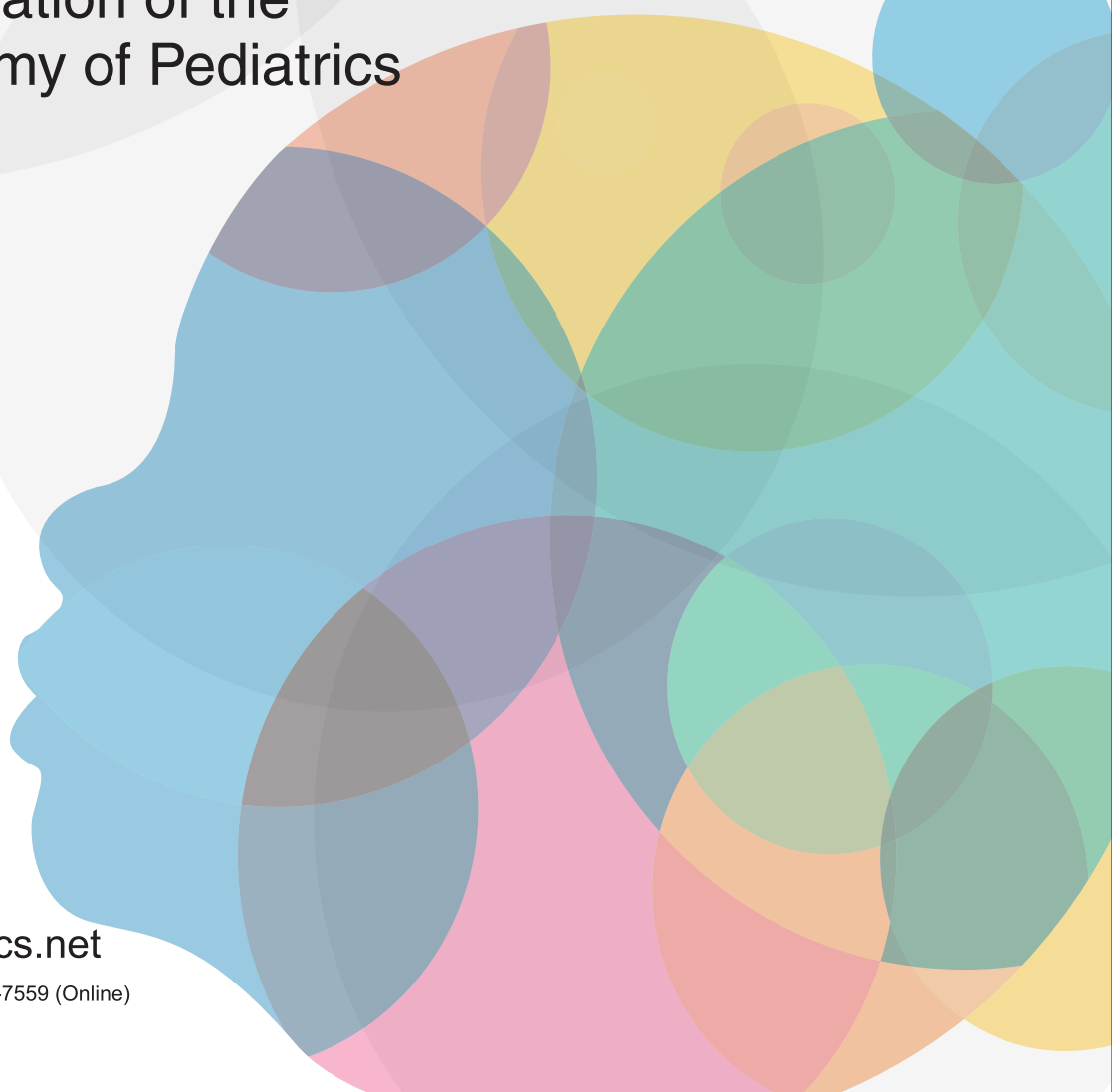
E-copy

Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 59
NUMBER 4
April 2022



www.indianpediatrics.net
ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

IAP Guidelines for pediatric skincare state that ideal care of newborn skin comprises of:[1]

