*Oral group (n=29)*	*P value*
Change in vitamin B12 (pg/mL)	600 (389,775)	399 (313,606)	0.016
Change in hemoglobin (g/dL)	2.7 (0.4,4.6)	0.5 (-0.1,1.2)	0.001
Change in WBC ($x10^3/\mu L$)	400 (-2500,2200)	0 (-1450,1350)	0.690
Fall of MCV (fl)	8.2 (1.1,18.8)	6.1 (2.0,13.9)	0.539
Change in neutrophils (%)	-4 (-17,16)	-2 (-11,17)	0.842
Change in lymphocytes (%)	6 (-8,20)	8 (-5,22)	0.895
Rise in platelet count ($x10^9/L$)	-30000 (-89000,138000)	-8000 (-93000,70500)	0.474

Values in median (IQR). WBC: white blood cell, MCV: mean corpuscular volume.

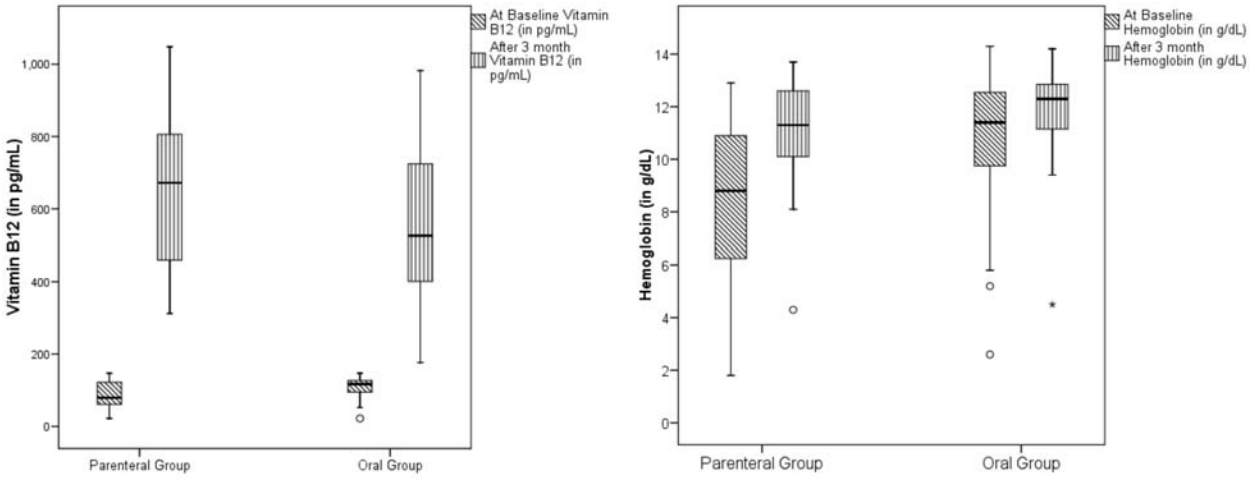

Fig. 2 Box plots showing levels of vitamin B12 and hemoglobin: baseline and after 3 months of treatment in both groups.

WHAT IS ALREADY KNOWN?

- Oral route of vitamin B12 is as effective as conventional parenteral route in adults, but role of oral treatment in children with nutritional vitamin B12 deficiency remains unclear.

WHAT THIS STUDY ADDS?

- The rise of hemoglobin and serum vitamin B12 level were significantly higher in children given parenteral vitamin B12, as compared to those given orally.

therapy with intramuscular injections in children [15-17]. Various studies have compared different protocols for treating vitamin B12 deficiency with duration ranging from 1 week to 3 months. One of the studies had used vitamin B12 ampules in oral form for participants in the oral arm, and the other group had received multivitamin tablets [17]. Earlier studies with similar designs on adults or children with megaloblastic anemia reported similar results after 3-4 months of treatment [7,13,15]. It was noted that oral vitamin B12 therapy could be an effective alternative that reduces treatment costs [14,18,19]. However, we noted a drop out of 11 (37.5%) children in the oral arm. We cannot ensure treatment completion and cure in this loss to follow up group; though, it may be cost-saving overall.

The main limitation of our study was that we did not investigate methylmalonic acid and homocysteine levels, which are more sensitive laboratory methods for vitamin B12 deficiency. An extensive workup for iron depletion/ repletion, pernicious anemia, or other etiology was not done, unless clinically indicated. However, we supplemented iron in both groups. No subjective assessment was done for participants' mental status or satisfaction level of their parents. Vitamin B12 has a longer half-life, so long-term follow up may be necessary for finalizing an effective regimen. However, in the future, this can be expanded further, and evidence for the long-term effectiveness of oral treatment needs to be studied for confirmation of efficacy.

In conclusion, there was more increase in serum vitamin B12 levels and hemoglobin with parenteral vitamin B12 than the oral route; though, both groups showed improvement. Pediatricians should take decision about route of giving vitamin B12 after considering the efficacy data, in addition to considerations about cost, compliance and discomfort.

Ethics clearance: IEC, Pramukhswami Medical College; No. HREC/ HMPCMCE/2015/129, dated March 14, 2015.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: RT, JT,: literature search, Interpretation of data, drafting the article, revising it critically for important intellectual content; UP,KT: concept and design of study, acquisition of data, analysis and interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version; MP: re-analyzing data and interpretation of data, revising it critically for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Web Table I Change in Laboratory Values After Vitamin B12 in Children With Nutritional Megaloblastic Anemia

	Parenteral group			*Oral group*		
Variables	*Pre-treatment (n=35)*[a]	*Post-treatment (n=35)*	*P value*	*Pre-treatment (n=29)*[a]	*Post-treatment (n=29)*	*P value*
Vitamin B12 (pg/mL)	85 (61,127)	653 (459, 835)	<0.001	112 (89,124)	506 (399,726)	<0.001
Hemoglobin (g/dL)	9.4 (6.5, 11.8)	11.3 (10.1, 12.8)	<0.001	11.3 (9.6, 12.7)	12.3 (11.2, 13)	0.007
White blood cell ($x10^3/\mu L$)	7.5 (5.05, 10.5)	7.8 (6.5, 8.6)	0.850	7.6 (5.9, 9.5)	7.9 (7.15, 8.75)	0.82
Mean corpuscular volume (fL)	86 (73, 97)	75 (69, 80)	<0.001	84 (79,98)	79 (73, 84)	<0.001
Neutrophils (%)	54 (34, 66)	50 (40,60)	0.939	53 (42,62)	54 (47,65)	0.87
Lymphocytes (%)	46 (31-57)	38 (32, 44)	0.043	44 (32, 57)	38 (30,43)	0.019
Platelet count ($x10^3/\mu L$)	330 (178.5, 441)	286 (256, 346)	0.436	314 (259, 410)	324 (265, 371.5)	0.60

All values are in median (IQR). [a]*data shown only for those who completed the study.*

RESEARCH PAPER

Development and Validation of the Intravenous Infiltration and Extravasation Risk Assessment Tool (IIERAT) for Pediatric Patients

SANDEEP KAUR, PARVINDER KAUR, YOGESH KUMAR, JYOTI SARIN, DHANESH GARG

From Department of Child Health Nursing, Maharishi Markandeshwar College of Nursing, Maharishi Markandeshwar (Deemed to be) University, Mullana, Haryana.

Correspondence to: Ms Parvinder Kaur, Assistant Professor, Child Health Nursing Department, MM College of Nursing, MMDU, Mullana, Ambala, Haryana. hparvinder88@gmail.com

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Objective: To develop and validate a new tool viz., Intravenous Infiltration and Extravasation Risk Assessment Tool (IIEART) for assessing risk of fluid extravasation in children.

Participants: 120 children (aged 2-18 year) undergoing peripheral intravenous cannulation were recruited from four hospitals of Haryana to determine the IIEART scale's psychometric properties.

Methods: The tool was developed under four phases with Modified Delphi rounds among nine experts. After experts' confirmation of final draft, the reliability and validity of the tool was ascertained.

Results: The final IIERAT with 11 items showed good internal consistency (α=0.81) with inter-rater reliability of (κ=0.88). To calculate predictive validity, sensitivity and specificity were assessed for 3 consecutive days from the day of cannulation. At a score >21, the sensitivity was 100% and specificity was 100% with area under curve of 1.0 (95% CI 1.0, 1.0) on second day of cannulation.

Conclusion: The IIEART developed was found to be valid and reliable and can be used by healthcare personnel to predict pediatric patients at risk for intravenous infiltration and extravasation.

Key words: *Risk assessment, Sensitivity, Specificity, Venous cannula*.

Trial Registration: CTRI/2017/07/009124 ***Published online*:** June 11, 2022; ***PII***: S097475591600432

Peripheral venous cannulation is one of the most commonly performed invasive procedures in clinical practice [1]. Children are more at risk of an infiltration injury because of their small and weaker blood vessels, immature skin, lack of subcutaneous fat, and constant movement [2]. Infiltration is defined as an inadvertent delivery of non-vesicant fluid or medication into surrounding tissue with the potential to harm the patient. If a vesicant fluid or medication has been infused into the surrounding tissue space, it is called extravasation [3]. Certain fluids and drugs can easily cause venous rupture when the venous endothelium and blood vessel walls are irritated, leading to intravenous infiltration or extravasation.

Peripheral infiltration injury rates among pediatric patients receiving intravenous infusions can range from 10-30% [8], but may be as high as 58% [9]. We developed and validated an objective tool to identify the risk of developing infiltration and extravasation among pediatric patients.

METHODS

A methodological research design was adopted to develop and validate the Intravenous Infil-tration and Extravasation Risk Assessment Tool (IIERAT) for pediatric patients undergoing peripheral intravenous cannulation. The IIERAT was developed by using a modi-fied Delphi technique with four rounds. The psychometric properties of the IIERAT were assessed by applying Cronbach alpha and Cohen kappa for calculating the reliability. For validation, we calculated the predictive validity, sensitivity and specificity. Area under ROC curve was used as measure of the accuracy.

We identified 11 parameters that are associated with the risk of developing infiltration and extravasation in a child viz., site, vein condition, cannula size according to age, indwelling cannula time, type of medication, body mass index (BMI), splint, assessment of cannula site, securement of cannula, flushing in case of intermittent infusion, and dressing status. These parameters or risk factors were also identified and included in Visual infusion phlebitis (VIP) score developed by Ray-Barruel and Polit [10].

A preliminary draft of the IIERAT was developed by review of literature in order to determine various risk factors that cause infiltration and extravasation in pediatric

patients. Selected items were pooled together to generate the first version of IIERAT tool and categorized as Site-associated factors, Mechanical factors, Chemical factors, Disease-associated factors, Physical factors, Nursing care- related factors and Self-care related factors.

Modified Delphi rounds were conducted amongst nine experts in the field of pediatric medicine and nursing, and response was documented after each round to reach final consensus for relevance, comprehensiveness and clarity of items. Expert suggestions were incorporated and modifications were done, followed by re-review.

After four rounds of revision and reviews, 100% consensus among experts was achieved, and face validity was established. For scoring of the IIERAT for the three categories of mild, moderate and severe risk, the median value was calculated by subtracting the minimum score of 11 from maximum score of 33 and dividing it by 3, which was approximately 7. Then, this value was added into the minimum score to get the range of scores in each level- Low risk (11-18), Moderate risk (19-26) and Severe risk (27-33). Content validity index for each item in the tool was found to be 1. Sensitivity and specificity were assessed for three consecutive days from the day of cannulation.

Ethics clearance to conduct the study was taken from the institutional ethical committee. The children eligible to participate in the study were those who had underwent peripheral intravenous cannulation, were available at the time of data collection, were between the age group 2-18 years, and children and their parents were willing to participate in the study.

A written informed consent was obtained from the parents and assent from children (verbal assent for the children aged 7-12 year and written assent for the children aged >12-18 year) before including them as research participants. The tool was administered to 50 pediatric patients undergoing peripheral intravenous cannulation admitted in pediatric medicine and surgical wards of our institution. A single researcher physically collected the data by scoring on the IIERAT from the day of cannulation till the occurrence of infiltration and extravasation. One patient was included only once for data collection.

To establish the reliability and validity of the tool, it was administered to 120 patients (aged 2-18 year) undergoing peripheral intravenous cannulation, available at the time of data collection and selected conveniently, admitted in four hospitals in Haryana viz., Pediatric Medicine and Surgical words of MMIMS&R Hospital, Mullana, Ambala; AVS Ravi Hospital, Model Town, Yamuna Nagar; Madan Memorial Hospital, Madan chowk, Yamuna Nagar; and Civil Hospital, Ambala; between November, 2019 and January, 2020. Patients who were critically ill and admitted in pediatric intensive care units of hospitals were excluded from the study.

Statistical analysis: The data were analyzed by SPSS Statistical software Version 20.0 (SPSS Inc). The psychometric properties of the tool were assessed by applying Cronbach alpha and Cohen Kappa for calculating the reliability. For predictive validity, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated for three consecutive days of hospitalization. Area under ROC curve was used as measure of the accuracy.

RESULTS

The overall internal consistency of the tool was high (α = 0.810). The total correlation was applied on 11 items in the tool and found that all IIERAT items had item score to total score correlation in between 0.32-0.81. To check the individual contribution of items, each item was deleted one by one to analyze the changes in the value of alpha, but no item showed increase in the value of alpha coefficient rather the value remained the same or it decreased, which indicated that all the items were equally contributing to the reliability of the IIERAT tool (**Web Table I**) [19].

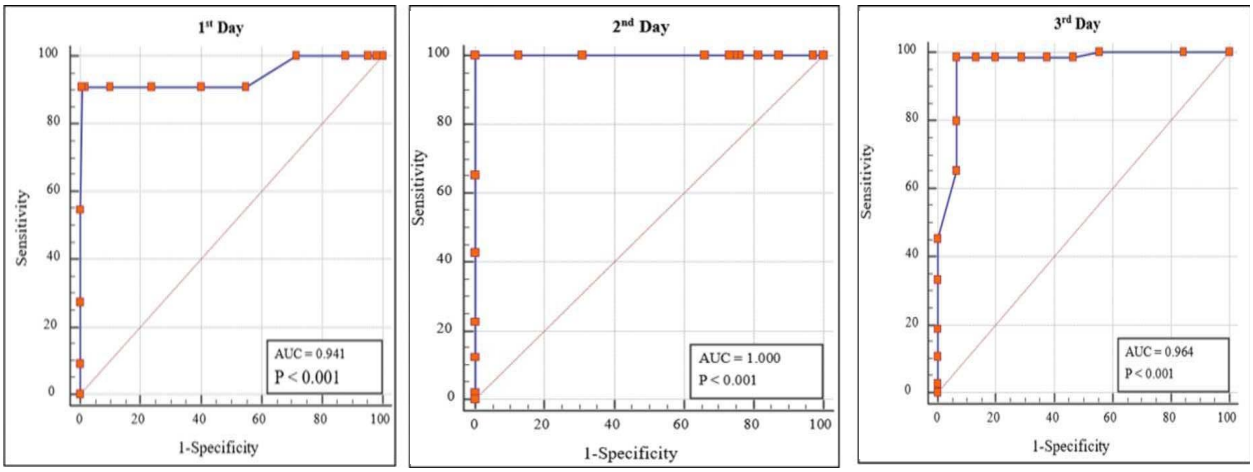
The inter-rater reliability was calculated by Cohen kappa and found to be 0.81. The items with perfect agreement were site, vein, cannula size, type of medication, BMI, splint, securement of cannula, and dressing status. Only two items demonstrated an agreement of <80%, viz., assess-ment of cannula, and flushing in case of intermittent infusion.

Predictive validity calculation shows that for day 1 of cannulation, at a cut-off point of 21, the best balance between the sensitivity (90.48%) and specificity (99.08 %) was achieved with PPV of 90.9% and NPV of 99.1%. For day 2, the optimum cut-off score was 21, with sensitivity (100%) and specificity (100%); while on day 3, a cut-off score of 20 was the optimum score with sensitivity and specificity of 98.67% and 86.67%, respectively.

The AUC shows the accuracy of the IIERAT at best cut- off point of 21 for first day with value 0.941 (95% CI: 0.833, 1.00) (**Fig. 1a**); at cut-of-point of 21 for second day, AUC was 1.00 (95% CI: 1.00, 1.00) (**Fig. 1b**); and at cut-off point of 20 on third day AUC 1.00 (95% CI: 1.00, 1.00) (**Fig. 1c**).

DISCUSSION

The IIERAT was developed with an aim to assess the risk of infiltration and extravasation among children receiving intravenous fluids/drugs. The final IIERAT was developed with 11 items that showed good internal consistency



(a) *(b)* *(c)*

a) The optimal cut-off point was 21, with sensitivity- 90.48% and specificity- 99.08 %; b) The optimal cut-off point was 21, with sensitivity-100% and specificity-100%.; c) The optimal cut-off point was 20, with sensitivity-98.67% and specificity-86.67%.

Fig. 1 Receiver operating characteristics curve for the IIEART from Day 1 to Day 3 of cannulation.

(α=0.81) and inter-rater reliability (κ=0.88). On the second day of cannulation, the sensitivity and specificity were found to be 100%.

Simin, et al. [21] reported that cannula involvement within joint area (*P*=0.03), use of elbow joint (0.018), age (*P*=0.011), diseases condition (*P*=0.016), cannula insertion site (*P*=0.02), presence of soiled securement device (*P*=0.001), cannula inserted by nursing staff and students (*P*=0.53), were the common risk factors for the development of infiltration and phlebitis in pediatric patients. Current guidelines also recommend cannulation limited to use of upper extremities [22], avoiding the wrist, and preferring distal areas for IV cannulation [23]. According to updated guidelines on infiltration and extravasation: prevention and management, healthcare personnel must choose a vein that feels smooth and resilient, not one that is hard or cordlike [24]. Site of venous puncture and cannula length were added as the parameters in detecting risk of developing infiltration and extravasation in pediatric patients. Kagel and Rayan [25] also found that selection of catheter insertion site had effect on infiltration development. This is because small and or fragile veins are more prone to cause infiltration [26].

Similar to our results, Schulmeister [27] also found that sterile, transparent dressings should be used by clinicians to protect the site from extrinsic contamination, and visual assessment in pediatric patients for redness, tenderness, swelling, numbness, or tingling on a regular basis.

In contrast to other assessment tools, the IIERAT provides a better way to assess the risk of infiltration and extravasation in pediatric patients. A higher score on the IIERAT indicates a higher risk of developing infiltration and extravasation. Though the IIERAT could not be done in a large number of pediatric patients, the results of statistical analysis suggest that this is a valid and reliable tool to assess risk of infiltration and extravasation.

Healthcare researchers may conduct further research studies to investigate patient care strategies according to the levels of risks (mild, moderate and high) of developing infiltration and extravasation among patients.

The IIERAT demonstrated adequate validity and reliability. It can be used by all health professionals, especially nursing officers, to identify the pediatric patients at risk for developing intravenous complications such as infiltration and extravasation.

Ethics clearance: IEC, MM Deemed University; No. 1513, dated July 19, 2019.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: SK, YK, JS: concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, review and final approval of the manuscript; PK: concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, review and final approval of the manuscript; DS: data acquisition, data analysis, manuscript editing, review and final approval of the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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WHAT IS ALREADY KNOWN?

- Many infiltration/extravasation tools have been developed that can assess the grades of these complications after the occurrence.

WHAT THIS STUDY ADDS?

- The IIERAT is specifically designed for assessing the risk of developing infiltration/extravasation complications before their occurrence in children.

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Web Table I Baseline Characteristics of Children Undergoing Intravenous Cannulation (*N*=120)

Patient Characteristics	**No. (%)**
Age (Y)	
2-6	61 (50.8)
7-12	36 (30)
13-18	23 (19.2)
Female gender	71 (59.1)
Affected system	
Gastrointestinal	64 (53.3)
Respiratory	32 (26.6)
Renal	11 (9.2)
Neurological	8 (6.7)
Cardiovascular	5 (4.2)
Inpatient ward	
Pediatric medicine	79 (65.8)
Pediatric surgery	26 (21.6)
PICU	15 (12.6)
Cannula Inserted By	
Staff nurses	98 (81.6)
Doctor	22 (18.4)

RESEARCH PAPER

Urine Specific Gravity Measurement for Fluid Balance in Neonates on Intravenous Fluids in a Neonatal Intensive Care Unit: *An Open Label Randomized Controlled Trial*

R JHA,[1] VV TEWARI,[2] D TEWARI,[3] A DEVGAN[1]

From Departments of Pediatrics, [1]Armed Forces Medical College, Pune, Maharashtra; [2]Command Hospital (SC) Pune, Maharashtra; [3]University College of Medical Sciences, New Delhi.

Correspondence to: Dr Vishal Vishnu Tewari, Professor, Department of Pediatrics, Command Hospital (SC) Pune, Maharashtra. docvvt_13@hotmail.com

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Background: Urine specific gravity reflects hydration status and correlates well with urine osmolality.

Objective: To compare intravenous fluid therapy guided with and without inclusion of urine specific gravity to the standard parameters for maintaining postnatal weight loss within permissible limits in neonates admitted to the intensive care unit.

Methods: An open-label randomized controlled trial was conducted, including neonates requiring intravenous fluids for ≥72 hours, randomized into the study (urine specific gravity guided fluids) and control arms. The outcomes of the study were to determine proportion of neonates with weight loss within permissible limits, mean percentage weight loss and number of days to reach maximum weight loss.

Results: 80 preterm and term neonates (40 in each arm) were enrolled. A comparable proportion of neonates had weight loss within permissible limits in study arm and in control arms [39 (97.5%) vs 36 (90%); *P*=0.165]. The (mean (SD) percentage weight loss was significantly less in the study arm compared to control arm [All neonates: 7.2(2.6) vs 9.3(3.5); *P*=0.004); preterm neonates: 7.7 (2.8) vs 11 (3.9); *P*=0.008)]. Preterm neonates in the study arm attained nadir weight significantly earlier than in the controls (*P*=0.03) and attained complete enteral feeding earlier. Urine specific gravity showed a moderate negative correlation with the percentage weight loss.

Conclusion: Using urine specific gravity to regulate intravenous fluids in neonates resulted in a significant reduction in postnatal weight loss, especially in preterm neonates.

Keywords: *Postnatal weight loss, Urine refractometry, Weight loss*.

Trial Registration: CTRI/2019/04/018661

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Neonates on intravenous fluid therapy require daily adjustments in their fluid volume and electrolyte intake in view of their changing total body water. While in term neonates, birth weight may reduce by 10%, postnatal weight loss of 10-15% is acceptable in preterm neonates [1,2]. This postnatal weight loss is primarily due to contraction of the extracellular fluid (ECF) compartment, and a higher ECF volume in preterm neonates accounts for their greater weight loss [3,4]. In preterm neonates, overzealous intravenous fluids increases the risk for symptomatic patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and hyponatremia, while fluid restriction places them at risk for dehydration and hypernatremia [5-9]. Neonatal kidneys have limited ability to excrete a water load and effectively dilute urine [10]. Despite daily adjustments of intravenous fluid based on change in body weight, clinical status, serum biochemistry, blood gas, urine output and urine specific gravity [11,12], a significant proportion of neonates experience postnatal weight changes outside the permissible limits [13].

In neonates, urine specific gravity has a linear correlation with urine osmolality, which mirrors the serum osmolality and reflects their hydration status, thereby being a potentially useful adjunct in regulating fluid management [14-18]. In euvolemic state with normal urine output of 1-3 mL/kg/hour, the urine specific gravity lies between 1.002-1.010 [4,12,17,19]. Despite the direct correlation and ease of measurement, urine specific gravity estimation is not routinely used for maintaining fluid balance in neonates [20], due to lack of data regarding its utility. We aimed to compare daily intravenous fluid adjustment with and without including urine specific gravity estimation to the standard parameters for maintaining postnatal weight loss within permissible limits in neonates admitted in neonatal intensive care unit (NICU).

METHODS

This open-label randomized controlled trial was conducted in the NICU of a tertiary care hospital between May, 2019 and October, 2020. The trial was approved by the institutional ethics committee and registered with the Clinical Trials Registry of India. Written informed consent was obtained from parents prior to randomization. All neonates in NICU requiring intravenous fluids for ≥72 h were included. Exclusion criteria included neonates with perinatal asphyxia, shock, congenital malformations, complex congenital heart diseases, antenatally diagnosed hydronephrosis, and when weighing the neonate was not possible due to the clinical condition. Enrolled neonates were randomly assigned within 3 hour of birth to either the study arm (urine specific gravity guided fluids) or the control arm (standard care). Randomization was done by computer-generated, permuted blocks stratified by gestational age (<37 weeks, preterm; ≥37 weeks, term) and serially numbered opaque sealed envelopes were used for allocation concealment. The investigators were not masked as they assessed the urine specific gravity to make daily fluid adjustments.

The usual standard of care for preterm and term neonates, including extreme preterm neonates using radiant warmers, cling film application, respiratory humidifiers, infusion pumps for intravenous fluid administration, early and exclusive use of breast milk and parenteral nutrition, was followed. Fluid volume was commenced with 60 mL/kg/day for term neonates, and 70 mL/kg/day, 65 mL/kg/day, and 60 mL/kg/day for preterm neonates with birth weight ≤1000 g, 1001 to 1500 g, and >1500 g, respectively [12,15]. A cumulative weight loss of up to 10% for term neonates was acceptable while for preterm neonates this was 15%, 12-15%, and 12% at birth weight ≤1000 g, 1001 to 1500 g, and >1500 g, respectively [4,6,21]. In the study arm daily fluid requirement was adjusted according to absolute and percentage weight change over the previous 24 hours, cumulative percentage weight change from the birth weight, and clinical parameters including hepatomegaly, edema, tachycardia and urine specific gravity.

Urine specific gravity was tested using a handheld prism-based refractometer and total daily fluid intake reduced by 5-10 mL/kg/day for urine specific gravity <1.006; increased by 5 mL/kg/day for urine specific gravity between 1.006 - 1.008 and increased by 8-10 mL/kg/day if the urine specific gravity was >1.008. Urine specific gravity by refractometry and urine osmolality show a linear positive correlation, with urine specific gravity of 1.006 and 1.008 indicating a urine osmolality of 275 mOsm/kg and 315 mOsm/kg, respectively [17].

In the control arm, total daily fluid intake was guided by all the standard parameters as in the study arm except urine specific gravity, with a daily increment of 10 mL/kg/day or continuation on the same total fluid volume. The maximum permissible daily fluid volume of IV fluids inclusive of drugs and milk feeds was 140 and 150 mL/kg/day for preterm and term neonates, respectively. The mean weight of the study population each day subtracted from the mean weight of the next day divided by the mean weight of that day was used to derive the rate of percentage decline in weight. Neonates with gestation ≤32 week or older neonates unlikely to receive enteral feeds for 3-5 days in both groups received parenteral nutrition from first day of life. Intravenous fluids were discontinued when target enteral intake of 80 mL/kg/day in term neonates and 110, 100 and 90 mL/kg/day in preterm neonates weighing ≤1000 g, 1001 g to 1500 g and >1500 g, respectively was achieved.

The primary outcome was to determine the percentage weight loss and number of days to reach the maximum weight loss in both the groups. The secondary outcomes of the study were the number of days to regain the birth weight, number of days for discontinuation of intravenous fluids (and to reach full feeds), correlation between urine specific gravity and weight loss, and adverse events related to fluid therapy.

Sample size was estimated based on a pilot study conducted earlier at our NICU enrolling 10 neonates each in the study and control arms over two months. The proportion of neonates showing weight change outside permissible limits was 50% in the control arm. Incorporating urine specific gravity in the decision-making algorithm reduced this to 20%. Keeping the relative risk at 0.4, α-error as 0.05 and β-error as 0.2, a sample of 40 neonates in each arm was required.

Statistical analysis: An intention to treat analysis was done. Differences in continuous variables were estimated using the student *t*-test or Mann-Whitney *U* test, and categorical variables using the chi-square test or Fischer exact test. Time to achieve was plotted using Kaplan-Meir curves and compared using the log-rank (Mantel-Cox) test. Spearman correlation coefficient was used to see relation between urine specific gravity and percentage weight loss. A *P* value <0.05 was considered as statistically significant. All the statistical analyses were performed using GraphPad Prism version 9 for Windows (GraphPad Software).

RESULTS

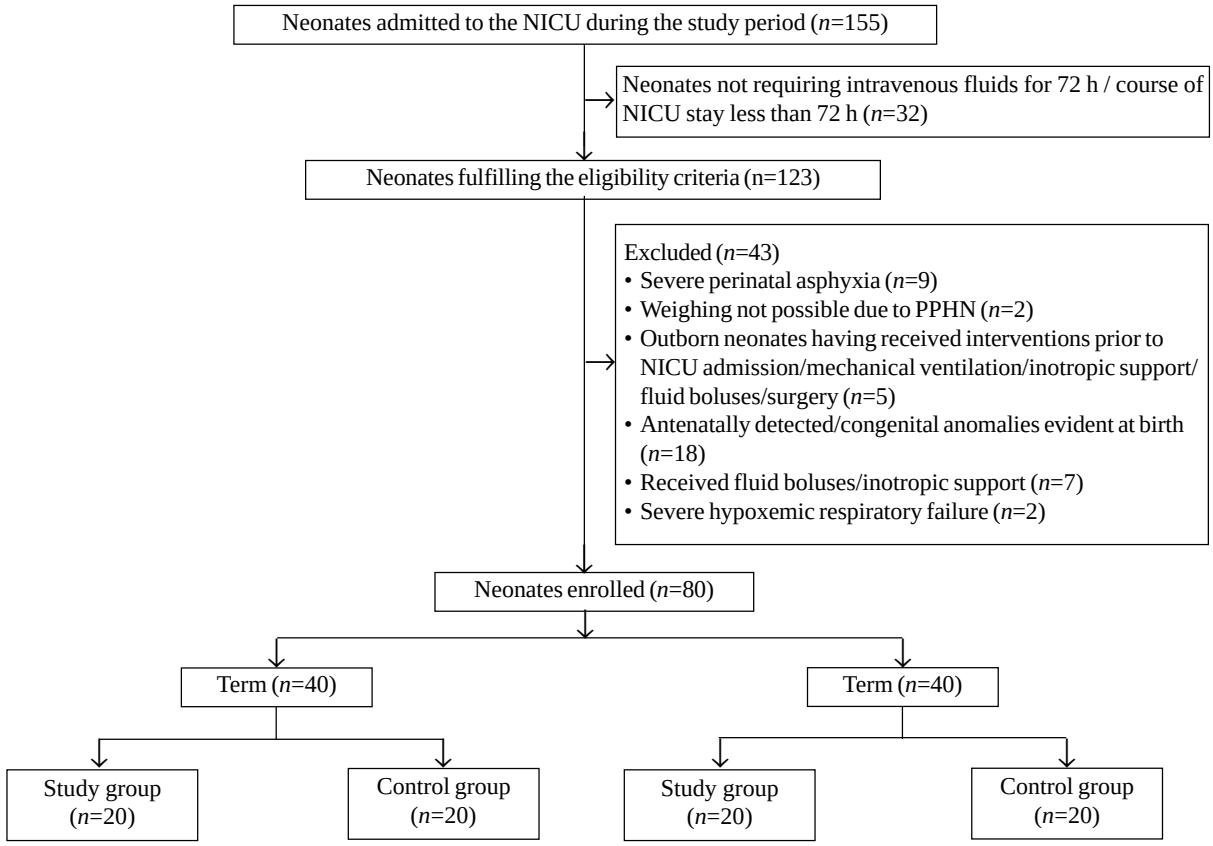
Of the 155 neonates admitted in the NICU during the study period, 123 were eligible and 80 were enrolled and

randomly allocated to either the study or the control arm (**Fig. 1**). Baseline characteristics were similar between the two groups (**Table I**).

There was no significant difference in the proportion of neonates with weight loss within permissible limits between the study arm (*n*=39, (97.5%) and control arm (*n*=36 (90%) (*P*=0.165). One preterm in the study arm (weight loss: 21.57%) and four term neonates in the control arm (weight loss: 10.6%, 11.9%, 12.25% and 13.88%) lost weight beyond permissible limits. The mean (SD) percentage weight loss was significantly lower in the study group than in the control population [7.2 (2.6)% vs 9.3 (3.5)% *P*=0.004] (**Fig. 2a**). This difference was comparable in term neonates [6.7 (2.5)% vs 7.9 (2.4)%; *P*=0.15], but not in the preterm population [7.7 (2.8)% vs 11 (3.9)%; *P*=0.008], respectively for study arm and control arm. This significant difference in the preterm population was also reflected in the mean (SD) absolute weight loss between the study arm and control arm [122 (40) g vs 172 (54) g; *P*=0.002] (**Fig. 2b**). The rate of percentage decline in weight was similar between the study and control arms (*P*=0.15), and between the term neonates (*P*=0.07) and preterm neonates (*P*= 0.46) (**Web Fig. 1**). The day of life by which maximum weight loss occurred was comparable for the study and control arm of the complete study cohort (*P*=0.11) and term neonates (*P*=0.71). However, among the preterm neonates, the study group attained the lowest weight significantly earlier than the control group (*P*=0.03). (**Table II**). There was no significant difference in the number of days to regain birth weight or number of days for discontinuation of intravenous fluids (**Web Fig. 2**).

The urine specific gravity showed a moderate negative correlation with the percentage weight loss for the entire study population (r= -0.23; 95% CI= -0.38, -0.06; *P*=0.006; *n*=143 pairs), and for the term neonates (r= -0.31; 95% CI= -0.52, -0.06; *P*=0.01; *n*=66 pairs). However, the percentage weight loss did not correlate with urine specific gravity among the preterm neonates (r= -0.17; 95% CI= -0.38, 0.07; *P*=0.15; *n*=77 pairs) (**Fig. 3a-c**). One preterm neonate in the control group was diagnosed with a hs-PDA.

The median (IQR) percentage weight loss was not significantly different in neonates whose mothers had received antenatal steroids compared to those whose



PPHN: primary pulmonary hypertension of newborn; NICU: neonatal intensive care unit.

Fig. 1 Flow diagram of study.

Table I Baseline Characteristics of the Enrolled Neonates (*N* = 80)

Variable	*Study group*	*Control group*	*Preterm neonates, n=40*		*Term neonates, n=40*	
	n=40	*n=40*	*Study, n=20*	*Control, n=20*	*Study, n=20*	*Control, n=20*
Maternal age (y)[a]	27 (4)	26 (3.6)	28 (4)	27 (4.0)	27 (3.9)	26 (3.2)
Primigravida	22 (55)	15 (37.5)	11 (55)	4 (20)	11 (55)	11 (55)
Gestational age (wk)[a]	35 (3.3)	35 (3.1)	32 (1.8)	33 (1.9)	38 (1.0)	38 (1.1)
Antenatal steroid course						
Completed	16 (40)	16 (40)	16 (80)	16 (80)	-	-
Not completed	4 (10)	4 (10)	4 (20)	4 (20)	-	-
Mode of delivery						
Cesarean section	28 (70)	28 (70)	17 (85)	15 (75)	11 (55)	13 (65)
Intravenous fluid units given to mother before delivery[a]	4.2 (0.65)	3.9 (0.76)	3.9 (0.64)	3.8 (0.62)	4.5 (0.51)	4.1 (0.89)
Maternal illnesses						
Pre-eclampsia	9 (22.5)	10 (25)	7 (35)	4 (20)	2 (10)	6 (30)
GDM	7 (17.5)	9 (22.5)	3 (15)	1 (5)	4 (20)	8 (40)
Hypothyroidism	12 (30)	8 (20)	5 (25)	3 (15)	7 (35)	5 (25)
APH	1 (2.5)	3 (7.5)	1 (5)	2 (10)	0	1 (5)
Seizure disorder	2 (5)	1 (2.5)	2 (10)	1 (5)	0	0
Others	2 (5)	8 (20)	0	7 (35) [b]	2 (10) [c]	1 (5) [d]
Antenatally detected abnormalities						
Oligohydramnios	5 (12.5)	4 (10)	4 (20)	2 (10)	1 (5)	2 (10)
FGR	3 (7.5)	2 (5)	3 (15)	2 (10)	0	0
A/REDF	1 (2.5)	1 (2.5)	1 (5)	1 (5)	0	0
Birthweight (g)[a]	2254 (768)	2111 (634)	1603 (271)	1663 (354)	2685 (495)	2560 (526)
Indication for intravenous fluids						
Extreme preterm	5 (12.5)	3 (7.5)	5 (25)	3 (15)	-	-
Respiratory illness[e]	25 (62.5)	27 (67.5)	11 (55)	14 (70)	14 (70)	13 (65)
Depression at birth	3 (7.5)	3 (7.5)	-	-	3 (15)	3 (15)
IUGR	3 (7.5)	2 (5)	3 (15)	2 (10)	-	-
A/REDF	1 (2.5)	1 (2.5)	1 (5)	1 (5)	-	-
EONS	2 (5)	3 (7.5)	-	-	2 (10)	3 (15)
Rh-HDN	1 (2.5)	1 (2.5)	-	-	1 (5)	1 (5)

Data are shown as no. (%), or [a]mean (SD). [b]Intrahepatic cholestasis (n=1), rheumatic heart disease (n=1), bad obstetric history (n=3), systemic lupus erythematosus (n=1), chronic hepatitis-C virus infection (n=1); [c]systemic lupus erythematosus (n=1), primary hypertension (n=1); [d]ventricular septal defect with bicuspid aortic valve (n=1); [e]preterm respiratory distress syndrome (n=16), transient tachypnea of newborn (n=25), meconium aspiration syndrome (mild-moderate) (n=11). APH-antepartum hemorrhage; A/REDF- absent/ reversed end diastolic flow on umbilical artery Doppler; EONS-early onset neonatal sepsis; FGR-fetal growth restriction; GDM gestational diabetes mellitus; IUGR: intrauterine growth restriction; LSCS-lower segment caesarian section; NVD-normal vaginal delivery; Rh-HDN- rhesus hemolytic disease of the newborn.

mothers had not received antenatal steroids.

DISCUSSION

The trial found the mean percentage postnatal weight loss to be significantly lesser in neonates when their intravenous fluids were adjusted using standard parameters as well as urine specific gravity, compared to those without adjustment made for urine specific gravity. Further analysis showed that this significant difference was only observed in the preterm sub group. Preterm neonates in the study arm showed lesser mean absolute weight loss and also attained the lowest weight significantly earlier than the control arm. These findings indicate a beneficial effect of incorporating daily bedside urine specific gravity for regulating intravenous fluids in neonates. [11,22-24].

Even though the average duration of intravenous fluid administration was comparable between the study and control arms, preterm neonates in the study arm transitioned earlier from parenteral to full enteral nutrition than neonates in the control arm.

Previous studies have evaluated correlation between urine specific gravity by refractometry and urine osmolality and found a linear correlation between the two, but not

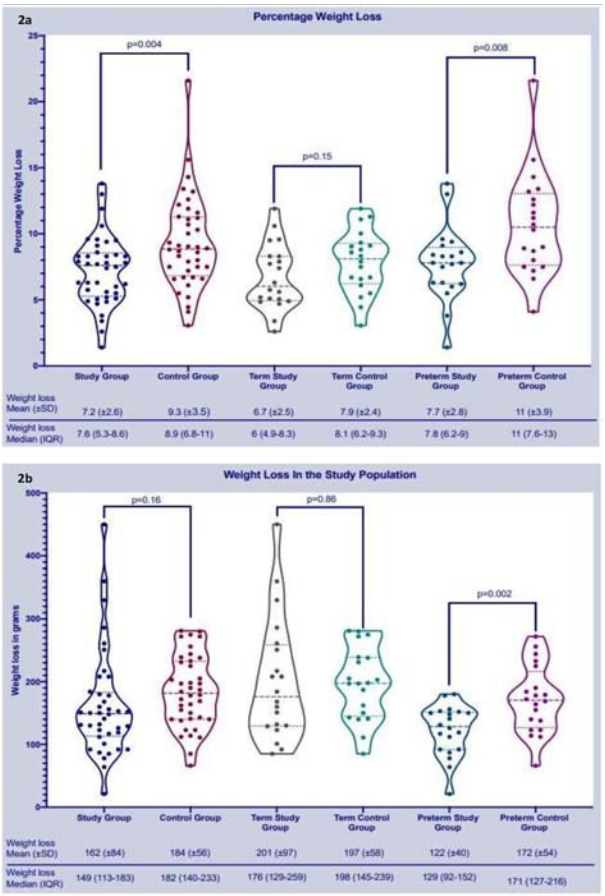


Fig. 2 Violin plots comparing *a*) percentage weight loss and *b*) absolute weight loss (g) between the study and control arms, and between the term neonate subgroups and preterm subgroups.

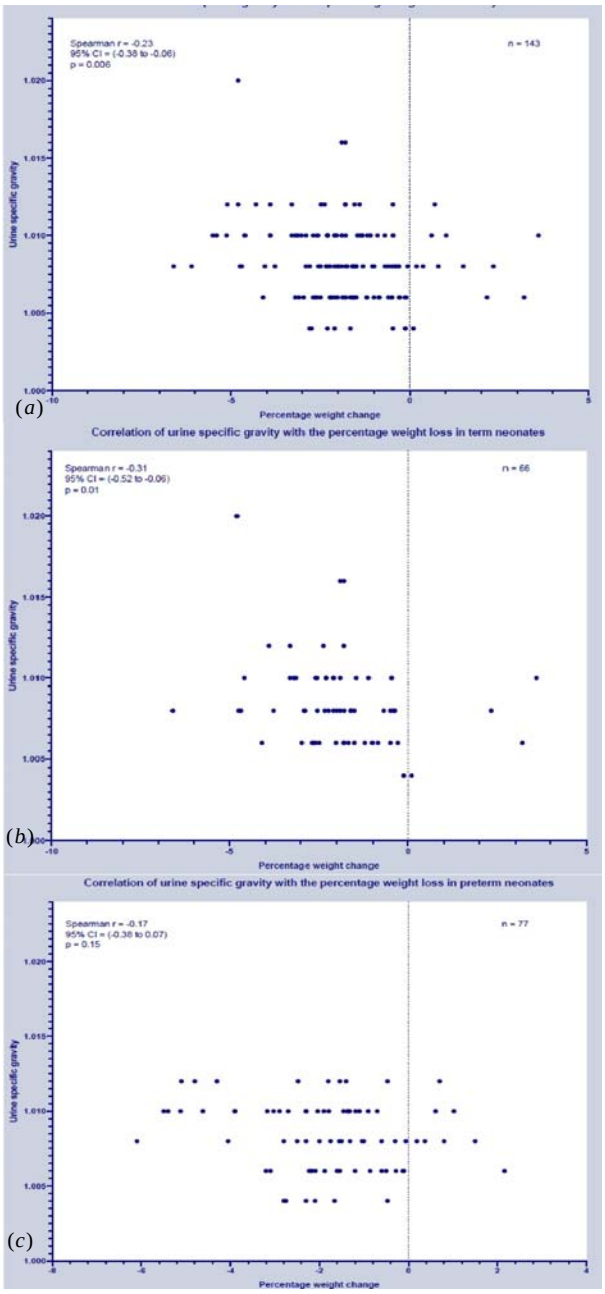


Fig. 3 Correlation between urine specific gravity and percentage weight loss *a*) in the entire study population, *b*) in term neonates, and *c*) preterm neonates.

with urine specific gravity done by dipstick evaluation [14,16,17,27]. Since serum osmolality governs urine osmolality, which in turn gets reflected as urine specific gravity, estimation of urine specific gravity indicates the hydration status. Our study did not demonstrate a strong correlation between urine specific gravity and daily weight change, as shown by the previous studies, probably due to inclusion of preterm neonates with immature renal concentrating abilities. We did not find any significant adverse events.

Relying on refractometry and not dipstick estimation of urine specific gravity, inclusion of preterm neonates, and assiduous care for reducing insensible water losses are the strengths of this study. The small sample size, non-availability of humidified incubators for the preterm neonates, and inability to directly estimate urine osmolality using an osmometer are the major limitations of this study.

To conclude, urine specific gravity measurement by refractometer is a bedside, non-invasive method, which may be helpful in modifying the estimated fluid intake in neonates and in optimizing weight loss during early neonatal period. It results in a lower mean absolute weight loss and an earlier attainment of nadir weight. Studies with larger sample size, including neonates with underlying hypoxia, shock and congenital cardiac anomalies are required along with measurement of osmolality of enteral intake.

WHAT IS ALREADY KNOWN?

- Urine specific gravity has a linear correlation with urine osmolality and in turn with serum osmolality, thereby reflecting the hydration state.

WHAT THIS STUDY ADDS?

- Including urine specific gravity estimation by refractometry to the daily intravenous fluid calculation of neonates in intensive care unit leads to decreased postnatal weight loss, especially among preterm neonates.

Table II Outcome Parameters of Neonates in the Study and Control Groups (*N*=80)

Outcomes	*Study group, n=40*	*Control group, n=40*	*Preterm neonates, n=40*		*Term neonates, n=40*		*P*
			Study, n=20	*Control, n=20*	*Study. n=20*	*Control, n=20*	
Weight loss (%)[ab]	7.2 (2.6)	9.3 (3.5)	7.7 (2.8)	11 (3.9)	6.7 (2.5)	7.9 (2.4)	0.15
Absolute weight loss (g)[b]	162 (84)	184 (56)	122 (40)	172 (54)	201 (97)	197 (58)	0.86
Time to regain birth weight (d)	11 (3.6)	12 (4.5)	14 (3.5)	15 (4.9)	9 (1.8)	9.5 (1.6)	0.36
Duration of IV fluids (d)	4.9 (1.5)	5.4 (2.7)	5.4 (1.9)	6.7 (3.4)	4.5 (0.8)	4.2 (0.4)	0.15
Serum sodium, day-7 (mEq/L)	134.5 (5.6)	138 (4.4)	-	-	-	-	-
Serum creatinine, day-7 (mg/dL)	0.5 (0.1)	0.5 (0.2)	-	-	-	-	-
Urine specific gravity	1.008 (0.0027)	-	1.0082 (0.0022)	-	1.0083 (0.0027)	-	-

All data expressed as mean (SD). [a]P<0.01 for comparison between the study and control group as a whole; [b]P<0.001 for comparison between study and control groups among preterm neonates.