- Gentle cleansing[1]
- Protection of barrier function[1]
- Prevention of skin dryness[1]
- Promotion of normal development of the skin[1]

Designed for newborn's sensitive skin

NEW Johnson's® cottontouch®

To promote normal development of the skin: Clinically proven to nurture infant skin microbiome[2,3]

- Ideal for infant massage[4]
- Gentle cleansing with HMP technology[5]
- Protection of barrier function with unique delivery system[6]
- Prevention of skin dryness[2]

RA/JB/BMar2021/05

IAP: Indian Academy of Pediatrics, HMP: Hydrophobically Modified Polymer

References: 1. Madhu R, et al. Indian Academy of Pediatrics Guidelines for Pediatric Skin Care. Indian Pediatr. 2021;58(2):153-161. 2. Data on File. 3. DOF3 Capone AAD 2017. 4. Johnson & Johnson Consumer Products Worldwide. Claim support and data summary for Johnson's Cottontouch Baby Oil. 5. Anwar S, et al. A scoring method to assess the gentleness of cleansers. Presented at the American Academy of Dermatology Annual Meeting, March 30–24, 2020, Denver, CO, USA. 6. Data on file. 6. Capone K, et al. Effects of Emollient Use on the Developing Infant Skin Microbiome. Presented at the American Academy of Dermatology Annual Meeting, March 1–5, 2019, Washington, DC, USA.

Indian Pediatrics

April 2022 Volume 59 Number 4

Contents

Impact Factor 2020 of *Indian Pediatrics* is 1.411

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 33,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

Address for ordinary letters: **The Editor-in-Chief, Indian Pediatrics, P. Box No. 3889, New Delhi-110 049, India.**
Address for registered/speed post letters: **Dr. Devendra Mishra, Editor-in-Chief, Indian Pediatrics, 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049, India. Tel: (011) 46052593**
E-mail: *jiap@iapindia.org*; Website: *www.indianpediatrics.net*; LinkedIn: *indianpediatrics*
Facebook: *www.facebook.com/Indianpediatrics;* Twitter: *@EditorIndPed;* Instagram: *@indianpediatrics*

PRESIDENTIAL ADDRESS

59th National Conference of Indian Academy of Pediatrics (PEDICON) 19-23 March, 2022, Greater NOIDA

Remesh Kumar R
National President, Indian Academy of Pediatrics 2022
president@iapindia.org

At the outset, on behalf of the entire IAP Community, I pay tribute and homage to the COVID martyrs. The only thing I would say is that- we will never forget your sacrifices!

To begin with, I take the opportunity to express my sincere gratitude to every member of the Academy for the confidence reposed in me by electing me as the President of the second largest specialty body of pediatricians in the world. I am humbled by the affection and love showered by one and all in the fraternity, and it shall be my earnest endeavor to give my very best to the Academy.

As I assume office, I am aware of the weight of responsibility that comes in leading a great organization. Certainly, I am inheriting the legacy of great stalwarts culminating with my predecessor Prof. Piyush Gupta, who has led IAP with great determination through the difficult days of the pandemic. I will strive to continue his good work and pass the baton on an equally strong platform to my successor, President-Elect Dr. Upendra Kinjawadekar.

Today I have the privilege of sharing this platform with our distinguished Chief Guest, Honorable Minister for Women and Child Development Smt Smriti Irani ji, who has set her goal for an India witnessing "rapid transition from women's development to women-led development". Child welfare has been very close to her heart. She has been the active proponent of the telemedicine support system introduced last year with the participation of IAP for the child care institutions across the country.

I am delighted to have Dr. Mahesh Sharmaji, former union minster and the incumbent Member of Parliament representing Gautam Budha Nagar. Being one amongst ourselves in the medical profession, he has gone to great lengths to support us in organizing this event. I must say he has been a mentor and patron to us and showed us that he is not just an MP for Noida, but an MP for the medical fraternity too.