Ethics clearance: IEC, Armed Forces Medical College, Pune; No. IEC/067/2018, dated Oct 22, 2018.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: VVT, RJ: conceptualized the study, collected the data, performed the statistical analysis, and drafted the manuscript; VVT: managed the cases; DT: Extracting information from study proforma and contributed to drafting the manuscript; AD: reviewed the manuscript for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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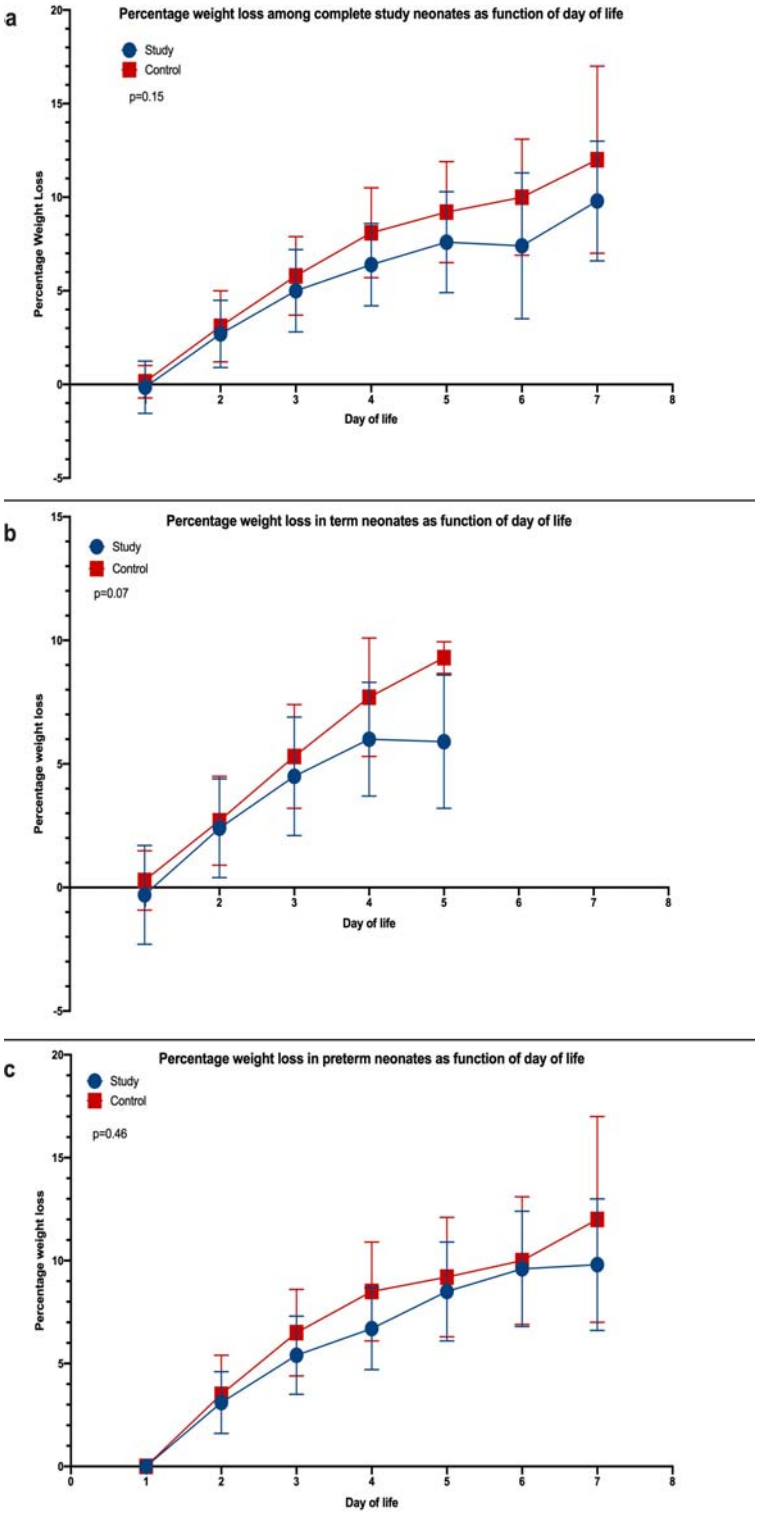
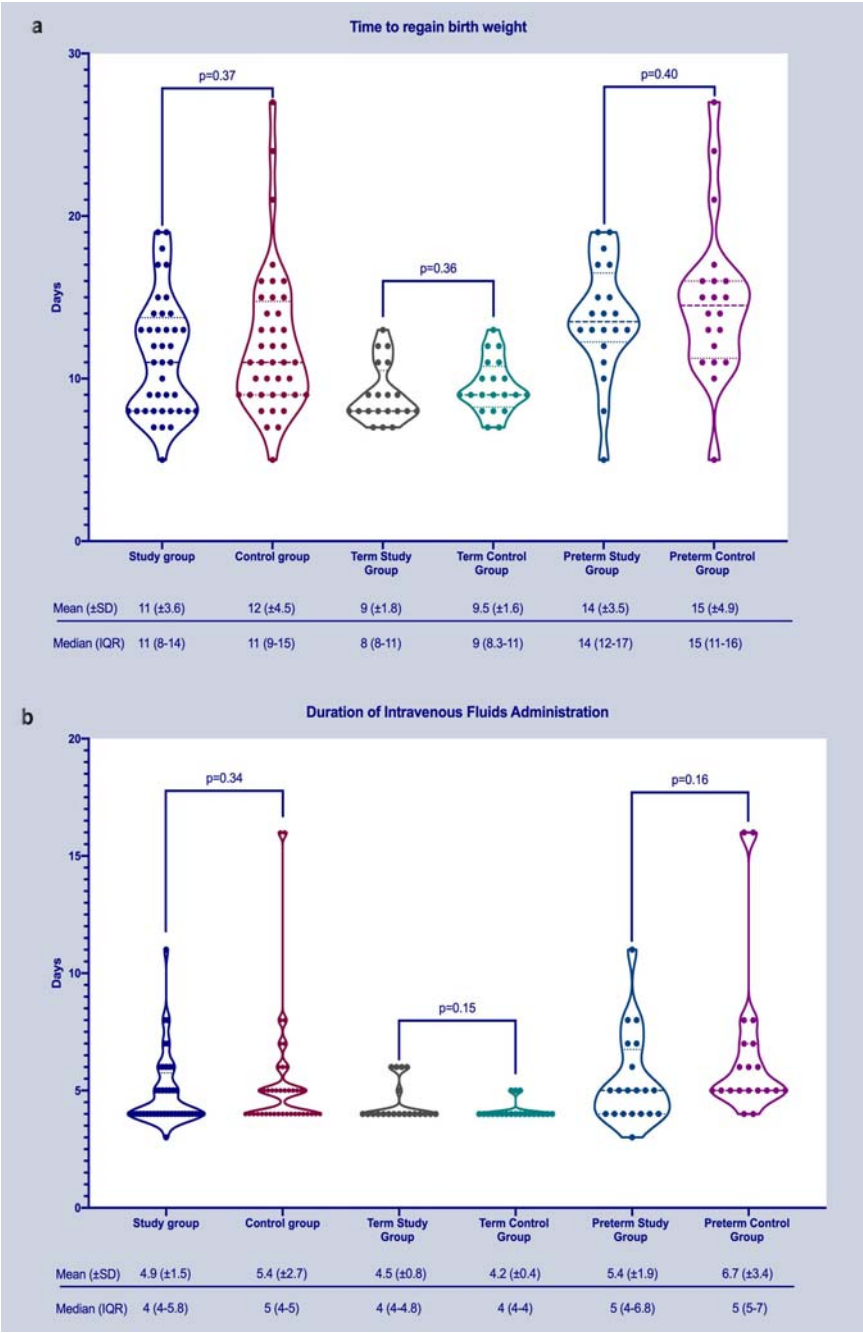


Web Fig. 1 Comparable rate of percentage weight loss as a function of postnatal age (%) (a) between the study and control arms, (b) between term neonates subgroup, and (c) in preterm subgroup.



Web Fig. 2 Violin plot showing (a) no significant difference in time to regain birth weight, and (b) no significant difference in duration of intravenous fluids, between the study and control arms.

RESEARCH PAPER

Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Metabolism: Single Center Experience Over Two Decades

VENKATESWARAN VELLAICHAMY SWAMINATHAN,[1] SATISHKUMAR MEENA,[1] HARIKA VARLA,[1] RUMESH CHANDAR,[1] INDIRA JAYAKUMAR,[2] BALASUBRAMANIAM RAMAKRISHNAN,[3] RAMYA UPPULURI,[1] REVATHI RAJ[1]

From Departments of [1]Pediatric Hematology, Oncology, Blood and Marrow Transplantation; [2]Pediatric Critical Care; and [3]Biostatistics; Apollo Hospitals, Chennai 600 035, Tamil Nadu.

Correspondence to: Dr Venkateswaran Vellaichamy Swaminathan, Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Apollo Hospitals, 320, Padma Complex, Anna Salai, Teynampet, Chennai 600 035, Tamil Nadu. vsv.mezos97@gmail.com
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Objective: We present outcome data on hematopoietic stem cell transplantation (HSCT) in children with inborn errors of metabolism (IEM). **Methods**: We retrospectively analyzed data on children up to 18 years of age, diagnosed with IEM, who underwent HSCT between January, 2002 and December, 2020. **Results**: 24 children, (mucopolysaccharidosis – 13, Gaucher disease – 4, X-linked adrenoleukodystrophy – 4, metachromatic leukodystrophy – 2, Krabbe disease – 1) were included. Donors were matched family donors in 24%, matched unrelated donors in 34%, and haploidentical fathers in 42% of the transplants, with engraftment in 91% of children. Overall survival was 72% (55-100%) with a median follow-up of 76.5 (10-120) months, and progression-free survival of 68% (MPS-76%, X-ALD - 60%, Gaucher disease – 50%, and 100% in MLD and Krabbe disease). **Conclusion**: HSCT is an available curative option, and early age at HSCT prevents end-organ damage.

Keywords: *Alternate donor HSCT, Gaucher disease, Leukodystrophy, Mucopolysaccharidosis.*

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Inborn errors of metabolism (IEM) are a unique group of diseases in children with disordered lysosomal and peroxisomal function resulting in multiple organ damage. Enzyme replacement therapy (ERT) is feasible; however, it has its disadvantage [1]. Hematopoietic stem cell transplantation (HSCT) is the standard of care in Hurler syndrome, metachromatic leukodystrophy (MLD) (late infantile and adult-onset), late-onset globoid leukodystrophy (Krabbe disease), and peroxisomal disorders like the cerebral form of X- linked adrenoleukodystrophy (X-ALD) [2]. The principle of HSCT in metabolic disorders is cross correction, where the engrafted leukocytes secrete the enzymes that are deficient in the host [3].

Accessibility to ERT can be challenging, particularly in developing countries, due to social and financial constraints and lack of local production [4]. We present our experience in HSCT in children with IEM in India, and aim to analyze variables that impact the outcome.

METHODS

This review of hospital records was conducted in the pediatric blood and marrow transplantation unit at a tertiary care referral center in Southern India. Inclusion criteria were all children up to 18 year of age, diagnosed with an IEM, who underwent HSCT between January, 2002 and December, 2020. Exclusion criteria included children diagnosed to have inborn errors of immunity other than those included in the definition of IEM.

In children suspected of having an IEM, the diagnosis was confirmed either by quantitative enzyme analysis or identifying the underlying gene mutation. All children were evaluated by pediatric cardiologist (including an echocardiography), and a pediatric neurologist evaluated all children with X-ALD and MLD. Skeletal manifestations were assessed with radiology images including *X*-rays. Visual evoked potential and brainstem auditory evoked potential tests were performed in all children. Neuroradiologic assessment included MRI brain in children with conditions including *X*-linked adrenoleukodystrophy. Neuropsychologic assessment was performed in the neurodevelopment clinic with a trained pediatric psychologist. In those with X-ALD, HSCT was offered only if the Loes score in their MRI brain was less than 8 [5]. All family members, particularly the siblings, were screened for the underlying condition at the time of the diagnostic evaluation.

High resolution HLA typing was performed for the child, siblings (if any), and both parents. In case of no compatible match within the family, search was performed

for unrelated donors in registries worldwide. The decision to proceed with an available matched unrelated donor or a haploidentical family donor was based upon the underlying condition, the urgency for transplant, and the family's decision. The study was approved by the Institutional Review Board, and written informed consent was obtained from parents/guardians of all children at the time of the conduct of the study.

RESULTS

Twenty-four children (18 boys) (mucopolysaccharidosis – 13 (MPS I –10, MPS II–1, MPS VI-2), Gaucher disease –4, X-ALD – 4, MLD – 2, Krabbe disease –1) underwent 26 HSCTs at our center for IEM.

Among the children with Hurler syndrome, eight were 2 years of age or younger at the time of HSCT, and one child each was aged 3 year and 5 year, respectively, with normal develop-mental milestones. The five-year-old boy with MPS I was diagnosed to have Hurler-Scheie syndrome, with pre-dominantly skeletal involvement and mild developmental delay. The child with MPS II was three-year-old, and among the two children with MPS VI, one each was younger and older than two year. Among the children with X-ALD, Loes score was 2 in three children and 8 in one child. Among the four children with Gaucher disease, two had undergone splenectomy before HSCT. We docu-mented mild peripheral neuropathy in the children with MLD, and right-sided foot drop in the child with Krabbe disease.

Of the 26 transplants, six children (24%) had fully matched family donors (MFD), nine (34%) had matched unrelated donors (MUD), and eleven children (42%) had a haploidentical father as the stem cell donor. Twenty one children (84%) received myeloablative conditioning. The conditioning regimen included treosulfan/fludarabine/thiotepa in 14 children, busulfan/cyclophosphamide in three children, and fludarabine/busulfan in four children. Reduced-toxicity conditioning was used in five children (16%), of whom three children received fludarabine/treosulfan, one child received fludarabine/melphalan, and one immediate second transplant received TBI 4 gray. Twenty children (76%) had received peripheral blood stem cells as their stem cell source, and we used bone marrow and umbilical cord blood unit in three children (11.5%) each.

One child died before engraftment due to diffuse alveolar hemorrhage. Of the remaining 23 children, 21 (91%) engrafted with complete chimerism. Two children had primary graft failure, and two children had secondary graft failure within 90 days. The engraftment rate and overall graft failure in this cohort were 91% and 17%, respectively.

Acute GVHD was documented in 14 children (56%) with grade I/II skin GVHD in 4 (17%), grade III/ IV skin in four children (17%), grade I/II gut GVHD in four children (17%), grade III/IV gut GVHD in one child (5%) and grade II acute liver GVHD in one child (5%). One child had limited chronic GVHD involving the skin (5%), and one had musculoskeletal GVHD (5%). Treatment included steroids and second line agents, including etanercept and ruxolitinib. Grade IV gut GVHD was the cause of death in one child who underwent MFD HSCT for Hurler's syndrome.

The median (IQR) overall survival was 72% (55-100%) with a median follow up of 76.5 (10-120) months and progression-free survival of 68%, with a median follow up of 68.5 months (**Fig. 1**). Disease-specific survival in our cohort was 76% in MPS, 60% in X-ALD, 50% in Gaucher disease, and 100% in MLD and Krabbe disease. Survival based upon donor source in our cohort was 83% in MFD, 75% in the MUD, and 70% in the haploidentical HSCT group (**Fig. 2**).

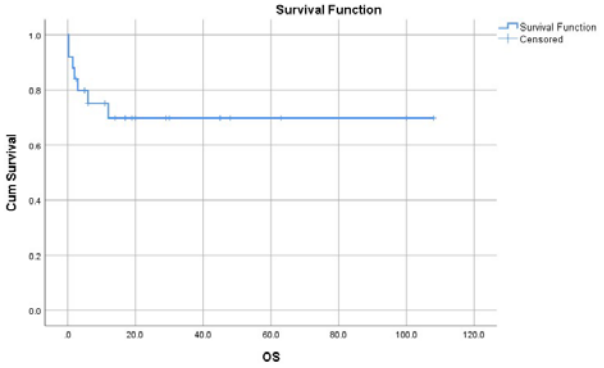

Fig. 1 Kaplan-Meier survival curve depicting overall survival of 72% with a median follow up of 76.5 (range 56.8-96.2) months.

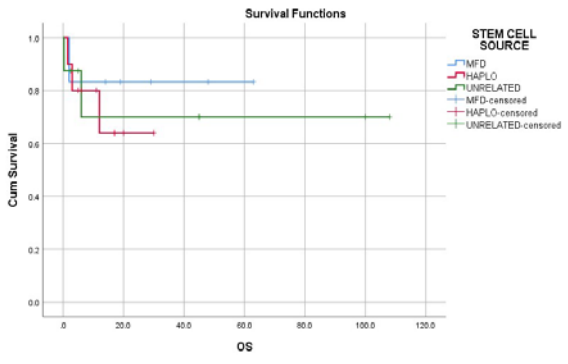

Fig. 2 Kaplan-Meier survival curve depicting overall survival based upon donor source - 83% in MFD, 75% in a MUD, and 70% in haploidentical HSCT.

WHAT THIS STUDY ADDS?

- Hematopoietic stem cells transplantation is an available curative option, and if offered early, may provide optimal outcome for these children.

Seven children died in our cohort. Among those who died, two children had Gaucher disease, two had X-ALD, and three children had Hurler syndrome. One child with X-ALD (Loes score 8) died of secondary graft failure and rapid disease progression.

Among those with MPS, the children who underwent matched unrelated HSCT had documented normal enzyme levels within one year post-HSCT (**Web Table I**). Children who received related and haploidentical HSCT had a low average enzyme level. Facial dysmorphism, corneal haziness, and organomegaly improved despite suboptimal enzyme levels. Bone disease with kyphoscoliosis required orthopedic correction. Children who underwent HSCT for Gaucher disease had resolution of organomegaly after six months. Children with X-ALD with a durable graft had stable MRI findings. Among children with MLD, we observed significant residual peripheral neuropathy requiring intensive physiotherapy and rehabilitation.

DISCUSSION

The present study reports outcome data on HSCT in children with inborn errors of metabolism in India, with overall survival of 72% and progression-free survival of 68%. Early referral for HSCT prior to onset of end organ damage resulted in better outcomes. The limitations of the study include the retrospective study design, the heterogeneous nature of underlying IEM disorders in the cohort, and the non-availability of enzyme levels for all children.

For HSCT in IEM, patient selection is the key to an optimal outcome. HSCT is better suited for MPS I, II, and VI and not suited for MPS type III and IV [6]. In X-ALD, the treatment options include observation for a score of zero to avoiding HSCT in a higher score (Loes score >9) as the HSCT accelerates the neurodegeneration in children with advanced disease [7].

The graft enzyme kinetics and the age at HSCT are the two main predictors of optimal outcome. HSCT performed early before the onset of organ damage results in a favorable outcome [8,9]. HSCT provides a constant source of enzyme production in vivo and helps in stabilizing the disease, particularly neuroregression, and corneal and cardiac-related issues [10]. The skeletal system is usually refractory to the HSCT and requires corrective surgery [6].

HSCT in IEM has an impact on the finances of the family as well. There has been a long-standing delay in diagnosis and treatment of children with IEM in India, with resultant late referral for HSCT [11]. The cost for a matched family donor HSCT in India would be approximately INR 15,00,000. For a 10 kg child with Gaucher disease, the cost for enzyme replacement would be approximately INR 7,20,000 per year, which needs to be continued throughout life.

The study highlights the curative potential of HSCT in inborn errors of metabolism and the impact of early HSCT on reversal of somatic features and halting further neuroregression. Long term follow-up with a multi-disciplinary team including cardiologists, neurologists, ophthalmologists, orthopedic surgeons and physiotherapists is essential to positively impact the quality of life. Shared care between pediatricians and specialists is paramount to early diagnosis and referral, particularly in developing countries where access to long-term ERT can be challenging.

Ethics clearance: IRB. Apollo Hospital, Chennai; No. ASH-C-S-004/03-22 dated March 23, 2022.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: VVS,RU,RR: conceptualized the study and wrote the manuscript; SKM,HV: data analysis; RC,MKM: data collection; IJ: proof reading; BR: statistical analysis. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Web Table I Pre- and Post-HSCT Enzyme Levels for Patients Who Underwent HSCT for Inborn Errors of Metabolism (*N*=10)

Type of donor	*Enzyme involved*	*Enzyme level at diagnosis*	*Post HSCT enzyme level*
Mucopolysaccharidosis I			
Matched unrelated donor	Alpha iduronidase	0.1	23(20-108)
Matched family donor	Alpha iduronidase	5.7	28 (20-108)
Haploidentical father donor	Alpha iduronidase	8.1	25 (20-108)
Haploidentical father donor	Alpha iduronidase	6.2	30(20-108)
Matched family donor	Alpha iduronidase	3.2	42 (20-108)
Matched unrelated donor	Alpha iduronidase	2.5	26 (20-108)
Mucopolysaccharidosis VI			
Matched sibling donor	Aryl sulfatase B	1.8	52 (84-452)
Haploidentidal father donor	Aryl sulfatase B	0.8	42 (84-452)
Gaucher disease			
Matched sibling donor	Beta glucosidase	0.1	6.2 (4-24)
Matched family donor	Beta glucosidase	0	4.7 (4-24)

HSCT – Hematopoietic Stem Cell Transplantation; [a]done 1 year post HSCT.

RESEARCH PAPER

Factor Affecting Duration of Exclusive Breast Feeding in Preterm Infants With Gestational Age ≤ 34 Weeks

APOORVA KUTAR, PADMASANI VENKAT RAMANAN

From Department of Pediatrics, Sri Ramachandra Institute of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu.

Correspondence to:
Dr Padmasani Venkat Ramanan, Professor, Department of Pediatrics, SRIHER (Deemed to be University), Chennai, Tamil Nadu.
padmasani2001@yahoo.com
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Objectives: To study the factors influencing the duration of exclusive breastfeeding (EBF) in preterm (≤34 weeks) infants. **Methods**: This study was done in 113 preterm infants with gestational age ≤34 weeks who were attending the well-baby clinic at the corrected age (CA) of 6 month. The birth details were noted from hospital records and feeding details were collected through a personal interview. **Results**: The mean (SD) duration of EBF was 3.61 (2.3) months, and 35.3% babies had received EBF till CA of 6 month. Operative delivery [aOR (95% CI): 3.8 (1.0, 13.4) *P*=0.037], delay in initiating tube feeding, [aOR; 1.5 (1.0, 2.1); *P*=0.017], and delay in establishment of oral feeds [aOR1 (1.0, 1.08) *P*=0.016] were associated with a shorter duration of EBF. **Conclusion**: The prevalence of EBF till 6 months CA in preterm ≤34 weeks was 35.3%. Earlier initiation and establishment of full oral feeds may help in improving the duration of EBF.

Keywords: *Cesarean section, Risk factors*, *Tube feeding.*

The benefits of exclusive breastfeeding (EBF) for the first 6 months of life are well known . Overall 54.9% of infants in India get EBF [1]. Preterm infants constitute 12% of all live births in India [2] but there is a paucity of data on the duration of EBF, specifically in preterms. This study was done to estimate the prevalence of EBF till six months corrected age (CA) in preterm babies born at ≤34 week gestational age, and to identify the factors influencing it.

METHODS

This cross sectional study was done between August, 2019 and March, 2020 in infants born preterm (≤34 weeks gestational age) in a university teaching hospital. The study was approved by the Institutional Research Ethics Committee of our university. Written informed consent was obtained from the parents of the subjects. The infants were enrolled consecutively for a sample size of convenience at 6 months (+2 weeks) CA from the high risk follow up clinic (routine visit scheduled at 6 months CA as per protocol). Those with congenital malformations, chronic systemic illnesses and with mothers who were employed outside the home or separated from the infant for any reason were excluded. The sociodemographic, birth and neonatal intensive care unit (NICU) stay details were noted from the discharge summary. After delivery, the mothers had received lactation support throughout hospital stay till discharge, and had been counselled to continue EBF after discharge. The details regarding type of feeding and the decision makers on the initiation of complementary feeds (CF) were collected through interview by a single researcher using a structured questionnaire. Modified Kuppusamy classification was used to grade the socio-economic status (SES). The preterm infants were cate-gorised according to the World Health Organization (WHO) definitions as extreme preterm: GA 24 wks+0 days to 27wks+6days; Very preterm: GA 28+0 days – 31+6; Moderate preterm: GA 32+0 days – 33+6 days.

EBF was defined as receiving only mother's breast milk, no other liquids or solids or even water, except oral rehydration solution or drops/syrup of vitamins, minerals or medicines [3]. Corrected age (CA) was defined as chronological age from birth reduced by the number of weeks born before 40 weeks of gestation [3]. Small for gestation age (SGA) was defined as birthweight <10th percentile for gestational age as per Intergrowth 21 chart [3]. Complementary feeding was defined as food, usually semisolid, that is offered in addition to milk to young infants [4].

Statistical analysis: The data were analyzed with IBM SPSS, Version 23.0. For statistical analysis of factors influencing the duration of EBF, duration was categorized as <4 month and ≥4 months CA since 4 months CA corresponds approximately to 6 months chronological age or older for preterm infants born with GA ≤34 weeks. Pearson chi-square test was used to compare the statistical significance of differences in categorical data.

Probability value <0.05 was considered significant. The variables were first analyzed in univariate models; subsequently the variables with a $P<0.5$ were analyzed in a multiple stepwise backward model. For multivariate analysis, logistic regression was done using backward Wald method to get Odds ratio.

RESULTS

Out of 156 eligible infants who presented during the study period, 43 were excluded (32 infants as the mother was employed outside the home, 6 infants due to chronic systematic illness and 5 due to parents' refusal) and 113 infants were enrolled. Of these, 61(54%) were males, 67 (59%) were singleton and 46 (41%) were twins (23 pairs).There were 9 (8%) extreme preterms, 50 (44%) were very preterms and 54 (48%) were moderate preterms. At discharge after delivery, 34 (30%) babies had been on EBF. The mean (SD) duration of EBF was 3.61 (2.3) months. Only 40 (35.3%) had received EBF till 6 months CA and 52 (46%) had received EBF for < 4 month CA. According to modified Kuppusamy classification of SES, 76% of the babies belonged to the upper middle class and 24% to the lower middle class. Among the babies in upper middle class, 57% received EBF for ≥4mon CA while among the babies in lower middle class, 43% received EBF for ≥4mon CA. The difference was not statistically significant.

The risk factors associated with shorter duration of EBF are depicted in **Table I**. The decision to initiate CF was taken by parents, grandparents and healthcare profession in 19.5%, 19.5% and 61% households, respectively. In 44 babies (38.9%), the advice to start CF before 6 months CA was given by a healthcare professional.

On multivariate logistic regression analysis, the independent factors significantly associated with a EBF duration for less than four months were cesarean section delivery [aOR (95%CI) : 3.8 (1-13.4) P= 0.037], delay in initiating tube feeding, [aOR (95% CI) 1.5 (1.0-2.1); P=0.017], and delay in achievement of full oral feeds [OR (95% CI) 1.0 (1.0-1.08), P=0.016].

DISCUSSION

In our study on preterms born ≤34 weeks, 30% were on EBF at discharge, with the rates among the extreme preterm, very preterm and moderate preterm being 12.5%, 14% and 44.8%, respectively. This rate is lower than that reported from Sweden (55%, 41% and 64%) [5] yet similar to that reported from Brazil (15.3%-29.2%) among all preterms [6]. The higher rates in Sweden could be due to the availability of social support and higher education status, since their overall rate of EBF till 6 month is 78% [7] while in India it is only 54.9%.

Table I Risk Factors Associated With Exclusive Breastfeeding for <4 Months (corrected age) in Preterms (<34 week)

Factors	*EBF <4 mo, (n=52*	*EBF ≥4 mo, (n=61)*	*Unadjusted OR (95% CI)*
Males	24 (39.4)	37 (60.6)	1.7 (0.8-3.8)
Gestational age <28 wk	6 (66.6)	3(33.4)	3.4 (0.7-15.1)
Gestation age 28 to <32 wk	26 (52)	24 (48)	1.8 (0.8-4.0)
First born	44 (53)	39 (47)	1.9 (1.0-3.7)
Birth order >1[a]	8 (26.7)	22 (73.3)	(Reference)
Cesarean section	42 (51.8)	39 (48.2)	2.3 (0.9-5.6)
Small for gestational age	8 (53.4)	7 (46.6)	1.4 (0.4-4.1)
Maternal education			
≤ Standard 8	1 (33.3)	2 (66.7)	1.3 (0.1-16.1)
9-12 standard	14 (40)	21 (60)	1.9 (0.1-22.4)
Graduate or higher	37 (49.3)	38 (50.7)	(Reference)
Previous abortions[a]	15 (65.3)	8 (34.7)	3.0 (1.1-8.1)
Duration of NICU stay[a]	26.21(22.6)	17.26(16.8)	1.0 (1.00-1.04)
Tube feed initiated (d)[a,b,c]	1.8 (1.5)	1.19 (1.13)	1.4 (1.0-1.9)
Direct breastfeed initiated (*d*)[b,c]	24.53 (27.9)	21.47 (19.5)	1.0 (09-1.0)
Full oral feeds achieved (*d*)[a,b,c]	18.32 (16.2)	9.16 (11.9)	1.0 (1.01-1.08)
Maternal age (y)[a,b]	31.0 (5.1)	28.62 (4.7)	1.1 (1.0-1.1)
Kangaroo mother care (*d*)[b,c,d]	15.11(12.4)	13.29(18.4)	1.0 (0.9-1.0)

Values in no. (%) or [b]mean (SD). NICU – neonatal intensive care unit. [c]postnatal age,[d]number of days; [a]P<0.05.

WHAT THIS STUDY ADDS?

- Prevalence of exclusive breastfeeding till 6 month corrected age in infants born preterm ≤34 weeks was 35.3%.
- Late initiation of tube feeds and late achievement of full oral feeds were the modifiable risk factors identified.

The prevalence of EBF till 6 month CA in this study was similar to the prevalence reported previously in other studies on preterms [8,9], but lower than the reported prevalence in term babies in NFHS-4 [1]. Previous studies have reported that the duration of EBF in term infants is reduced by maternal factors like insufficient milk production and anxiety as well as medical conditions in the baby including difficulties in establishing suck and swallow [10]. In preterms all these factors are more prevalent.

We found that the EBF rates improved in the very preterm and remained unchanged in the extreme and moderate preterm after discharge, possibly due to the neurological maturation of the infant and maternal psychosocial factors. Other studies have reported the prevalence of EBF till 6 months to be 9.9% in very preterm [11] and 48.5% in the late preterms [12].

In 44 (38.9%) babies, the advice to start complementary feeds before 6 months CA was given by healthcare professional. Though this could have been due to valid concerns of weight, currently there are no clear guidelines on the ideal duration of EBF for preterm babies. The guideline given for term infants is being extrapolated with no clarity on whether the 6 months should be the CA or chronological age for a preterm.

The study had certain limitations. The rate of EBF at discharge was suboptimal (30%). The reason for the HCP advising early initiation of CF was not explored. Also, the mothers were interviewed only when the infants were 6 months CA. Hence some recall bias is expected. However, all mothers seemed to recollect the time of initiation of complementary feeding without any difficulty. The study was private-sector hospital-based with the subjects belonging primarily to the middle class and the mothers had a minimum educational status of grade 8. The factors operating in the other socioeconomic classes may be different.

There is a need to provide clear guidelines on whether the recommended duration of EBF in preterm infants should be based on the CA or the chronological age or on factors other than age such as growth rate or developmental readiness.

Ethics clearance: Research and Ethics Committee, SRIHER (DU); No. NI/19/JUL/70/60, dated Dec 27, 2019.
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RESEARCH PAPER

Profile of Children With Child Abuse From Serbia

MAJA ZECEVIC,[1] DRAGOLJUB ZIVANOVIC,[1,2] TAMARA ADAMOVIC,[1] DRAGANA LAZAREVIC,[2,3] VESNA MARJANOVIC,[2,4] ZORICA JOVANOVIC,[1] JELENA LILIC[4]

From Clinics of [1]Pediatric Surgery, [2] Faculty of Medicine, [3] Pediatrics, and [4] Anesthesiology and Intensive Therapy, University Clinical Center Nis, Nis, Serbia.

Correspondence to: Dr Maja Zecevic, Clinic for Pediatric Surgery, University Clinical Center Nis Blv. dr Zorana Djinjica 48, 18 000 Nis, Serbia. maja.zecevicmd@gmail.com
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Objective: To study the demographic and clinical profile of children with suspected physical or sexual abuse. **Methods:** Retrospective records of children who were admitted to hospital between January, 2015 to December, 2020 with suspected physical or sexual abuse were evaluated. **Results:** The records of 52 children [mean (SD) age 12.24 (5.32) y, 39 boys] were retrieved. Contusions were the most common injury in 53.8% of boys and 69.2% of girls. The majority (70%) of 8-18 year-old-children were abused by peers, and parents/caregivers were the main perpetrators in 72.7% of younger children. **Conclusion:** Child abuse is often underreported, and requires a high index of suspicion and multidisciplinary approach of management.

Keywords: *Abuse, Brain injury, Contrusions, Sexual abuse, Abuse*.

Children in Balkan countries are exposed more to violence than in European countries as rates for physical violence range from 50.7-76.4% for lifetime experience [1]. Sexual violence exposure ranged from one in twelve to one in six children for lifetime exposure with higher rate in boys than girls in Serbia [1]. The aim of this study was to study the demographic profile of child abuse and to identify the common types of injuries and indications for hospitalization.

METHODS

The records of children hospitalized between January 1, 2015 to December 31, 2020, at the Clinic for Pediatric Surgery, University Clinical Center Nis with suspected physical or sexual abuse were evaluated. Abuse was suspected based on clinical findings, inconsistency in the history given by the child and the accompanying adult, and in the provided explanation of injury. Medical documents and data referring to age, gender, place of origin, type of abuse, perpetrators, injury type, injury severity, duration of hospitalization, and outcomes were collected and analyzed. Contusions of the head and body, multiple excoriations and simple cuts were classified as minor injuries; fractures, tendon sections, stab wounds, and parenchymal organ injuries were classified as major injuries. The study did not include outpatient cases and patients with self-inflicted injuries. In all cases, a social worker was actively involved, according to the state protocol, in managing children suspected of being abused or neglected. The study was conducted in line with in-country legislation after taking parental consent. It was approved by the Institutional Ethics Committee.

Statistical analysis: Anonymized data were entered in Microsoft Excel (Microsoft Corporation). Numerical values were analyzed by Kruskal-Wallis test and categorical variables by chi-square test. All tests were used with a statistical significance of $P<0.05$. Analyses were performed using R software, Version 3.0.3 (R Foundation for Statistical Computing) [2].

RESULTS

A total of 52 children (39 boys) with mean (SD) age 12.24 (5.32) years with suspected abuse were hospitalized, majority (73.1%) of these beyond the urban area. The demographic and clinical profile of children is shown in **Table I**. The average hospitalisation rate was 8.6 children per year with similar annual trends across the study period ($P=0.79$). The average (range) duration of hospitalization was 4.7 (1-23) days. There were no lethal outcomes in any child with physical or sexual abuse.

In children younger than 7 years ($n=11$), the perpetrators were predominantly parents/caregivers (72.7%), while children aged 8-18 years ($n= 41$) were mostly abused by their peers (70.0%). The injuries reported in majority (62.5%) cases of peer-violence were minor. Unknown perpetrators were noted in 1 and 8 children in 0-7 and 8-18 year age group, respectively. Sexual abuse was suspected in two (both 4-year- old) and one 12-year-old girl, two of these three children had evidence of external injury.

WHAT THIS STUDY ADDS?

- Majority of injuries in children hospitalized with suspected abuse, in this regions, were minor, and recovered with conservative management.

Table I Characteristics of Children With Child Abuse Enrolled in the Study (*N*=52)

Characteristics	*Boys*	*Girls*
Age[a]	12.19 (5.30)	12.40 (5.61)
0-3 y	5 (12.8)	2 (15.4)
4-12 y	7 (18)	1 (7.7)
12-18 y	27 (69.2)	10 (76.9)
Minor injuries	23 (59)	9 (69.2)
Major injuries	16(41)	4 (30.8)
Type of injuries		
Burns	2 (5.1)	0
Upper extremity fractures	2 (5.1)	0
Lower extremity fractures	2 (5.1)	3 (23.1)
Semiamputations of fingers	1 (2.6)	0
Head injury	4 (10.3)	0
Tendon sections	0	1 (7.7)
Contusions	21 (53.8)	9 (69.2)
Stub wounds	8 (20.5)	0
Cuts/simple wounds	10 (25.6)	2 (15.4)
Thorax injuries	7 (17.9)	0
Abdominal injuries	1 (2.6)	1 (7.7)
Pelvis and genital injuries	2 (5.1)	1 (7.7)
Multiple injuries	16 (41)	6 (46.2)
Type of management		
Surgical	16 (42.1)	3 (23.1)
Conservative	22 (57.9)	10 (76.9)
Sequelae	4 (10.5)	2 (16.7)

Values in no. (%) or [a]*mean (SD). All P>0.05.*

DISCUSSION

This study provides the demographic and clinical data of childhood abuse in different age and gender groups in Serbia.

In this study, boys were identified as more susceptible for physical and sexual abuse than girls. Minor trauma like head and body contusions was the predominant injury in both genders without any deaths; although, mortality rates as high as 15.8% have been reported [3]. Peer violence was common in school children aged 8 to 18 years, similar to an earlier study [4], that reported peer violence in 48-80% of school children. Parents, and parents and teachers were identified as perpetrators in an interview-based study in adolescents and young adults aged 13 to 24, respectively [5].

In Serbia, 69.2% children aged 11-16 years had experienced physical violence, 8.5% sexual violence, and 4.9% reported contact sexual violence [1]. The proportions were different in the present study as patients with a wider age-range were included. Almost 10% of children experience violence by more than one perpetrator, similar to our study [6]. In majority of the cases, victims knew the perpetrator(s), as has also been reported earlier [7]. Almost one-third of physically abused children require orthopedic treatment [3]. A significant proportion required surgical management in this study too.

Usually, physical findings in sexual abuse as trauma of the genital region heal rapidly, and it is present in less than 10% of abused girls, and rarely seen in boys [8,9]. Children with sexual abuse in this study had external injury as perhaps the study had enrolled hospitalized patients only.

Although reporting child abuse is mandatory, it is estimated that only one out of three child abuse cases is reported [10,11]. Maltreatment of children takes many forms, and it is necessary to increase awareness of child abuse for improved child health outcomes.

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Delivering Electives the Clerkship Way: Consolidating the Student Doctor Method of Training

JAYA SHANKAR KAUSHIK,[1] P RAMACHANDRAN,[2] SAHIBA KUKREJA,[3] PIYUSH GUPTA,[4] TEJINDER SINGH[5]

From [1]Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Assam; [2]Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamil Nadu; [3]Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab; [4]Department of Pediatrics, University College of Medical Sciences, Delhi; [5]Center for Health Professions Education, Adesh University, Bathinda, Punjab.

Correspondence to: Prof Piyush Gupta, Professor of Pediatrics and Principal, University College of Medical Sciences, Delhi 110 095. prof.piyush.gupta@gmail.com

Student doctor method of clinical training or clinical clerkship provides students with exposure to the entire longitudinal illness of the patient. The students participate in patient care as a part of treating team and can refine their clinical, communication and procedural skills. It provides them with an opportunity to work with the faculty and experience the future workplace. Although the graduate medical education regulations (GMER) provide for student doctor method of training, the time provided is too little and opportunistic. Electives have also been recently added to the new curriculum for the first time. We propose a model to deliver the electives using the clerkship method, so as to consolidate what students learn from the ongoing clerkship. This model is feasible, practical and can be introduced in the current GMER for Indian medical undergraduates without any major disruptions.

Keywords: *Longitudinal integrated clerkship, Rotational clerkship, Self-directed learning.*

Student doctor, student physician, and medical student are the commonly designated terms for medical students pursuing medicine as a career [1]. Many 'student doctors' are expected to learn through clinical experience by staying in the wards or outpatient unit with the treating team and interacting with patients on a continuous basis. This 'student-doctor method of clinical training' provides an opportunity to the students to be a part of the treating team. It also improves their clinical, communication, and professional skills [2]. They get to learn first-hand about the dynamics of health, and disease and the importance of teamwork in health care.

STUDENT DOCTOR METHOD OF CLINICAL TRAINING

In the traditional clinical postings, the students usually get involved in care of a patient at one point of time, mostly once the diagnosis is established. They do not get to directly observe the process of managing a sick person starting from the clinical presentation, reaching at differentials, planning work-up, treatment, monitoring, discharge, and follow up. This lack of opportunity to be involved in the continuity of care is important learning gap among medical undergraduates in India. [3] Relationship with faculty is also cross-sectional, which often leads to sub-optimal learning. [4] The faculty who can serve as role model and mentors, does not have continuous, longitudinal relationship with the students. To avoid any confusion, we would be referring to the student-doctor method of training as clinical clerkship in this paper.

Concept of Clerkship

In "clerkship," the student is a part of the treating team and stays in the ward, and is assigned patients to eva-luate, examine, and communicate regarding the diagnostic and therapeutic plan [5]. All this happens under the supervision of a faculty preceptor. This provides the student with a real-world experience of their future career. The term clerkship is often confused with internship and observership. Internship refers to real-world experience after acquiring the primary qualification, whereas clerkship is during the training period before acquiring the desired qualification [6]. Observership refers to clinical experience, but it does not involve direct patient care [6]. During the clerkship, the student gets an opportunity to interact one-to-one with the faculty preceptor, as well as with the assigned patients and their families.

This longer exposure of students to clinical care could be beneficial for the learning outcomes. They can have a first-hand experience of the difficult procedures and unpredictable conditions by staying round the clock. This provides the student with advantages of 'tacit transmission' of skills by just being with an experienced resident or faculty [7]. The student presents the history, examination, diagnosis, and progress of the patient during the clinical rounds. He is expected to be updated on the health status of the allotted patient, and aware of their

patient's investigation reports and management. The student-doctor can participate in any procedure or investigation performed on the patient to acquire procedural skills but cannot take independent decision on diagnosis and management of the patient [8]. The student will be a part of daily work rounds, formal teaching rounds, and departmental teaching conferences. It is an opportunity for the student to explore the future workplace.

Objectives of Clinical Clerkship

Three key components of clinical clerkship are *i*) exposure to the entire longitudinal illness of patient, *ii*) learning from experienced faculty, and *iii*) observing the breadth of core clinical problems [9]. Different institutions may define their objectives differently, but the key benefits remain the same. The goals of clinical clerkship method of training are outlined in **Box I**. In line with the stated GMER goals [10] of enabling the students to be a part of longi-tudinal health care and the treating team, in addition to getting hands-on experiences, the objectives of clinical clerkship are as follows:

At the end of clinical clerkship, the student must be able to:

- Integrate the basic science knowledge with clinical reasoning.
- Establish and maintain a therapeutic relationship with the patient.
- Elicit complete medical history, perform examination, arrive at clinical differentials, develop sound clinical reasoning, communicate to the family, and participate in the decision making.
- Work effectively as a member of team and demonstrate professional behavior.
- Understand the dynamics of health and disease in the milieu of financial and socioeconomic conditions.

Box I Goals of Student-Doctor Method of Training (Clinical Clerkship)

- Application of medical knowledge and skill development
- Delivery of effective and compassionate patient care
- Developing interpersonal and communication skills
- Developing professionalism
- Developing practice-based and system-based learning.

The benefits of clinical clerkship method of training are summarized in **Table I**.

Models of Clinical Clerkship

Various clerkship models have been created to suit the local needs and context. The clerkship could be either a rotational clerkship, longitudinally integrated clerkship (LIC), or longitudinal ambulatory clerkship (LAC) [11]. When the students are posted in a core specialty department like internal medicine, general surgery, obstetrics, pediatrics, and family medicine, by rotation for a fixed period, it is called rotational clerkship [12,13]. In longitudinal integrated clerkship (LIC), students learn all core competencies across all disciplines simultaneously [14,15]. In longitudinal ambulatory clerkship (LAC), selected students are paired with preceptors in core specialties and assigned to ambulatory clinic sites for 5-10 hours in a week [16-18].

Clerkship in the New Curriculum

In GMER, learner doctor method of clinical training (clinical clerkship) has been introduced in the section 9.5 under the broad heading of new teaching or learning

Table I Benefits of Clerkship Program to Various Stakeholders

Benefits to students	*Benefits to faculty*	*Benefits to institution and patients*
Opportunity to deal with real patient in a supervised environment	Better job satisfaction	Student doctor can serve as patient advocate and can act as a bridge between the patient and the treating physician
Exposure to clinical cases from presentation to outcome	Improved quality of faculty clinical teaching	Improved patient satisfaction with an approachable student doctor to take care of their needs
Confidence in clinical skills and professional behavior	Teachers enjoy sharing their expertise and mentoring their students to develop professionally	Decreased burden on clinical services with student doctor as an additional manpower to the treating team
Develop deep learning strategy with sound clinical reasoning	It is an opportunity to identify potential students for recruiting in their specialty	Improved quality of teaching in the institute
Motivation to self-directed learning. Better opportunity to receive feedback on student's performance	Ability to directly observe the student on clinical and professional skills	Improved competency of the outgoing students with better placement on long-run

elements [10]. The goals of clerkship program are to provide learners with experience of longitudinal patient care, being a part of health team, and hands-on care of patients in outpatient and inpatient settings. The structure and assessment have been suggested in the document [10]. In Phase I, the students are expected to understand and get sensitized to the hospital environ-ment. In Phase II, students are expected to take the history, perform examination, and arrive at possible diagnosis. In Phase III, they are additionally expected to plan investigations, and finally assist in management and decision-making.

There is a lack of clarity with reference to the structure of the module and timeframe where the same could be introduced at different levels. As of now, the students have not been provided any dedicated time and must squeeze in time within the ongoing timetable. Given the directive that students should not miss their existing classes/postings and work on this program till 6 PM only, the gains from this intervention are going to be highly variable, inconsistent and opportunistic. Introduction of clinical clerkship module within the existing time frame of the new curriculum is therefore likely to be challenging. If we keep the duration very short, the learner will not understand the expectation and the preceptor would not understand the level of learning by the student and to provide feedback on possible benefits. If we keep it too long, it will have logistic constraints.

Some of the possible issues are listed in **Box II**.

ELECTIVES IN UNDERGRADUATE HEALTH PROFESSIONAL TRAINING

Electives are gaining importance in health professional education in shaping the student's professional development [19]. Electives provide an opportunity for students to gain exposure in their future field of interest. Students develop transformative learning during the electives, and have previously rated this experience as innovative [20]. National Medical Commission (NMC) has introduced eight weeks of elective posting for medical undergraduates [10]. The first slot of electives devotes a few hours to basic sciences, the second slot provides for full time exposure in the chosen area.

Box II Possible Issues With the Clinical Clerkship Program as Provided under GMER, 2019

- No dedicated time provided. Only opportunistic visits between ongoing teaching.
- Students may not find time due to ongoing teaching or miss out on important events related to the illness.
- Faculty may not be available when students visit the wards.
- Rounds, collection of samples etc. and procedures may not be practicable for students without a dedicated time.
- The program may get reduced to just completing logbooks without meaningful learning.
- Professional bonding and continuity of care may not happen.
- Assessment may be haphazard and unequal for different students.

CONSOLIDATING CLERKSHIP WITH ELECTIVES

We propose that the slots earmarked for electives be utilized as a dedicated clerkship period, which can also be used to post students in the speciality chosen by them (subject to local situation and logistics). At present, there are no models to deliver electives. Individual colleges can develop a mechanism to provide clerkship experience in the chosen elective. As we gain more experience of running this prog-ram, the scope and number of electives can be redefined.

It is suggested that out of the eight weeks, four weeks each may be devoted to medical specialties, and the remaining four weeks to surgical specialties. The modalities for dividing the students could be as per their choice or any other criteria, and the maximum number in each group can be as per the discretion of the institutions. A student can be allowed to opt for only two weeks slot for a given department to increase the breadth of experience (can work in four departments).

The daily schedule could include ward rounds with residents/senior residents (8-9 AM) and consultants (9-10 AM). The next slot of 10 AM-1 PM could cover ward work, sampling, procedures, operation theatre, special clinics and laboratories. After the lunch break (1-2 PM), evening rounds could be scheduled with residents with discussions on laboratory reports (2-4 PM) and consultants (4-6 PM).

This will be an additional input to the clerkship program already provided in the GMER, running from second year onwards, and will consolidate the immersive learning opportunity. Similarly, the electives experience will also become more structured and oriented to clinical care. This proposal is to orient the students in the process of healthcare rather than in the specific diseases, which will anyway be taught during routine ongoing postings. The training could be tailored to the local needs of the students and faculty instead of a one size-fits all approach. Reflections should provide an opportunity to think of applying this knowledge to routine patient care.

Advantages and Challenges

The proposed consolidated model of clinical clerkship with electives has several advantages. It is a time efficient

model which can be fitted into the existing timeline schedule set by NMC and will provide dedicated time for getting involved in longitudinal care. It should be acceptable to majority of medical institutions in India, with less burden on students and faculty. This model takes care of elective component and will obviate the need to send students outside the institutions for elec-tives. There will be no additional financial burden on the institutions for incorporating this consolidated model. It also provides students with opportunity for one-to-one mentoring.

This model also brings in a few expected challenges. The phased incorporation of clerkship starting from the first year where the student would develop orientation to the hospital cannot be executed with this model. Ideally clerkship model must be longitudinal, and the suggested model of 8 weeks falls short of this expectation, but it is expected that the students would have already experienced being student-doctor in an already running program. However, any model needs to be suggested within the liberty provided by regulations and this suggested model would be better than the present unstructured model. Replacement of the existing elective model with the suggested consolidated model might raise another concern. In the current elective model, the student gets four weeks exposure to laboratory and research in pre- and para-clinical subjects, which might be compromised with this consolidated model. This might defeat the essence of the student choosing the departments on their liking/ understanding for getting diverse learning ex-perience in laboratory sciences. However, during the new model postings, treating clinicians can build in exposure to laboratory, or research methodology, including consulting literature related to the alloted patient.

Acceptance of the model among the faculty and administrators might be challenging. All faculty including those from super-specialties would need to get oriented on electives and clerkship module to become effective preceptors. The students' compulsion to perform in the summative examinations, and their focus on postgraduate entrance examinations may demotivate them to spend their time on clerkship unless it is incorporated as part of the internal/formative assessment. [19]

There are many factors that would determine and influence the implementation of consolidated clerkship program. These include the length of clerkship, and the number of students and faculty [4]. Number of beds in inpatient setting, outpatient burden (patient turnover), and availability of departmental resources are crucial factors for the successful implementation of the training. Lack of clarity in clerkship objectives, content, timetable and process of evaluation, and sub-optimal training and motivation of faculty are some other hurdles to its implementation.

Introduction of clerkship may be challenging in centers with limited patient turnover. In such a situation, liaison with a nearby center with adequate exposure could be chosen or if that is not feasible, the student can be expected to go to a higher level of complexity of learning [21]. Similarly, in centers with excessive patient load, it may be difficult to take time out. The student may spend time on activities with little educational or learning value. There might also be lot of variation in the nature and quality of supervision [22]. A simple shadowing by a student-doctor without getting feedback could be another major challenge.

Assessment During Clerkship

Assessment of learner in clerkship is mainly formative with the purpose to provide feedback to students. The student can be expected to fill the logbook with the details of the assigned patient, and the quality of the report is assessed by the faculty keeping in mind the objectives of the clerkship program [22]. This can be a part of the inter-nal assessment, which forms one of the eligibilities for appearing in the final examinations. Student can be assessed by longitudinal preceptor in each discipline by clinical skills evaluation, Direct observation of proce-dural skills (DOPS), mini-clinical evaluation exercise (mini-CEX), review of portfolios, observed interviews and case formulations [23]. More the number of assessors, greater will be the reliability of the clerkship assessment [22]. Apart from the method of assessment, the content of the task is important determinant of validity of assessment in clerkship [22]. In an internal medicine clerkship, three principal components of assessment viz., information processing, professionalism, and declarative knowledge have been suggested [24].

In addition, students may be encouraged to write reflections of their learning experience using Rolfe model [25] of 'what happened,' 'so what,' and 'what next.' Student's progress needs to be periodically reviewed. Student's self-assessment, and formative feedback might help in setting new goals [26]. The learning strategy used by the students during clerkship will be determined by the mode of assessment. Feedback to students from the preceptors is an essential component of clerkship program [27]. Supervisor narratives are also useful, and help in course-correction and program evaluation [28].

Faculty Training

Departmental heads, medical education units and curriculum committees must be involved in training the faculty, residents, and paramedical staff on clerkship. Faculty's

role is to motivate the students, facilitate learning, promote independent thinking, express their ideas, encourage compassionate care, and equip the students for lifelong learning [29]. The faculty involved in clerkship rate teaching and involvement in the program positively [29]. They develop familiarity with students and find more interactive learning and students developing clinical reasoning skills [29].

Feedback and Program Evaluation

Program evaluation must consider students' attitude, perceptions (from mid-year and end-of- year questionnaire), and focused group discussions [30]. It must also assess the fund of knowledge and accuracy of self-assessment. Extent of clinical experience can be retrieved from the patient log. This includes ability of the student to witness the whole illness episode, meeting the patient before diagnosis, following him through hospitalization, and after discharge. Ability to get individual one-to-one feedback should be additionally assessed [31]. Soliciting and utilizing the patients perspective on the student-doctor may provide additional information for student assessment and also program evaluation; though, it has been infrequently utilized.

CONCLUSION

The consolidated model of delivering the electives in clinical clerkship way would provide medical undergraduate students with experience of longitudinal patient care and ability to work with clinical teams by providing a dedicated time within the existing framework. It will also provide a successful integration of newer teaching methods. This model, with a motivated and trained faculty and students, could result in successful consolidation of student-doctor method of training in Indian medical colleges.

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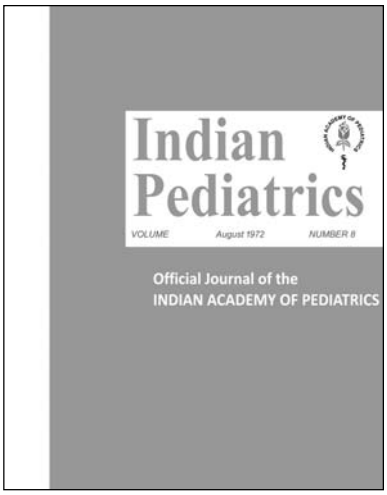
Foreign Body Ingestion in Children: The Menace Continues

UJJAL PODDAR, ARGHYA SAMANTA

Department of Pediatric Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh. Correspondence: Dr Ujjal Poddar, Professor & Head, Department of Pediatric Gastroenterology, SGPGIMS, Raebareli Road, Lucknow 226014, Uttar Pradesh. ujjalpoddar@hotmail.com

Foreign body ingestion poses a significant health hazard in children, potentially leading to morbidity and mortality if impacted in the gastrointestinal tract. As opposed to adults, the majority of foreign body ingestions in children are accidental, often not witnessed, and mostly asymptomatic. Fifty years back in August, 1972, a research article was published in the journal on 'Acute dysphagia due to foreign bodies in esophagus' [1]. Through this communication, we present the changes and challenges in the management of foreign body ingestion in children which evolved over the last five decades.



THE PAST

The scenario described by Tandon, et al [1], half a century ago, highlights the magnitude of esophageal foreign body in children based on a hospital-based data from Agra, Uttar Pradesh. They reported a large series of 198 children who presented with impacted esophageal foreign body. The study population comprised of children aged 12 years or younger with a male to female ratio of 6:5. Though the maximum reported incidence of foreign body ingestion occurred in the age group between 6 months to 3 years, in that series, it was found evenly distributed across all age groups. As expected, the majority (63%) of the foreign bodies were stuck at the cricopharynx followed by middle third of esophagus (28%) and lower end of esophagus (9%). Plain *X*-ray of chest was performed in all to identify the nature, site and size of foreign body. Fortunately foreign bodies were radio-opaque in 90% of cases. Pre-existing gastrointestinal tract abnormalities such as strictures, diverticulum etc. increases the risk of impaction of a swallowed foreign body. Tandon, et al. [1] observed pre-existing esophageal abnormalities in 10% cases; 6% had benign esophageal stricture and 4% had congenital web. All endoscopies were performed under general anaesthesia with rigid endoscope, as per the standard practice those days, which often resulted in slippage of foreign body into stomach, as was seen in 3% cases in the series. Endoscopic removal of foreign bodies is not without risk of complications, especially when rigid endoscopes are used. Only one child (0.5%) developed mediastinal emphysema following foreign body removal in that series.

THE PRESENT

Foreign body ingestion continues to be one of the major causes of pediatric emergency department visits, even though the nature of ingested foreign bodiess has undergone a considerable change over the years. Children usually swallow the foreign body from household products such as coins, toys, fishbone, jewelry, magnets, and button batteries. As the economy grew and metallic coins gave way to printed notes, the spectrum of ingested foreign bodies changed. Nowadays, we see fewer reports of metallic coin ingestion but more often button battery ingestion and food bolus impaction due to underlying eosinophilic esophagitis [2]. With the wide abundance of detachable batteries in consumer electric toys, the incidence of button battery ingestion has gone up exponentially [2,3]. The National Poison Data System (USA) outlined 83,459 battery ingestions from 1985 to 2017, 77% in children younger than 6 years [4]. In a recent Indian study, it was observed that 50% of ingested batteries in children were removed from a product (mainly from hearing aids, remote controls), 30% from toys, and the remaining 20% from unused cells, watches etc. [5]. Related morbidity and mortality have sharply risen in the last decade due to the use of more powerful (3.0 V vs 1.5 V) and bigger (>20 mm) lithium battery as compared to traditional alkaline button battery. Button battery causes necrosis of esophageal walls due to electric current, leakage of chemicals as well as pressure necrosis [6,7].

In 80-90% of cases, the foreign body passes without complications and is evacuated with feces within a few days. Around 10-20% of cases may require endoscopic removal because of impaction or its potential harm – less than 1% may require surgery [3]. The morbidity related to foreign body ingestion depends on three factors; nature of foreign body (button batteries, sharp-pointed objects), site of impaction (esophagus), and duration since ingestion.

Highlighting the clinical relevance of the situation, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has recently published guidelines on how to manage button battery ingestion cases and its complications [8]. This guideline recommends early referral to the emergency department and getting bi-plane *X*-ray of neck, chest, and abdomen done in all patients with suspected foreign body ingestion, even if they are asymptomatic. A "halo or double-rim" sign on the antero-posterior view and "step-off" on the lateral view differentiates a button battery from a coin. Although, most foreign bodies in the gastrointestinal tract pass spon-taneously without complications, endoscopic or surgical removal may be required in a few children. Management of ingested foreign bodies remains a challenging endoscopic dilemma faced by pediatric gastroenterologists. As per ESPGHAN recommendations, blunt foreign bodies and coins or impacted food bolus from the esophagus should be removed urgently (within 24 hours), even in asympto-matic children [2]. If the child is symptomatic, it should be removed on an emergency basis (within 24 hours), especially for sharp, pointed objects and button batteries [3,8]. Button batteries in the stomach are removed as soon as possible in symptomatic children, in cases of ingestion of more than one battery and if coin-gestion with a magnet [8]. In cases of asymptomatic children, endoscopic removal of button battery from stomach/intestine is considered if it remains in the same position after 7-14 days, with a follow-up *X*-ray to confirm position [8].

Advances in endoscopic equipment, accessories and technique have made quantum leaps in the last 50 years. Use of rigid endoscope, Foley catheter and bouginage made way for flexible endoscopy, which is the current therapeutic modality of choice for most patients. The key principles for endoscopic management of esophageal foreign bodies are to protect the airway, to maintain control of the object during extraction, and avoid causing additional damage. Endotracheal intubation is sometimes necessary, especially in younger children and those at higher risk for aspiration. The use of devices such as an esophageal overtube and a latex protector hood may facilitate the safer extraction of sharp/pointed objects.

CONCLUSIONS

It is important for all clinicians to be able to recognize symptoms of foreign body ingestion, radiographically identify them (especially button batteries and sharp objects), and ensure prompt endoscopic removal to minimize the risk of negative outcomes. Parents must be made aware of the hazards and take necessary actions to prevent ingestion. Community efforts should be made to diminish the burden through stricter legislation, product innovation, and redesign. As button batteries are the most commonly ingested foreign body with a potential risk of adverse outcomes, addressing this issue by raising awareness will certainly reduce the magnitude of the problem.

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Screen-Based Media Use Among Children During the COVID-19 Pandemic

This questionnaire-based study was conducted to assess screen-based media use during the coronavirus disease 2019 (COVID-19) pandemic in children (*n*=278) aged between 1 to 12 years. Television was the most common media available for use (246, 88.5%), and mobile was the next most commonly available media (230, 82.7%). Daily screen time exposure and use of television (*P*<0.001), computer/Laptop (*P*<0.001), and tablet (*P*=0.001) were significantly more common in those aged 5-12 years. Majority (214, 76.9%) were using screen-based media for educational purposes.

Keywords: *Children, Lockdown, Screen time*.

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Coronavirus disease 2019 (COVID-19) pandemic related lockdown has led to an increased use of screen-based media among children. Indian Academy of Pediatrics (IAP) guidelines on screen time and digital wellness have recommended no screen time for children below 2 years, less than one hour per day for children between 24 to 59 months, and less than 2 hours per day for children aged 5-10 years [1]. With this background, this study was done to estimate the types, duration and purpose of screen-based media usage among children aged 1-12 years during the COVID-19 pandemic.

This cross-sectional study was done from September, 2020 till December, 2020, after obtaining institutional ethical committee clearance. All children (1-12 years) who were staying indoors for at least preceding three months were eligible to be enrolled. A questionnaire was generated on Google Forms comprising 20 questions related to screen-based media types, duration, content, and purpose. The questionnaire was validated using Delphi technique wherein it was mailed for review to five experts in the field, and was modified as per the suggestions received. The modified questionnaire was validated further by pilot-testing among 20 participants. Electronic data collection was done as per the online survey Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines [2]. Mixed-mode survey method was used where the participants were enrolled through emails, teleconsultation services and social media platforms by snowballing method of recruitment via Google form link. The link had an inbuilt mechanism for parental/caretaker consent. Information was also collected from patients attending the institution's outpatient department physically through printed study questionnaire.

A total of 278 children aged 1-12 years were enrolled in this study, out of which 82 (29.5%) and 196 (70.5%) were enrolled via physical interview and online link, respectively. Among these, television, computer, laptop, mobile and tablet use was seen in 246 (88.5%), 45(16.2%), 129 (46.4%), 230 (82.7%) and 66 (23.7%) children, respectively. Total daily screen time exposure and comparison, reasons for media use, between children under 5 years and 5-12 years of age are summarized in **Table I**. The most common content watched by children was cartoons, 196 (70.5%); followed by online classes, 185 (66.5%). Youtube videos, 161 (57.9%); online games, 96 (34.5%); movies 28 (10.1%); and daily soaps, 20 (7.2%). Usage of screen-based media (SBM) for watching cartoons in younger children (*P*=0.001) and online classes and games in older children (*P*<0.001) were significantly higher. Among participants, 86.3% (*n*= 240) children could operate the screen-based media independently. The percentages of children who used screen-based media fully under adult supervision, under occasional supervision and unsupervised was 62.9%, 26.6% and 10.8%, respectively.

We found that television was the most common media available for use in 1-12 years of age whereas mobile was the most commonly available media for use in under-5 children. This is worrisome as under-5 children exposed to prolonged mobile phone use can have deleterious effect on their development and vision [1]. Increased screen times is of concern in the era of unlimited internet availability in each household, particularly with respect to the type of content children are getting exposed. Smartphones were found to be the most commonly used device among children aged 10-18 years in Switzerland during the COVID-related lockdown [3]. Another Indian study reported use of mobile in 96% and television in 89% of children before lockdown [4].

Online schooling has contributed more to screen time exposure during COVID than other reasons like socialization and entertainment in 5-12 years age group [5]. Another Indian study reported higher screen time for cartoons and YouTube

Table I Screen Time Exposure and Purpose of Media Use Among Children Aged 1-12 year (*N*=278)

Parameter	*Age group, n (%)*		*P value*
	1-5 year (n=82)	*5-12 year (n=196)*	
Daily screen time (h)[a]	2.84 (1.8) h	4.87 (2.3) h	<0.001
Purpose of use [b]			
Education (*n*=214)	42 (19.6)	172 (80.4)	<0.001
Socialization (*n*=177)	32 (18.1)	145 (81.9)	<0.001
Parental break (*n*=97)	14 (14.4)	83 (85.6)	<0.001
Games (*n*=45)	22 (48.9)	23 (51.1)	0.002
Entertainment (*n*=20)	6 (30)	14 (70)	0.95

Data in no (%) or [a]mean (SD). [b]Multiple responses received. Parental break: allowing media use in children in order to avoid active parental supervision; Socialization-connecting with friends/ family/ relatives with the help of screen-based media via social media apps.

videos before COVID [6]. Young children were also exposed to screen-based media for parental break as most parents were working from home and used screen based media as a tool to engage children. IAP screen time guidelines 2021 recommends that screen use should not be used as a way out for calming uncomfortable children by parents [1]. UNICEF recommends media use for positive outcomes like educational or socializing as a quality measure of screen use [7]. As per interactional theory of childhood problematic use (IT-CPU model), parents can play a crucial role in positive assumptions for quality of media use [5,8]. Parents can be an active mediator where they can discuss the media content with children or co-view with children where they can just be an observer or a restrictive moderator where they just restrict some unsuitable content [1,8]. It is important to regulate the use of screen-based media in children as increased usage is associated with psychological issues, abnormal eating patterns, sedentary lifestyle and excessive weight gain [9,10].

The main limitation of our study was the possibility of recall bias. We conclude that online classes among school going children and cartoons and YouTube videos in pre-school children were main reason for screen-based media usage. The usage of screen-based media needs to be regulated among children with parental supervision.

Ethics clearance: AIIMS, Mangalagiri; IEC, No. AIIMS/MG/IEC/2020-21/48 dated Nov 01, 2020.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: RP,LJ,TA: conceived the study; RP,LJ,TA,KSR: collected data and performed statistical analysis; RP,LJ,KSR: reviewed the literature and drafted the initial version of the manuscript which was critically reviewed by TA. All authors contributed to drafting of the manuscript and approved the final version of the manuscript.
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RACHNA PASI,[1] THIRUNAVUKKARASU ARUN BABU,[1]* LIMALEMLA JAMIR,[2] KUMAR SATISH RAVI[3]
[1]Departments of Pediatrics, and
[2] Community and Family Medicine, AIIMS, Mangalagiri, Andhra Pradesh;
[3]Department of Anatomy, AIIMS, Rishikesh, Uttarakhand.
**babuarun@yahoo.com*

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Diet, Fluid Intake, Urine Output and Urinary Sodium/Potassium Ratios in Children With Urolithiasis

We performed a cross-sectional study on 25 children (17 boys) with urolithiasis with normal glomerular functions at a tertiary care teaching hospital between March, 2018 to March, 2019. Dietary assessment showed that caloric intake was below recommended dietary allowance (RDA) in 68% patients while the median protein intake was 34.3% more. The fluid intake was below the recommended standards in 56%, and 48% of the children had urine output below 1.5 mL/kg/hour. The urinary sodium was elevated in 96% of the children, urinary potassium was low in 40%, and hypercalciuria was seen in 28%. While metabolic causes predominate in childhood urolithiasis, other factors like dietary changes, liberal fluid and low sodium intake are advised for prevention of recurrences as they have a contributory role too.

Key words: *Dietary assessment, Nephrolithiasis, Salt intake*.
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Childhood urolithiasis constitutes about 2-3% of all stone formers. Metabolic causes play an important role and also increase the risk of recurrence; hypercalciuria and hypocitraturia being the commonest causes (present in almost 34-97%) [1,2]. A diet rich in carbohydrates and animal proteins has been associated with an increased risk of urolithiasis in predisposed individuals. On the other hand ingestion of fresh fruits and vegetables and low salt diet has a protective role [3].

A liberal fluid intake is often recommended for preventing stone recurrences and urine output is a good way of assessing intake in presence of normal glomerular functions. Dietary assessments for sodium and potassium intake are often cumbersome and use of urinary sodium and potassium excretion as a surrogate appears to correlate well [4].

This cross-sectional study was done at a tertiary care teaching hospital between March, 2018-March, 2019. All new confirmed cases of pediatric urolithiasis between 2-18 years and old cases of urolithiasis, where specific therapies had been stopped for two weeks prior to evaluation were included in the

study after obtaining consent; the study was approved by the institute's ethical committee. Children with underlying tubulopathies, chronic kidney disease (CKD) stages 3 or more or those with secondary causes of stones were excluded.

The primary objective of the study was to assess the dietary intake of macronutrients (carbohydrates, fats, proteins), micronutrients (sodium, potassium, calcium, phosphate, oxalates), fluid intake and 24-hour urinary volume in children (2-18 years) with urolithiasis with normal glomerular functions. The assessment of 24-hours urinary electrolytes including urinary sodium/potassium (Na/K) ratios was the secondary objective.

A total of 25 children (17 boys) were enrolled; baseline information like age of presentation, symptoms at diagnosis, family history of stones, site of urolithiasis were recorded and detailed examination was done. A dietary assessment was done under the guidance of a skilled pediatric dietician; data from three 24 hours dietary recalls (2 of weekdays and 3rd on weekend) was taken over a span of one month. Each dietary assessment lasted for approximately 30-45 minutes and an average of the three dietary intakes was recorded. A software programme DIETSOFT (National Institute of Nutrition Standards, ICMR-2017) based on Indian diets was used for calculation of dietary components. These values were compared to standard charts for RDA and percentage intake of macronutrients and micronutrients was calculated.

The European Food and Safety Authority recommends use of 24-hour recall method on two non-consecutive days as the preferred methodology for fluid intake assessment [5]. Hence a diary was provided to the enrolled patients to record their fluid intakes which included water and any other beverages. This was done on two non-consecutive days over a 1-month span and an average of the two was taken. The fluid intake among children was compared to the standards given by the British Dietic Association (BDA), in the absence of Indian standards [6]. During the same period, 24-hour urinary volume collections were done; samples were sent for estimation of sodium, potassium, calcium and creatinine.

The data was compiled in an Excel sheet and analyzed using the SPSS v 25 software. Chi square test, Student *t*-test or one way analysis of variance was applied for comparisons, and *P* values <0.05 were considered significant.

Of the 25 children enrolled, 15 (60%) were already on follow up while 10 (40%) were newly diagnosed with urolithiasis. The median (IQR) age of the onset of the symptoms and enrollment were 8 (6,10) and 9 (7.5,11) years, respectively. Positive family history of urolithiasis was present in 48%; past history of surgical intervention was present in 20%. Cause of stone was established in 11 (44%) patients; 7 (28%) had hypercalciuria, 8% had hyperoxaluria, and 4% each had uric acid and triple phosphate stones.

The dietary assessment showed that median caloric intake was below RDA in 68% while protein intake was 34.3% more. Intake of sodium was more than the RDA in 72%, potassium intake was lower in 96% and both calcium and phosphate intakes were below RDA in 72% children.

When compared to the recommendations for fluid intake given by the BDA-2017, 14 children (56%) had an inadequate intake, with a low urine output (<1.5 ml/kg/hour) in 48% children. Urinary electrolyte estimation showed that urinary sodium was elevated in 96%, of the children while urinary potassium was low in 40%. Mean urinary Na/K ratio was 3.69 and an elevated ratio was seen in 72% of the participants; hypercalciuria was seen in 28% with median 24-hr urinary calcium excretion of 3.2 (1.98,4.1) mg/kg/d. Details of urine output and electrolytes are provided in **Table I**.

There has been an increase in the overall incidence and prevalence of urolithiasis in the last few decades, possibly due to changing lifestyle and dietary habits; in developed countries partly attributed to high animal protein consumption (3-5 times higher than the RDA). The median sodium intake of our patients was 1,873 mg/day (33.1% above the RDA) and overall intake was high; children between 4-8 years had a higher intake. These values were more than those reported from a previous study from Pakistan [9]. Positive correlation was seen between urinary sodium excretion and sodium estimated by dietary intake (r = 0.35; r^2=0.12). The National Academy of Science (USA) has reported that sodium intake in children between 6-11 years of age has increased from just 200 mg in the 1970's to around 3000 mg in year 2000 [10]. Dietary sodium restriction is an important preventive measure for recurrence of urolithiasis, especially in children with hypercalciuria [11]. Also, a high proportion of our children (96%) did not meet the RDA for potassium intake.

Table I Dietary Assessment, Urine Output and Urinary Electrolytes of Children With Urolithrasis (*N*=25)

Variable	*Value*
Daily intake of macronutrients (%RDA)	
Calorie intake	-12.7 (-32.8, 5.85)
Protein intake	34.3 (10.1, 67.45)
Fat intake	11.4 (-1.15, 31.85)
Daily intake micronutrients (% RDA)	
Sodium	+33.1 (4.3, 66.7)
Potassium	-53.9 (-75.6, -32.3)
Calcium	-23.5 (-47.1, 1.25)
Phosphorus	-14.3 (-37.2, 29.1)
Mean urine output	
<1 mL/kg/h	2 (8)
1 - 1.5 mL/kg/h	10 (40)
>1.5 mL/kg/h	13 (52)
24-hr urinary electrolytes	
Na (mEq/d)	66.7 (44.5,106.5)
K (mEq/d)	22.5 (17.15,26.4)
Ca (mg/kg/d)	3.2 (1.98,4.1)
Mean urinary Na/K ratio[a]	
<1	2 (8)
1.1-2	5 (20)
>2	18 (72)

All values in median (IQR) or [a]*no. (%).*

Calcium intake in adequate amounts has a protective role in the prevention of urolithiasis by binding to dietary oxalates; 72% of our children had calcium intake below the RDA. Hypercalciuria was seen in 28% children in this study and has been been reported in 34-97% of pediatric urolithiasis patients [1,2,9].

Assessment of fluid intake showed that as many as 56% of the children did not meet the criteria for adequate fluid intake; three-fourth of those between 4-8 years had an inadequate fluid consumption. Stone formers have a lower urine output when compared to the general population. The average urine output observed amongst our patients was 1.9 mL/kg/hour; 48% showed a low urine output (<1.5 mL/kg/hour). In a previous study on 220 American and 180 Brazilian children showed that 63% of American and 49% Brazilian children had a urine output that was less than 1 mL/kg/hour [12]. The mean urinary Na/K ratio in the present study was 3.69 (>2 in 72%), the normal ratio being two [4]. Patients with a higher urinary Na/K ratio are at a greater risk of developing nephrolithiasis [13].

A limitation of this study was a small sample size and lack of a control group. However, a major strength of the study was that multiple records for diet and fluid assessments were taken rather than a single 24-hour dietary recall, which provided a more reliable snapshot of dietary intakes. Urinary sodium/ potassium spot ratio appears to be a useful simple tool to assess dietary intake of these minerals and could be done at regular intervals to check dietary compliance of nutritional advice. However, more studies are required in future to confirm these findings.

Ethics clearance: IEC; No.17/IEC/MAMC/2017/Peds/11 dated Oct 27, 2017.
Contributors: MM: conceptualized and designed the study, drafted the manuscript; DG: collected the data, compiled and analyzed it; RG: analyzed the data and drafted the manuscript; BM: supervised the laboratory tests and data analysis; MS: helped in conduct of the dietary interviews and counselling. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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MUKTA MANTAN,[1*] RUCHI GOEL,[1] DEEKSHA GUPTA,[1] BHAWNA MAHAJAN,[2] MONIKA SETHI[3]
Departments of [1]Pediatrics, [2]Biochemistry and [3]Dietics, Maulana Azad Medical College and associated Lok Nayak Hospital and Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, University of Delhi, New Delhi.
**muktamantan@hotmail.com*

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Favorable Outcome in Infants Hospitalized With COVID-19: Single Center Experience from Athens, Greece

This study aims to describe the clinical characteristics and outcome of 92 infants (aged <12 months) with community-acquired coronavirus disease 2019 (COVID-19) between March, 2020 and June, 2021 at a single center in Athens. Infants with COVID-19 developed mild disease (89, 96.7%), and were infected mostly by their household contacts (74, 80.4%). Disease complications were rare, indicating that hospitalization is the result of low threshold for admission rather than disease severity.

Keywords: *Community-acquired, Outcome, Hospitalization, Management, Severity.*

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Children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically have a milder and often asymptomatic course of illness [1]. Severe disease is rare and mortality is associated with existing comorbidities or disease complications such as the multisystem inflammatory syndrome (MIS-C) [2]. Coronavirus disease 2019 (COVID-19) in infants was a major concern when the disease was first described, in view of their immunological immaturity and close contact with household members infected with SARS-CoV-2 [2]. Reports indicate that 62% of children hospitalized with COVID-19 are <1 year of age, although it is not clear if this is related to disease severity or to a lower threshold for admission [3,4].

There are limited data on disease severity in infants with community-acquired COVID-19 and these largely come from case reports and small case series. The primary aim of this study was to describe disease characteristics, transmission and outcome of COVID-19 in infants. The secondary aim was to identify clinical or laboratory markers linked to disease severity.

This single-center medical record review was conducted for the period between March, 2020 and June, 2021 in infants (aged <12 months) admitted to a COVID-19 referral pediatric hospital in Athens, Greece, following a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. After clearance from the Institutional ethics committee, medical records of infants included in the study were reviewed for demographic, clinical and laboratory characteristics, and disease outcomes. Amplification cycle threshold (Ct) values were recorded, with lower values indicating a higher viral load. Ct cutoff for negativity was 35-40 cycles [5]. Contact tracing was performed by standard interview of parents for suspected COVID-19 symptoms, and reason and timing of PCR testing in any family member. The severity of COVID-19 was defined as asymptomatic, mild, moderate, severe and critical, according to the National Institutes of Health (NIH) classification [6].

Statistical analysis was performed using SPSS, version 25.0. Associations between infants' characteristics were evaluated with spearman's Rho correlation coefficient. *P*-value <0.05 was considered as statistical significant.

Overall, 92 previously healthy infants (56.5% boys) with mean (SD) age of 3.3 (3.1) months were admitted during the study period. Demographic and clinical characteristics of these infants are shown in **Table I**. The majority of the infants (89, 96.7%) had a mild illness. Three patients required supplemental oxygen administration, while only one developed moderate respiratory distress and required pediatric intensive care unit (PICU) admission for short course non-invasive ventilation.

Table I Characteristics of Infants With COVID-19 in Athens, Greece (2020-21) (*N*=92)

Characteristics	
Age at admission (mo)	3.3 (3.1)
Girls	40 (43.5)
History of COVID-19 exposure	74 (80.4)
Household COVID-19 case	74 (100)
Ct value	16.7 (5.3)
Symptoms and clinical findings	
Fever (>38ºC)	62 (67.4)
Low-grade fever (<38ºC)	33 (35.9)
Cough	20 (21.7)
Rhinitis	43 (46.7
Poor feeding	38 (41.3)
Gastrointestinal (vomiting, diarrhea)	25 (27.2)
Respiratory distress	3 (3.3)
Febrile seizures	1 (1.1)
Laboratory findings[a]	
White blood cells ($x10^3$/µL)	9429 (4139)
Neutrophil count ($x10^3$/µL)[b]	3088 (2280)
Lymphocyte count ($x10^3$/µL)	4862 (2527)
Neutrophil/Lymphocyte count	0.9 (0.9)
C-reactive protein (CRP) (mg/L)	7.9 (32.4)
Platelet count ($x10^3$µL)	373196 (127003)
Creatinine (mg/dL)	0.3 (0.1)
Alanine aminotransferase (ALT) (U/L)	30.8 (27.6)
Aspartate aminotransferase (AST) (U/L)	47.9 (26.9)
Abnormal chest radiograph	3 (3.3)
Disease severity[c]	
Mild	89 (96.7)
Severe	3 (3.3)
Treatment	
Antimicrobials	22 (24.2)
Corticosteroids	3 (3.3)
Remdesivir	2 (2.2)
Supplemental oxygen[d]	3 (3.3)
Non-invasive ventilation	1 (1.1)
No respiratory support	89 (96.7)
Outcome[e]	
Co-infection	2 (2.2)
Hospital stay (d)[a]	4.1 (1.9)
Pediatric intensive care unit (PICU) admission	1 (1.1)

Values in no. (%) or [a]mean (SD); [b]24 (26.1%) had neutropenia; [c]None had moderate or clinical disease; [d]No infant required invasive ventilation; [e]No infant developed any complications or died.

Mean (SD) Ct value was 16.7 (5.3), indicating high viral load. Two infants were diagnosed with concominant bacterial infection on admission (one with urinary tract infection and one with gastroenteritis caused by *Campylobacter* spp). Antimicrobials were administered in 22 (24.2%) of the infants and the majority of them (18, 81.2%) were infants <3 months old that were initially admitted with fever with no focus. Antibotics were given in these, pending culture results, with a median treatment duration of 3 days. Mean (SD) duration of hospitalization was 4.1 (1.9) days, and all infants had a favorable clinical outcome without complications. No infant to adult transmission was reported during hospitalization or during follow-up.

Results from a multivariate analysis identifying risk factors related to disease severity showed that higher Ct values (hence lower viral loads) were seen in older infants (P=0.01), and were associated with higher white blood cell (WBC) (P=0.04) and neutrophil count (P=0.3), as well as increased C-reactive protein (CRP) (P=0.005). There was no significant association between patient's age and days of hospitalization, and between Ct values and laboratory results with the duration of hospitalization.

There is now growing evidence that children, especially infants and toddlers, develop mostly asymptomatic or mild COVID-19 [1]. This may be due to the immunological characteristics of this age group, the physiology of their respiratory tract where ACE2 receptors are not abundant, and the interaction with seasonal coronaviruses in older children [7]. Also, despite recent evidence that children have comparable viral loads with adults [8] and that infants and toddlers may spread SARS-CoV-2 [9], the current study findings support the notion that infants can rarely be a primary case and possibly not a source case for other members of their households either.

This study has some limitations. Firstly, this is a retrospective, single-centre study. However, it represents the general population, as the hospital is one of the two COVID-19 referral pediatric hospitals in Athens. Secondly, in this cohort, there were only three infants with severe COVID-19 disease and all infants were previously healthy with no co-morbidities. Finally, the study period reflects the hospitalizations during the first and second COVID-19 wave, but not the period when the delta and omicron variant were dominant.

We can safely suggest that infants with COVID-19 can be treated at their home environment since hospitalization can lead to unecessary laboratory testing, parent-infant separation and increased risk for SARS-CoV-2 in-hospital transmission. It is of prime importance to deteremine the expected benefit of young child vaccination, and the number of adult cases prevented, especially when the vaccination coverage in other age groups is high. Studies on antibody kinetics and risk of reinfection from SARS-CoV-2 in this age group are under way and will further support decision-making.

Ethics clearance: Institutional ethics committee, 'P. and A. Kyriakou' Children's Hospital, Athens, Greece; No.4336, dated 9 March, 2021.
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DIMITRA DIMOPOULOU,[1*] MARIANTHI LIASKA,[1] IRINI ELEFTHERIOU,[1] ELENI KOURKOUNI,[2] MARIA TSOLIA,[1] NIKOS SPYRIDIS[1]
*[1]Second Department of Paediatrics, National and Kapodistrian University of Athens, School of Medicine, 'P. and A. Kyriakou' Children's Hospital, Athens, Greece; [2]Center for Clinical Epidemiology and Outcomes Research (CLEO), Non-Profit Civil Partnership, 5 Chatzigianni Mexi str.,11528 Athens, Greece. *dimi_med@hotmail.com*

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Hematochezia in a 36-Hour-Old Well-Appearing Infant

A term male newborn with birthweight of 3,460 g was fed breast milk at one hour after birth, and cow's milk protein-based infant formula at 24 hours. He was found to have visible blood in the stools at 36 hours. Examination revealed stable vital signs, no signs of peritonitis or organomegaly; but multiple large areas of port-wine stain at the left-sided abdominal wall, buttock and pelvic area including left thigh and lower leg. Abdominal radiography and complete blood counts were unremarkable. The physician introduced extensively hydrolyzed formula (EHF), which led to a disappearance of bloody stools in 24 hours. On the fourth day after birth, the infant had fresh blood and mucus in five small-volume bowel movements, although he remained well. Despite an exclusive EHF feeding, bloody stools persisted.

Initial investigations showed leukocytosis with absolute eosinophil count of 1.2×10^9/L, and normal hemoglobin, red blood cell indices, and platelet count. Coagulogram and abdominal radiography were unremarkable. Blood and stool cultures were negative after 48 hours. We decided to perform recto-sigmoidoscopy and found erythematous and slough mucosa with several scattered ulcers. Biopsy showed significant tissue eosinophilia including eosinophilic cryptitis and massive degranulation (**Fig. 1**). Magnetic resonance imaging revealed no gross intrabdominal arteriovenous or lymphatic malformation. After 72 hours of exclusive amino acid formula, bloody stools subsided. At 24 days after birth, breast milk was reintroduced after the mother's strict avoidance of dairy products. Atopic dermatitis on both cheeks was noted. The mother decided to withhold breastfeeding for another two weeks, and then resumed again without bloody stools or rash. He was switched to EHF and regular cow's milk at 15 and 18 months, respectively, which he tolerated well.

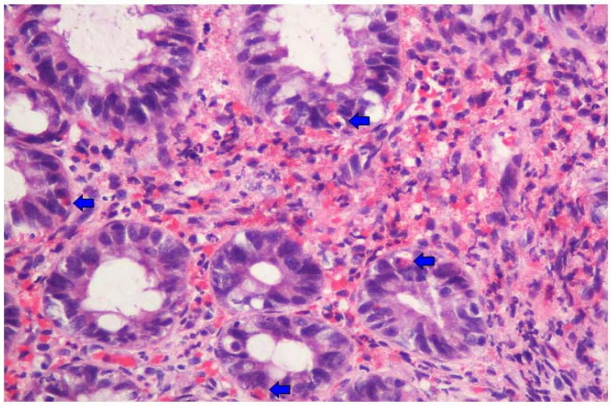

Fig. 1 Rectal biopsy showing prominent eosinophilic infiltrate with significant degranulation of eosinophils in the lamina propria and intraepithelial infiltration (arrows) (HE, 400X).

We made a dignosis of food protein-induced allergic proctocolitis (FPIAP), with the supportive evidence including: *i*) improvement after removal of dairy products in the lactating mother and change of cow's milk-protein infant formula to EHF; *ii*) data from endoscopy and histopathology suggestive of this condition; and, *iii*) tolerance developed at a young age. However, this case did not undergo an initial cow's milk challenge to confirm the diagnosis due to a high level of caregiver concern. Furthermore, we also performed MRI of the abdomen to rule out vascular malformation in the gastrointestinal tract that can also cause significant hema-tochezia, especially in an infant with multiple port-wine stains in the lower extremity. Kumar, et al. [1] reported three cases of full-term newborns that were introduced cow milk within the first hour after birth and presented with bloody stool at the age of 25-28 hours. Friable and edematous colonic mucosa with tissue eosinophilia in the lamina propria were also noted in all cases, which also improved after a switch to EHF [1]. Another series by Kaya, et al. [2], which included 60 patients, revealed that the youngest age of onset of FPIAP was seven days. We believe that cow milk protein in the breast milk of lactating mother may induce symptoms in the newborn during the first week of life. Matangkasombut, et al. [3] demonstrated that beta-lactoglobulin can be detected in breast milk up to seven days after cow milk ingestion. Faber, et al. [4] reported a preterm newborn with a proposed diagnosis of FPIAP that responded well to a switch to amino acid formula. However, we believed that the switch from EHF to amino acid formula in our case may be quite premature, as per the recently established protocols [5]. Studies hypothesized that early development of lower gastrointestinal bleeding derives from in utero food-antigen sensitization, which is likely caused by the passage of IgG across placenta during the third trimester [6].

FPIAP can occur shortly after birth and should be in the differential diagnosis of a newborn presenting with bloody stools. Histopathological finding of tissue eosinophils in the rectosigmoid biopsy may provide useful data. Appropriate dietary avoidance of the triggering antigen with a proper wait-and-see duration is the mainstay management of this condition.

JIRACHART PHROMMAS, PORNTHEP TANPOWPONG,*
CHATMANEE LERTUDOMPHONWANIT
Division of Gastroenterology, Department of Paediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.
**pornthep.tan@mahidol.ac.th*

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Juvenile Dermatomyositis With Macrophage Activation and Severe Encephalopathy

Central Nervous System (CNS) involvement is rarely reported, and is possibly an under-recognized feature in juvenile onset inflammatory myositis. We report a 11-years-old boy with juvenile dermatomyositis (JDM) who was initiated on steroid and methotrexate but developed macrophage activation syndrome (MAS). He recovered from MAS but continued to have persistent severe CNS disease.

An 11-year-old boy presented with 3 weeks history of weakness of both upper and lower limbs, difficulty in swallowing, speaking and mild periorbital swelling with reddish discoloration around the eyes suggestive of heliotrope rash. Investigations showed elevated muscle enzymes, characteristic muscle edema on magnetic resonance imaging (MRI) and electromyography revealed a myopathic pattern in both lower limbs. Myositis specific antibody profile (anti Jo-1, anti TIF1 gamma, anti NXP2, anti MDA5) was sent but values were within normal range. The child was diagnosed with definite JDM as per EULAR/ACR criteria with a total aggregate score of 7.5, and he was initiated on intravenous methylprednisolone at 30 mg/kg/day for 3 days followed by oral prednisolone (2 mg/kg/day) and weekly subcutaneous methotrexate (15 mg/m^2).

Within a week of completing pulse methylprednisolone, he developed shallow respirations due to respiratory muscle weakness, with profuse mucosal bleeding from the oral cavity and progressive drowsiness. He was transferred to the pediatric intensive care unit (PICU); intubated and ventilated. Investigations showed pancytopenia with high serum ferritin (4059 ng/mL) suggestive of MAS. Methotrexate was stopped; pulse doses of methylprednisolone 30 mg/kg/day were restarted and a single dose of 10 g of intravenous immunoglobulin (IVIg) was given. As child did not improve after 3 days of pulse methylpredni-solone; oral cyclosporine (4 mg/kg/day) was added. Over the next 3 days, blood counts improved with lowering of ferritin level (1800 ng/mL). On the day-10 of PICU admission, he started having refractory generalized seizures which were controlled by antiepileptics. MRI brain showed acute ischemic lesions in bilateral parieto-occipital, right posterior temporal and left hippocampal region and features of posterior reversible encephalopathy syndrome (**Fig. 1**). Tracheostomy was done in view of need for prolonged intubation. He recovered from MAS but later developed fever; bronchoalevolar lavage culture grew *Stenotrophomonas maltophilia*, for which appropriate antibiotics were started and cyclosporine was stopped.

Over the subsequent 4 weeks, fever subsided but he remained drowsy with episodic abnormal limb movements. Repeat MRI brain showed extensive brain atrophy with multiple white matter hyperintensities in bilateral frontal regions. Since, he continued to have persistent mucosal bleeds with normal coagulation studies and blood counts, vasculopathy was consi-dered as the possible etiology and the persistent encephalopathy in the absence of any other explanation was ascribed to underlying CNS vasculopathy. MR angiography of cerebral arteries showed no obvious abnormality. CSF examination was not done in view of poor general condition.

Considering CNS vasculopathy, four pulses of cyclophosphamide (750 mg/m^2) were started monthly and two doses of rituximab, (750 mg/m^2) at 15 days interval. With gradual improvement, we started tapering the prednisolone dosage and the tracheostomy tube could be removed after 3 months. After five months of hospitalization, he was discharged and remains stable and ambulatory on tapering doses of prednisolone.

No data is available regarding the incidence of MAS and CNS vasculopathy in JDM. Ramanan, et al. [3] reported two children with JDM who later developed CNS manifestations, and were diagnosed to have a possible cerebral vasculopathy. One child

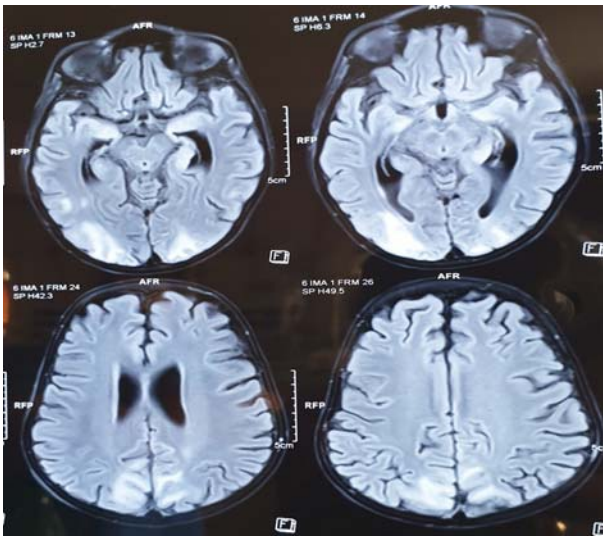

Fig. 1 Axial flair plain MRI brain showing white matter hyperintensities involving bilateral parieto-oocipital and inferiomedial temporal lobes suggestive of ischemia.

succumbed with MRI suggestive of hyperintensiles in thalamus and basal ganglia, the other responded to aggressive immunotherapy without any complications.

Elizabeth, et al. [4] reported three cases of JDM who developed generalized tonic clonic seizures two weeks after the initiation of immunosuppressive therapy. Out of the three, two patients had cerebral vasculopathy showing prominent fontal blood vessels on CT angiogram. One patient had assymetric perfusions in both hemispheres whereas the other had multiple infarctions in MRI brain.

The vascular pathology in JDM is not a true vasculitis. It is limited to small arterioles and capillaries demonstrating fibrinoid necrosis on biopsy. Seizures in JDM can be due to vasculopathy, true cerebral vasculitis of small to medium sized vessels, hypoxic ischemic encephalopathy, hypertensive encephalopathy, cyclosporine induced encephalopathy or secondary infections. In our child, the cause of seizures was attributable to CNS vasculopathy as supported by MRI changes. Although MR angiography provides supportive evidence of CNS vasculopathy, but it has a low diagnostic detection rate [2]. Hence MRI angiogram being normal in our case does not rule out the possibility of CNS vasculopathy. Though biopsy is the gold standard, but considering the patient's moribund condition, it was not done.

Most centers treat severe JDM initiate treatment using a combination of IV methylprednisolone and methotrexate, with addition of IVIg. However, treatment of refractory disease remains controversial with limited reports on the use of cyclophosphamide [5], and rituximab [6]. Our patient was steroid and IVIg refractory, and finally showed response to a combination of cyclophosphamide pulses along with rituximab, and remains asymptomatic on follow up.

HARSHITA JAGWANI, ANURAG MONDAL, PRIYANKAR PAL*
Department of Pediatrics,
Institute of Child Health, Kolkata.
**mailme.priyankar@gmail.com*

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Congenital Neuronal Ceroid Lipofuscinosis: An Important Cause of Unexplained Seizures in Newborns

Neuronal ceroid lipofuscinoses (NCL or CLN) are the largest group of neurodegenerative diseases in childhood. The overall incidence is 1 in 12,500 live births [1]. There are 13 known types (CLN 1-13) based on age of onset and genetic mutation involved. Among these, CLN type 10 can present as neonatal or juvenile phenotype. It is caused by homozygous or compound heterozygous mutation in the *Cathepsin D* gene (*CTSD*) on chromosome 11p15. Neonatal onset phenotype is rare and has a poor outcome with rapid deterioration. We report a case of neonatal onset CLN 10.

A male baby delivered vaginally at 34-36 weeks of gestation, birth weight of 2200 g, was well till day 26 of life when he developed seizures, lethargy and breathing difficulty. There was history of third degree consanguinity and the previous sibling had microcephaly, who had died at day 15 of life with similar complaints. On examination, our patient was lethargic with dysmorphic facies, microcephaly (head circumference 29 cm) and hepatosplenomegaly. Sepsis workup was normal. The seizures were refractory to multiple antiepileptic drugs like phenobarbitone, phenytoin, leveteracitam, clonazepam and pyridoxine. Arterial blood gas, serum ammonia, uric acid and EEG were normal. Fundus revealed a cherry red spot. Lysosomal storage disease panel (Gauchers, Neimann-Pick type A and B, Krabbe, Pompe, Hurler, Fabry) was sent, which was non-contributory. MRI brain showed cerebral and cerebellar atrophy with diffuse, thinning of cerebral cortex, shallow sulcal spaces suggestive of microcephaly, with simplified gyral pattern. Whole exome sequencing (WES) showed a missense variant NM_001909.5 (*CTSD*-Catepsin D gene):c.299C>T (p.Ser100Phe) causing amino acid substitution from serine to phenylalanine at codon 100 in exon 3 of the *CTSD* gene. The diagnosis of NCL type 10 was made. According to the American College of Medical Genetics and Genomics (ACMG) classification, this mutation was a likely pathogenic variant. The patient was discharged but succumbed to seizures on day 80 day of life. Genetic counseling was offered to the family for subsequent pregnancies.

Till date, five cases of neonatal onset phenotype of CLN 10 with microcephaly have been reported. Three babies carried homozygous mutations in *cathepsin D*, a gene coding for a lysosomal aspartic protease and succumbed within first 10 days of life. Some affected babies also had intrauterine seizures that were not present in the index case. CLN 10 should be kept as a differential diagnosis in neonates with seizures and microcephaly

[2]. The index case and his siblings, both had microcephaly. Two neonates (brother and sister) with CLN 10 presenting with intractable seizures after birth have been similarly reported [3]. A female baby with CLN 10 presented with severe microcephaly and hypertonia, with MRI showing generalized hypoplasia of the cerebral and cerebellar hemispheres and expired on day 2 of life [4]. Postmortem examination revealed a small, firm brain with extensive neuronal loss and gliosis and an identical mutation as the index case. Another term infant with microcephaly, and status epilepticus, who died 36 hours later, is described [5]. At autopsy, atrophic brain with microscopic changes consistent with NCL were reported [5].

To conclude, NCL should be suspected in newborns and infants presenting with unexplained microcephaly and intractable seizures with radiological features of cerebral and cerebellar atrophy. Genetic work up and counseling helps to offer prenatal diagnosis.

SHALINI TRIPATHI,* SMRATI JAIN, MALA KUMAR
Department of Pediatrics, King George's Medical University, Lucknow, Uttar Pradesh.
**shaliniawasthi@kgmcindia.edu*

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Is Cystic Fibrosis Contributing Significantly to Infant Mortality Rate in India?

Cystic fibrosis is a life-limiting, genetic disease. Over the last 80 years, predicted life expectancy of affected individuals has improved from less than one year to the fifth decade of life, largely due to early initiation of aggressive supportive treatment [1]. In India, diagnosis of cystic fibrosis is made at an average age of 4.5 to 6.5 years and is associated with high mortality in childhood [2-4].

Over the last decade, at a tertiary care center in southern India, blood samples for *CFTR* mutation analysis were stored, with the permission of the parents after genetic counseling, for all critically ill young infant in the PICU with a presumptive diagnosis.

In this retrospective study, we reviewed the mortality data of young infants between 1 and 6 months of age during 3.5 years period from July, 2018. Institutional review board approval was obtained. There were total 81 young infant deaths. The diagnosis of cystic fibrosis was confirmed posthumously in six infants (mean age 3.7 month) by *CFTR* mutation analysis on stored blood. The clinical diagnosis at the time of death were severe community-acquired pneumonia in five and intracranial bleed in the sixth baby. Notably, all had failure to thrive, anemia (mean hemoglobin 6.9 g/dL, range 4.7-10.6g/dL) and hypo-albuminemia (mean serum albumin 1.9 g/dL, range 1.5 - 2.9g/dL). During the study period, cystic fibrosis was found to be the fourth most common cause of death in this age group, after cardiac disease (48%), pneumonia/sepsis (25%) and other congenital conditions (19%).

We believe, that these undiagnosed cystic fibrosis cases may be contributing to the infant mortality, especially in tertiary care centers located in geographic areas where *CFTR* mutation carrier frequency is high and endogamous marriages are practiced. Infant deaths due to cystic fibrosis can be prevented with timely genetic counseling, early diagnosis and initiation of supportive treatment. Accurate data on incidence and genetic profile of cystic fibrosis in India need to be generated to understand the true burden of this disease and the related infant mortality.

Pediatricians in India should have high index of suspicion for cystic fibrosis clinically. It should be suspected if there are two or more features of recurrent pneumonia, oily stools, history of consanguinity, history of sibling death, hypochloremic hypo-kalemic metabolic alkalosis and isolation of pseudomonas from respiratory specimens. With a presumptive diagnosis of cystic fibrosis, treatment can be started even without sweat chloride or genetic tests and confirmation may be done when feasible.

SNEHA VARKKI,* EBOR JACOB G JAMES
Department of Pediatrics,
Christian Medical College,
Vellore, Tamil Nadu.
**cfcare@cmcvellore.ac.in*

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Referencing Made Easy: Handling Reference Management Softwares

As a long-time user of the Zotero reference management system, I read with interest the recent article on reference management softwares [1]. I consider reference management systems (RMS) to be one of the most useful tools that have been brought for writers in the last two decades. Developments in the RMS field have been quite dynamic in recent years and therefore, I would like to underscore additional points regarding them.

The authors stated in Table I that Zotero does not allow reference sharing. I have been using groups in Zotero (*https://www.zotero.org/groups/)* for reference sharing for many years. Second, the authors stated that users of other RMS than Endnote, Mendeley and Citavi cannot use annotations as sticky notes and highlight texts in PDFs directly in RMS. This feature has been added to Zotero since version 6 was released in 2021 (*https://www.zotero.org/blog/zotero-6/*).

The authors have also stated that each author needs to meet the specific citation requirements of the journal. It is worth noting that many journals and international publishers do not

require strict formatting manuscripts and references by authors in the spirit of "Your Paper, Your Way" [2]. It may be mentioned that RMS can be used by editorial office to format references in manuscripts according to journal's requirements and authors do not need to meet journal's requirements when submitting a manuscript [3].

I would also like to comment on the CSL language mentioned in the paper. The CSL is a universal language and several dozen RMS use it for formatting citations and bibliography (*https://citationstyles.org/*). In contrast, other RMS use other (custom) style editors to format citations and bibliography. I consider the main advantage of RMS that use CSL is the support from the community, which has been able to add missing citation styles to the style repository in a short time since request by researchers (*https://github.com/citation-style-language/styles/blob/master/REQUESTING.md*). Thus, researchers do not have to learn to use the style editor function of the RMS to create bibliography in the missing format.

In the end, RMS is a powerful tool. However, there is no "the best" RMS because every RMS has its own strengths and weaknesses. Just like each of us has different working habits and everyone has different needs. Articles comparing different RMS, which can be found in the literature, are great for pre-selecting suitable RMS, but they are no substitute for personal experience. Therefore, I encourage everyone to try several RMS and after that he/she chooses the best one that suits them personally or the work team they work with.

LIBOR ANSORGE
Výzkumný ústav vodohospodárský TG Masaryka, Podbabská 2582/30, 16000 Praha 6, Czech Republic.
libor.ansorge@vuv.cz

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AUTHOR'S REPLY

We thank the reader for interest in our article and thank them for pointing out the updates in the reference management softwares (RMS). We also agree with the statement that since every single RMS has unique advantages and disadvantages, each user must find the RMS that best suits their needs [1].

We acknowledge their point regarding Table I. Zotero does allow for creation of groups (private; public, closed and public, open). Once a group is created and members invited, the Group folder appears in each member's Zotero (the software on their computer). Each member may add content to the shared folder, then sync. However it is important to note that group libraries are wholly separate from 'My Library' section on Zotero, and items may need to be dragged and dropped in the appropriate sections, if the permissions of the groups allow it [2,3].

It was interesting to know that Zotero 6, in its latest update has added many new tools which allow the user to open PDFs in a new built-in reader within the main Zotero window (in a new tabbed interface), allow them to mark up PDFs with highlights, notes, and image annotations, and allow addition of annotations to Zotero notes with automatic citations. It also allows for non-English spell checking [4[.

We agree some international/Indian journals do allow authors to submit their articles without meeting stringent formatting norms, atleast for the first draft, enabling them to primarily focus on the content and also increasing submission rates to journals. This was adopted primarily under the 'your paper, your way initiative' and currently many journals (mostly Elsevier) allow format free submissions [5,6]. But still, many Indian and international journals are very particular about submission being in a particular style and format, with articles being sent back at the initial stage.

We agree that most well established RMS have a huge support community, which keep on adding missing reference styles. But in some cases, the authors may not find the style that matches specific journal requirements (where they intend to submit). In such cases, knowing the style editor function may help bridge the gap.

ROMIT SAXENA,[1]* JAYA SHANKAR KAUSHIK[2]
From Departments of Pediatrics , [1]Maulana Azad Medical College and associated LN Hospital, New Delhi; and [2]AIIMS, Guwahati, Assam.
**drromit@gmail.com*

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Monkeypox Disease Outbreak (2022): Correspondence

We would like to put forth our views on monkeypox disease, in the light of the recent article by Lahariya, et al. [1].

First, the precise nature of the issue is yet unclear. The illness was formerly exclusive to Africa. It is still unclear how the illness spreads to become a new emergent disease in Europe, America, and Asia. The propagation of zoonotic diseases is verified in Africa, but the new situation outside of Africa in 2022 may or may not be tied to animals [2]. The newly imported animal could provide a problem, but the precise epidemiological pattern in instances outside of Africa at the moment is unclear. Additionally, the condition may be diagnosed as an acute febrile illness with rash, albeit it may also present otherwise. Only atypical manifestations in some patients, like diarrhea and dysphagia, are possible [3,4]. As a result, the practitioner must be aware of the potential for atypical clinical characteristics in monkeypox.

The term 'prevention' is frequently invoked, but the question is "how to prevent?" It may be difficult to handle the issue because the specific pathophysiological process of transmission of the 2022 monkeypox is still unknown. It has to be seen whether there is a genetic variant problem that is causing the outbreak.

At the moment, prevention should be based on universal principles that include both human and animal contact as a single health concept [5]. The problem of recycling smallpox vaccine to prevent sickness has been thoroughly researched, and expert consensus is essential. Since sickness progresses, we should advance to prepare for any potential crises, just as we did for the coronavirus disease 2019 (COVID-19).

RUJITTIKA MUNGMUNPUNTIPANTIP,[1*] VIROJ WIWANITKIT[2]
[1]Private Academic Consultant, Bangkok, Thailand;
[2]Dr DY Patil University, Pune, India.
**rujittika@gmail.com*

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AUTHORS' REPLY

We thank authors of this correspondence for their observations [1]; however, we do not agree with some of the observations.

Our paper; although, about monkeypox disease and outbreak [2], also raises broader issues on emerging and zoonotic diseases. We do not fully agree with the authors of the correspondence that ''the precise nature of the issue is not clear [1].'' Though there is need for better understanding; the monkeypox disease has been known for more than five decades and there is enough scientific understanding to act and take measures. It is just that the disease was never given due priority in global health, which reflects the challenge of global health inequities [3].

The authors of correspondence suggest that atypical presentation is a possibility and should be given importance. Though the idea of atypical presentation is worth exploring; in settings where there are only a few cases, it may put undue burden on the health system and may also result in unnecessary panic amongst citizens. Nonetheless, the medical and scientific community should epidemiologically analyze the emerging data and document the atypical presentations for informed decision making.

In case of emergence and re-emergence of diseases, prevention must be one of the key strategies along with preparedness and response, and stronger disease surveillance etc. The pathophysiology of monkeypox has been known for a long time and there is no evidence to assume that the 2022 outbreak situation is different in terms of pathophysiology. Understandably, there is need for continuous research and additional epidemiological analysis, supported by data collection, not only for monkeypox disease but for all emerging and re-emerging diseases; the neglected tropical diseases and many other infectious diseases which largely affect low- and middle-income countries.

Specifically, the zoonotic diseases are increasingly becoming a major public health problem and potential threats. In the last five decades, around 1,500 pathogens have emerged, most having jumped from animals to humans. Between 1940 and 2004, nearly 330 diseases had emerged, of which nearly 200 were zoonotic in origin and of these, 70 percent were from wildlife [4,5]. A recent study has projected that with an estimated rise in Earth's temperature by 2°C in the next fifty years, by 2070, people could be exposed to about 10,000 to 15,000 new pathogens previously confined to wild animals and forests. This could result in a 4,000 times likelihood of cross-species transmission. Since a majority of these microbes will be new with no prior immunity in people, it will increase the likelihood of disease spread and epidemics [6]

In this backdrop, the stronger implementation of international health regulations (IHR) 2005 and enhanced outbreak, epidemic and pandemic preparedness, and response readiness, should be the priority of every country. It is also the time for a renewed attention on 'One health' approach more than ever and act upon to improve animal, environment, and human health.

CHANDRAKANT LAHARIYA,[1*] ARCHANA THAKUR,[1] NONITA DUDEJA[1,2]
[1]Foundation for People-Centric Health Systems; New Delhi
[2]Human Capital Lighthouse (Consulting) Pvt Ltd, New Delhi.
**c.lahariya@gmail.com*

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NEWS IN BRIEF

Inexpensive Rapid Diagnosis of HCV

In 2016, WHO decided to eliminate viral hepatitis as a public health threat by 2030, by setting the targets to reduce the new chronic infections by 90% and HCV mortality by 65%. With the availability of directly acting antivirals (DAA) pan-genotypic treatment regimens this seems to be an achievable target, but still the limited availability of time consuming expensive diagnostic tests is a big hurdle to be crossed. Recently, a team from Florida Atlantic University, USA developed a reverse-transcription loop-mediated isothermal amplification (RT-LAMP)-based diagnostic test for rapid detection of hepatitis C virus infection. All the steps required for the detection of HCV - nucleic acid isolation, purification, amplification, and detection are incorporated in a small microfluidic chip. Results are based on colorimetric method, which can be detected by naked eye, and are available in 45 minutes only. The best part of this chip is that it is inexpensive, disposable, fully self-driven, does not require any trained manpower, with a sensitivity to detect ~500 viral copies/mL. Features like low cost, and automated accurate results make this an ideal test to be considered for HCV diagnosis in low- and middle income countries, which need mass screening to achieve the targets set by WHO for 2030. *(Biosensors 5 May, 2022)*

Telomere Length an Indicator of Hypertension

Telomere is the segment of nucleoprotein complexes situated at the end of each chromosome, consists of repetitive sequences of DNA. Telomeres decides the maximum life span of a cell, as during each division a part of telomere is lost and shortening of the length of telomere beyond a certain point prevents further division and the cell dies. Thus, the length of telomere at a particular point is biological indicator of age of the cell. The length of telomere (TL) at birth is variable and to some extent it can predicts the later life TL. Many of the antenatal and perinatal factors are known to play an important role in the development of adult onset diseases. Cardiovascular diseases is one such group, which may be related to the biological cell aging. Studies have shown a relation between the telomere length and cardio-vascular disease and mortality in adults. In a recent study from Belgium, researchers studied the association of newborn telomere length with the early life blood pressures in a prospective birth cohort of 485 newborns with a mean follow up of 4.6 years. The results of collected data showed that a 1-IQR increase in cord blood TL was associated with lower diastolic blood pressure (-1.54 mmHg; 95% CI -2.36 to -0.72), lower mean arterial pressure (-1.18 mmHg; 95% CI -1.89 to -0.46), and lower odds of having high BP at 4 to 6 years age (aOR 0.72; 95% CI 0.53 to 0.98). Thus indicating the role of TL in the onset of the cardiovascular health at birth. *(JAMA Network Open 05 August 2022)*

Injury Pain Management in Children

Early life experiences by a developing brain form the foundation of the beliefs and behavior during the adulthood, especially in reference to the injury pain. Studies have shown that childhood pain experiences can be modulated by multiple factors like response of parent/caregiver, relationship with peers/siblings, associated events, and social and environmental factors. Teaching the children, "How to handle everyday pain" at a young age helps them in better understanding and handling of pain as a grown up. In order to identify the key messages to be used by the parents while talking with children about everyday pain, in order to promote recovery and adaptive pain behaviors, a Delphi survey was done by the University of South Australia. Pediatric pain specialists, child psychologists, development experts, educators and parents were part of the team. The expert consensus was achieved that caregivers must teach the children about the relation between injury and pain, reassuring them after injury, body's healing mechanism, supporting child's emotions by letting them express themselves, by involving the child in first-aid care of self and others. According to the experts, these message when delivered effectively may be helpful in promoting adaptive pain behavior, and decreases the risk of development of pain problems in later life. (*European Journal of Pain 13 July, 2022)*

Oral Lactase - Treatment of Infantile Colic

Infantile colic is one of the common complaints encountered by the pediatricians in outpatient department. According to ROME IV criteria, it is characterized by recurrent and prolonged episodes of irritability, crying, or fussing in an infant aged <5months without an identifiable cause. Persistent crying of the child with no relief make the caregiver feel insecure about their nurturing skills. In the past, multiple treatment options like use of pain relieving agents, dietary modifications, parent training program, and the probiotics for infantile colic were tried but of no help. Systematic reviews assessing the role of probiotics in treatment of infantile colic showed some promise, but another review with larger number of participants did not reported similar results. In a recent study, the researchers evaluated the role of oral lactase in the management of infantile colic. This was a randomized, double-blind, placebo-controlled trial involving 162 infants, allocated into two groups receiving either 5 drops of oral lactase (80 infants) or placebo (82 infants) in the milk for a duration of four weeks. The findings showed a significantly lower number of days with colic in the infants receiving lactase compared to those receiving placebo (12.1 (7.8) vs 17.6 (8.4); $P<0.001$), and the parental satisfaction was also better in the lactase receiving group at the end of 4th week. The results of this study provide promising results for the treatment of a condition with no definitive treatment. *(BMC Pediatrics 3 August, 2022)*

RAJESH KUMAR MEENA
raj.mamc@gmail.com

Children with acute hepatitis and human adenovirus infection (N Engl J Med. 2022 Jul 13)

Human adenoviruses typically cause self-limited respiratory, gastrointestinal, and conjunctival infections in healthy children. In late 2021 and early 2022, several previously healthy children were identified with acute hepatitis and human adenovirus viremia. In this series 9 children who had hepatitis without a known cause were identified, of which 8 (89%) tested positive for human adenovirus. These 8 patients plus one additional patient referred to their facility for follow-up were included in this case series (median age, 2 years 11 months). Liver biopsies indicated mild-to-moderate active hepatitis in 6 children, some with and some without cholestasis, but did not show evidence of human adenovirus on immunohistochemical examination. PCR testing of liver tissue for human adenovirus was positive in 3 children (50%). Sequencing of specimens from 5 children showed three distinct human adenovirus type 41 exon variants. Two children underwent liver transplantation; all others recovered with supportive care. The authors concluded that human adenovirus viremia was present in the majority of children with acute hepatitis of unknown cause, but whether human adenovirus was causative remains unclear. Sequencing results suggest that if human adenovirus was causative, this was not an outbreak driven by a single strain.

Effect of three days of oral azithromycin on young children with acute diarrhea in low-resource settings (JAMA Netw Open. 2021;4:e2136726)

World Health Organization (WHO) guidelines do not recommend routine antibiotic use for children with acute watery diarrhea. However, recent studies suggest that a significant proportion of such episodes have a bacterial cause and are associated with mortality. This multicentric, randomized, double-blind, clinical trial was conducted to determine whether the addition of azithromycin to standard case management of acute non-bloody watery diarrhea for children aged 2 to 23 months who are dehydrated or undernourished could reduce mortality. A total of 8266 children (4463 boys [54.0%]; mean [SD] age, 11.6 [5.3] months) were randomized to receive either oral azithromycin, 10 mg/kg, or placebo once daily for 3 days in addition to standard management. A total of 20 of 4133 children in the azithromycin group (0.5%) and 28 of 4135 children in the placebo group (0.7%) died (relative risk, 0.72; 95% CI, 0.40-1.27). The study did not detect a survival benefit for children from the addition of azithromycin to standard WHO case management of acute watery diarrhea in low-resource settings. Therefore, expansion of antibiotic use is not warranted in low-resource settings.

Effect of open-label placebo on children and adolescents with functional abdominal pain or irritable bowel syndrome (JAMA Pediatr. 2022;176:349-56)

Although, it is widely believed that concealment is required to elicit a placebo response, recent studies with adults suggest that open-label placebo (OLP) can yield significant benefits. This multi-center crossover randomized clinical trial evaluated the efficacy of OLP for the treatment of children and adolescents with functional abdominal pain or irritable bowel syndrome. Thirty patients [mean (SD) age, 14.1 (3.4) years; 24 female participants (80%)] completed the study. The mean (SD) pain scores were significantly lower during OLP treatment compared with the control period [39.9 (18.9) vs 45.0 (14.7); difference, 5.2; 95% CI, 0.2-10.1; P =0.03)]. The authors concluded that open-label placebo may be an effective treatment for children and adolescents with functional abdominal pain or irritable bowel syndrome.

Clinically meaningful BMI change impacts pediatric non-alcoholic fatty liver disease (J Pediatr. 2022. S0022-3476(22)00623-0)

In this retrospective single center study, the authors investigated the prevalence and characteristics of children with non-alcoholic fatty liver disease (NAFLD) who reduce their body mass index (BMI) *z*-score (BMIz) by >-0.25, a goal reached for in obesity medicine, and to determine the BMIz decrease needed for serum aminotransferase normalization. Of the 784 children that met study criteria (median age 13 years, 66% male, 24% Hispanic), 168 (31%) changed their BMIz>-0.25 from baseline over a median 367 days (IQR: 201-678). Decreases in serum aminotransferase and lipid levels were seen in both groups (with/without BMIz change>-0.25); however, these were more pronounced in children who achieved BMIz drop>-0.25. The BMIz decrease associated with an ALT normalization was 0.27. The authors concluded that a BMIz reduction of >-0.25 is associated with significant changes in serum aminotransferase levels. These findings can further guide the clinical management of children with NAFLD.

Odevixibat treatment in progressive familial intrahepatic cholestasis (Lancet Gastroenterol Hepatol. 2022:S2468-1253(22)00093-0.)

Progressive familial intrahepatic cholestasis (PFIC) is a group of inherited pediatric liver diseases resulting from mutations in genes that impact bile secretion. In this study, the authors evaluated the effects of Odevixibat, an ileal bile acid transporter inhibitor, versus placebo in children with PFIC. Patients eligible for this 24-week, randomized, double-blind, phase 3 study were pediatric outpatients diagnosed with PFIC1 or PFIC2 who had pruritus and elevated serum bile acids at screening. Sixty-two patients (median age 3·2 [range 0·5-15·9] years) were randomly allocated to placebo (n=20), odevixibat 40 µg/kg per day (n=23), or odevixibat 120 µg/kg per day (n=19). It was found that odevixibat effectively reduced pruritus and serum bile acids versus placebo and was generally well tolerated. Odevixibat, administered as once a day oral capsules, is a non-surgical, pharmacological option to interrupt the enterohepatic circulation in patients with PFIC.

RISHI KUMAR BOLIA
rishibolia@yahoo.co.in

Institute of Child Health, Kolkata, 1956-2022

APURBA GHOSH,[1] SURUPA BASU,[2] RITABRATA KUNDU[1]

From the Departments of [1]Pediatrics and [2]Pediatric Biochemistry, Institute of Child Health, Kolkata, West Bengal.
Correspondence to: Dr Surupa Basu, 11, Dr Biresh Guha Street, Kolkata 700 017, West Bengal. basusurupa@gmail.com

Institute of Child Health, Kolkata is an iconic pediatric institution of India, which had its inception as one of the first pediatric hospital of the country. Pediatrics, as a separate branch of medicine, different from the principles and practices of adult medicine, was conceptualized and materialized in India by the founder of this institution, who is referred to as one of the Father of Indian Pediatrics, Dr. Kshirode Chandra Chaudhuri. This article portrays the journey of ICH, the popular acronym of the famed Institute, through the last seven decades from 1956 till the present, trying to capture the initial years of its establishment in the late 1950s, followed by its gradual evolution to an institution of central importance in pediatric healthcare, medical education, research and development, and service to the society, particularly in Eastern India.

Pediatrics – as a branch of medicine- was conceptualized in Bengal in India. This was realized by Dr. KC Chaudhuri in Calcutta (now, Kolkata). The movement was promoted by Dr. ST Achar in Madras (now, Chennai) and Dr. G Coelho in Bombay (now, Mumbai) in the early 1950s-60s [1].

THE BEGINNING: 1956-1957

Laying the Foundation of Pediatrics in India

Dr. Kshirode Chandra Chaudhuri, the founder of Institute of Child Health, Kolkata, had been a pioneer and visionary in the truest sense (**Fig. 1**). His experiences in Vienna and Tubingen as a post graduate student of pediatrics motivated him to build a similar institution in India, which would be solely dedicated to the holistic care of children, as well as to introduce teaching of pediatrics as a separate subject of medicine. While these thoughts were maturing, Dr. Chaudhuri founded the *Indian Journal of Pediatrics*, the first pediatric journal in India, in October, 1933, which brought Indian pediatricians in contact with pediatric research from the outside world [2].

Dr. Chaudhuri founded the first Pediatric Society in Calcutta in 1948 and became its first President. The Society worked for the comprehensive advancement of pediatrics and promotion of scientific collaboration amongst its members. In 1950, at the All India Pediatric Conference in Calcutta, a resolution was adopted to establish four Institutes of Child Health in India – Calcutta, Bombay, Madras and Delhi. In May, 1953, the Institute of Child Health Trust with Justice PB Chakrabarty as president and Dr. KC Chaudhuri as secretary, and eighteen founder members, was formed with the objective of establishing an Institute of Child Health in Calcutta [2,3].

With the help of donations by philanthropists, including even marginalized population residing in remote villages, with subsequent donation of land by Corporation of Calcutta, and grants from Ministry of Rehabilitation, West Bengal government, this Institute was born in 1956. The college section was inaugurated on the first of July, 1956 by eminent historian and educationist, Sir Jadu Nath Sarkar. In less than a year's time, the hospital's outpatient department was attended by over 100 young patients each day. The University of Calcutta recognized the Institute as a postgraduate medical college for higher studies in pediatrics. The first batch of fifteen medical graduates was admitted for training in the diploma course (DCH) of the university. The hospital units of 50 beds were put into operation. In rapid succession, three students were admitted for MD and D.Phil. degrees. Institute of Child Health, Kolkata was officially inaugurated on January 16, 1957, by Shri Jawaharlal Nehru, the then Prime Minister of India (**Fig. 2**). Labelling ICH as a unique institute of India, Pandit Nehru lauded the purpose and objective of ICH in its service to children, who are the beginning of the new India. Srimati Padmaja Naidu, the then Governor of West Bengal and Dr Bidhan Chandra Roy, the Chief Minister of West Bengal, had also graced the inauguration ceremony [3,4].

THE INITIAL YEARS: 1958-1970

The Developmental Phase

By 1959, the Institute had expanded to an area of 40,000 sq ft – notably, the surgical unit had become functional with 15 beds. Dr. UC Chakraborty, father of pediatric surgery in India, set up the pediatric surgery department.

Later, Dr. Godrej Karai was in-charge of the cardio thoracic department. Dr Anjali Mukherjee joined as the chief of Plastic surgery division, Dr GC Dey as chief of ENT, and Dr. BP Ray as chief anesthetist [5, 6].

Dr. Chaudhuri laid appreciable stress on research activities. Soon, the entire third floor of the eastern wing was dedicated to research laboratories, developed and equipped by generous grants from the Rockefeller Foundation, especially for studies in pediatric pathology and pediatric radiology. The department of basic medical sciences was one of a kind in India, helmed by Dr. J Nag Chaudhuri. Novel projects supported by many national and international grants such as from ICMR, Indian Medical Association, CSIR and Lady Dufferin Scholarship were carried out [6]. The Institute library was built to provide access to knowledge in the field of pediatrics to the newer generation of pediatricians. The academic progress of the Institute made it known as "*a temple of learning*" by educationists and political leaders of the era [6].

The out-patient department (OPD) special clinics of ICH like child guidance, orthopedics, chest disease and heart diseases and eye diseases were started, catering to 24,667 young patients in 1958. One of the prime focus of ICH was to serve also as a community health center. It was one of the first hospitals in India to start immunization clinic, which along with the Well Baby Clinic, championed the promotion of breast feeding parallel to the WHO dictum, with frequent educational activities [6].

The Preventive department headed by Dr. Momota Chowdhury, catered to the all-round health of the child – both physical and mental health. School Health Service, Infant and Child Welfare service, Day nursery for 8 children, and a Kindergarten school for 16 children were started. Mothers could leave their children and go to work, a continental concept that was new to Calcutta [6].

The number of indoor beds was increased and pathological laboratories, radiology and other facilities were expanded, including the Ultrasonography department. Under the guidance of the biochemist, Dr. AC Majumdar, the department was engaged in preparing pyrogen free infusion fluids as ORS sachets were not in vogue. Another stalwart in the field of Biochemistry was Dr. Kanai Lal Mukherjee. Under his tutelage, ICH offered doctoral program to more than 12 dedicated researchers, including works on nephrotic syndrome by Dr. GK Mehrotra. Research activities on nutritional dis-orders (kwashiorkor and marasmus, comprising 60% of indoor admissions), physiological development of human fetus, avian malaria, study of apoptosis by immunological works including estimation of in-house insulin assay developed soon after Yalow and Berson's observations. Dr. Amala Chaudhuri, wife of Dr KC Chaudhuri, took special classes in Genetics and Endocrinology [6].

To name a few doyens who contributed significantly to pediatrics during their tenure in ICH as great teachers and researchers were Dr. Sisir Kumar Bose, Dr. Naren Banerjee, Dr. SP Ghoshal, Dr. AK Dey (master of medical journalism), Dr. PC Sengupta, Dr. Dilip Mahalanabis, Dr. Ashoke Sengupta, the versatile plastic surgeon and kidney transplant specialist Dr. Amalkanti Das, and Dr. SK Mukherjee [6].

Dr. Sisir Kumar Bose (**Fig. 3**), a Fellow of Boston Children's Hospital and trained in pediatric radiology, developed one of the best pediatric radiology departments in ICH. Aptly, he was called the Father of pediatric radiology in India. It is interesting to know that Dr. Bose is the nephew of Netaji Subhas Chandra Bose, who drove the car with Netaji in disguise, to help him escape the country during the freedom movement [6]

Prof. SP Ghoshal (**Fig. 4**) was a visionary who was instrumental in building the neonatology program in ICH. In 1988, he discovered the Ghoshal Hematodiaphyseal Dysplasia, a rare autosomal recessive disease, characterized by diaphyseal dysplasia and metaphyseal dysplasia of the long bones and refractory anemia, and associated with a deficiency of an enzyme. Prof. Pratap Chandra Sengupta, a renowned pathologist, and an emeritus medical scientist in the Indian Council of Medical Research, along with Prof. Ghoshal was associated with discoveries such as bilirubin crystals in neutrophils and Noma neonatorum [6].

Prof. Ashoke Sengupta was an orthopedic surgeon whose singular work in cost-effective rehabilitation procedures earned worldwide recognition and his original work on the operations to cure club foot in developing countries earned him a place in the prestigious referral book, 'Club Foot-The Present and View of the Future' [6].

The Indian Academy of Pediatrics (IAP) was formed in 1962 with the amalgamation of Dr. Chaudhuri's Indian Pediatric Society and Dr. Coelho's Association of Pediatricians of India. The IAP's official journal, *Indian Pediatrics*, commenced publication in 1964 with its editorial and business office in ICH. Dr. Sisir Bose was its first editor. Later, Dr. SP Ghoshal and Dr. Dilip Mukherjee became the national presidents of the apex body.

In 1965, Smt Indira Gandhi, the then Prime Minister of India, visited the Institute and praised the vision with which ICH had been serving the nation (**Fig. 5**).

THE GROWING YEARS: 1971-2000

The Expansion Phase

Dr. UC Chakraborty became the director of the Institute after the demise of Dr. Chaudhuri. The baton of directorship was later passed on in the able hands of Dr. Sisir Kumar Bose. The later decades of the 20th century saw the emergence of a new and enthusiastic generation of pediatricians who maintained the pace of progress. Outpatient attendance markedly increased from 15,000 in 1961 to 70,000 in 1980. The large number of scientific publications and presentations both in basic sciences and clinical pediatrics from the Institute, at national and international conferences, bear testimony to the volume and range of academic work that was being carried out [9].

Towards the end of 1973, the first fully equipped air-conditioned premature baby unit in Calcutta was established in ICH [9]. Another important development was the establishment of a day care center for handicapped children in 1973, which later, with the support of Ministry of Education and Social Health Welfare, Government of India, procured modern teaching aids and equipment [9].

Intensive care unit for the critically ill children was established in 1975. The department of surgery was upgraded in 1975. Valuable work in microvascular surgery was carried out during these years. The Heart Clinic and another chain of other specialty clinics began in 1976, including clinics for nutrition, kidney (started in 1986, under Dr. G K Mehrotra), allergy, eye, ear-nose-throat and skin diseases. The allergy unit was started as a research project under Prof. S N Choudhury for children from 5 to 12 years but later expanded to include adult care as well. It collaborated with Palynology division of Bose Institute for novel research papers. Apart from skin prick test and spirometry facilities, the unit claimed the necessary drug license in 1999 for preparing vaccines for immunotherapy [9].

Another unique and innovative feature of the Institute was that it had the several mother and child cubicles where the mother stayed with the children under round the clock supervision of the pediatricians. In 1976, the institute launched a pioneering three-year course for training batches of young girls in practical pediatric nursing, who were later absorbed as permanent staff in the Institute as nursing assistants [9].

By the beginning of 1979, following the Great Flood of 1978 in West Bengal, the institute had taken up a bold plan of holistic rural health care program to alleviate the flood hit people. In the Memari blocks of Burdwan district, medical, paramedical and administrative personnel of the institute worked in tandem and motivated the people of 218 villages to help themselves for their own development. So successful was this holistic Rural Health program that the UNICEF and USAID came forward with the Government of India to help the Institute. UNICEF helped establish a hypochlorite solution manufacturing plant in the Jabui village to provide safe drinking water and control diarrheal diseases during floods. The program became a huge success, and UNICEF later replicated it in many backward countries of the world [9].

The Institute celebrated 25 years of completion in 1981, its silver jubilee celebrations being marked with several academic activities and publications.

In 1993, the day care center evolved in to a new three-storied building called the Centre for Handicapped Children, founded by the dedicated efforts of Mr. Biswaranjan and Ms. Mamata Sarkar (**Fig. 6**). Today, a coordinated team of psychologists, psychiatrists, pediatricians, special educators, physiotherapists, and social workers provide holistic guidance and support to children with special needs. Over the years, the special school has led some of the students to normal schooling and higher education; some have even participated and won medals in state Special Olympics [9,10].

The infrastructure of the hospital was tremendously boosted with serial donations from the Government of Japan in 1994 and 1997, and Child Relief and You (CRY).

THE MATURING YEARS: 2000-2022

The Progressive Phase

In 2001, a new ward of 15 beds was developed and by 2006 there were more than 100 beds functional. New specialized outdoor clinics – Asthma clinic, Neurology clinic, Lactation clinic, Cancer rehabilitation and care, Growth and Dysmorhology, Endocrinology and Cardiology clinics were started. The establishment of a modern auditorium within the Institute opened the floodgates of academic seminars, discourses and deliberations by in-house experts, students and invited academicians. Dr. KC Chaudhuri Memorial oration, Dr. Sisir K Bose Memorial CME Program of pediatric radiology, Dr. SP Ghoshal Memorial post graduate quiz were many of the important calendar events of the Institute (**Fig. 7**). Now, 15th August has been marked as the annual day of the Institute, which celebrates the academic furlongs in pediatrics by deliberations on current issues by national experts and institute faculty, and is attended by approximately 1000 pediatricians of Bengal.

On the occasion of completion of 50 years of service, '*Celebration 50*' was marked with the foundation ceremony of the Golden Jubilee Building, which presently

houses the Blood Bank, Maternity wing and the 29-bed state of the art Neonatal Intensive Care units (NICU) with room-in facility for mothers. The NICU has thrived with quality treatment procedures and protocols. The center today is well equipped with modern ventilators, double surface phototherapy, resuscitators; and offers one of the best neonatal intensive cares of the city at nominal costs, and prides in its high success rates. Premature intensive care has been the focus of NICU as it has been specially designed to maintain strict isolation.

In the biochemistry laboratory, analysis became automated in 2012. The lab is a referral center for sweat chloride analysis in eastern India. The state health sciences university recognized ICH as a center for paramedical courses in laboratory technology in the same year. The establishment of molecular biology laboratory gave an impetus to deciphering the etiologies of infectious diseases. Several panels of RT-PCR based diagnostics in respiratory, gastroenterological ailments, sepsis have been devised apart from molecular diagnosis of HLAB27, thalassemia, cystic fibrosis to name a few. Recently, it was accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL).

In 2012, a six-bedded designated ward for kidney patients was started, which has graduated to a 14-bedded unit. Hemodialysis services started in March, 2012. The unit has emerged as an advanced referral center to treat all types of kidney diseases in children from newborn to adolescent kidney problems.

The year 2014 marked the expansion of the modern pediatric intensive care unit (PICU). The tertiary care level 3 services expanded to 14 beds and four isolation. Total bed strength increased to 180, and dedicated areas of clinical research center, department of molecular biology, thalassemia clinic, rheumatology and gastroenterology wards were opened. The rheumatology division and the gastroenterology division have also been upgraded recently. Both departments have started fellowship courses giving unique training opportunities in these specializations.

The clinical research department, under the earnest efforts of senior researchers, has been very active, being involved in several important global and national clinical trials in vaccine, drugs for rare diseases and the pediatric COVID vaccine trial [12]. Academic research, which has been the forerunner of Institute activities since its heydays, continues to be pursued with equal zeal by the faculties and students contributing several high impact publications in international and national journals, only a few of which are cited here [13-15]. Senior faculty members have contributed to the development of important national guidelines in pediatric infectious diseases [16,17], pediatric nephrology [18,19], pediatric rheumatology diseases [20] and pediatric dermatology [21-23].

The pediatric surgery department has continued to evolve under the able leaderships of many renowned pediatric surgeons. Average number of children seen in surgical out-patient department is 20,000 per year; the average number of operations done is about 2500 per year. The department received accreditation to offer a 6-year DNB course in pediatric surgery since 2016. The pediatric orthopedic surgery division has also flourished simultaneously.

ICH delved into pediatric hemato-oncology care in 2017, with the Mrinalini Cancer Research Centre, started with 11 beds. In 2022, it has 16 beds, with over 2000 patients having been treated in the unit. The Malobika Bagchi Memorial Thalassemia unit takes care of children with various blood disorders like thalassemia and hemophilia.

In response to coronavirus disease 2019 (COVID-19) emergency, especially in the second wave of the pandemic, the ARI ward was developed to treat pediatric COVID-19 infections and cases of multisystem inflammatory syndrome in children (MIS-C).

In 2020, ICH opened its own nursing college with 120 seats, affiliated to the state Nursing Council, with GNM and B.Sc. Nursing courses. Recently, the Institute has been recognized by the West Bengal University of Health Sciences for Ph.D. program in pediatric medicine and molecular biology; it has also got affiliated with Presidency University for non-medical Ph.D. courses in 2022.

ICH is rapidly expanding its academic base and hospital activities, the current footfall of patients in the outdoor department being about 90000/year and annual indoor admissions over 10000/year. It has envisaged construction of a new 300 bed hospital complex to meet its space and infrastructural requirements, the foundation of which was laid down on 11 February, 2021.

The Institute has remained steadfast in its mission to provide the best quality care in pediatrics but at nominal costs, in spite of rising healthcare costs. The administrative machinery gears up to arrange for funds for those families who are unable to afford any treatment costs for their sick child. Many-a-times, the hospital faculty and staff have gone out of the way and contributed at personal levels to buy necessary gadgets for sick kids [24].

THE CORE OF ICH, KOLKATA

The constellations of students, ex-students, professionals, teachers, academicians, researchers, doctors who have been associated with the Institute have grown with the Institute. In turn, they contribute to its everyday growth with their insights and experience.

The Institute continues to proudly uphold the principles of its founders who had for their patients the concern of a parent for its ailing child, and the first-class knowledge and skill to treat and cure. A wonderful concoction of holistically treating the poorest of the poor with compassion is what embodies those who bear the legacy of the Institute.

The journey of ICH has been a long one – having a rich history filled with many landmark events. The mission of ICH is its hallmark: To help cure diseases and offer protection to the physical and mental health of every child regardless of their socioeconomic circumstances; to carry out research programs; to conduct post graduate courses in pediatric medicine and surgery; to offer training to nurses, technicians and social workers; and to help build a healthy population in India.

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Fig. 1 Dr KC Chaudhuri.

Fig. 3 Dr Sisir K Bose.

Fig. 4 Dr SP Ghoshal.

Fig. 2 Pandit Jawaharlal Nehru with Dr KC Chaudhuri and founder members.

Fig. 5 Prime Minister Mrs. Indira Gandhi visiting ICH in 1965.

Fig. 6 Smt. Mamata Sarkar at the Center for Handicapped Children.

Fig. 7 Dr. Sisir K Bose Memorial Quiz awards distributed by Dr G K Mehrotra and Dr Apurba Ghosh.

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