A friend, choosing to be a pediatrician has been one of the most worthy choices in my life. Pediatrics is a specialty which enables you to touch the lives of hundreds of families and feel pride in nurturing the future of humanity. Through IAP, I was able to see the vast canvas of our profession and got opportunities to contribute my knowledge and resources to make a difference to child health. As the President, I have identified two broader arms for the activities in my presidential tenure: primarily, Contribution to child health, and Contribution to the profession through IAP.

Going forward in this track, IAP today stands at a new juncture whereby we propose to become a broad based organization and focus on the more difficult phase of childhood, namely adolescence. This is in preparation to our future role as a profession dealing with both Pediatrics and adolescence. In this context, I must congratulate my predecessor Dr Piyush Gupta for his sustained efforts to get the domain of Pediatrics to be renamed as 'Pediatrics and Adolescent Medicine,' to which the Government of India has already agreed.

One immediate and primary concern on child health should be reduction of under-5 mortality. As of 2020, under-5 mortality rate for India revolves around 35, which means 35 out of 1000 children born in our country do not get the opportunity to celebrate their fifth birthday. IAP has identified the goal of achieving under-5 mortality rate of 25 by the year 2025 as an important component in the country's journey to Sustainable Development Goals 2030. This is a stiff target, but nothing is impossible if we aim it on a mission mode. In our country, under-5 mortality rate has wide disparity interstate as well as intra state.With an indepth district wise secondary data analysis, we have identified 57 high priority districts with high U5MR for urgent intervention.We understand one size does not fit all. As such, district-specific road maps have been devised. We are primarily aiming at catalyzing the activities of Government of India in these focused districts with the collaboration of other major stake holders like WHO, UNICEF, FOGSI, NNF and TNAI.

My dears, it is a fact of life that children cannot express all their needs. We, the pediatricians, as the custodians of child

health need to raise our voice for them. Our responsibility for the child's well-being goes way beyond the physical health of individual patients. IAP needs to be more vociferous and visible in various domains of child advocacy like child rights, child abuse, gender discrimi-nation and many more. We need to continue our proactive support to child health initiatives from GOI like INAP (India Newborn Action Plan), Anemia Mukth Bharath, NSSK and the various nutrition support programs. I humbly request our strong force of 35,000 IAP members to continue to remain socially committed in all these realms of public health and augment the Government programs in your own regions.

In this digital era, we propose to set up an online Member Benefits Portal, which will be giant stride in organization and profession development. A wide range of Member Benefits are envisioned in this portal, the most significant of which will be the QR Code based digital ID Cards, the PeD card, which apart from providing IAP identity, will privilege the members for loyalty services from many renowned service providers. I am sure, all these will result in a complete transformation of our organization functioning and make IAP more member and branch friendly.

Friends, academics is our forte. Keeping pace with new developments and recapping the basics is vital to optimal patient care. To this end, we have formulated the Standard Treatment Guidelines in Pediatric Office Practice. We have started releasing guidelines on one common pediatric illness every Monday, Wednesday and Friday from January 1, 2022 Academy year. I am proud that the STG Team has been on the dot and as of today, we have been able to publish 33 guidelines in the last 11 weeks. Parallelly, we have 12 physical modules including the ambitious ECD-Early Childhood Program and 5 virtual academic modules already lined up for the year, with 8 TOTs happening at Noida itself with PEDICON.The 300 workshops on TB eradication planned in next two years is a reflection of our true commitment to Honorable PM Shri Narendra Modiji's vision of End TB 2025 project. I assure that all the 340 branches of IAP will have the opportunity to conduct one or the other of these as district level workshops in physical real time mode with academic grant from Central IAP Office.

My dear friends, as I stand before you as the President, I look back and recap my journeyof 5½ decades. The dream of a rustic boy from Kuttanad, the water logged backwater village of Kerala to come up high in the medical profession would not have been realistic, but for the vision, nurturing care and the sacrifices made my late parents. On this very special occasion, I offer my respectful *pranams* to my father Shri PG Ramachandran Nair and mother Smt. Kalyani Amma L, both of whom earnestly desired to see me as a successful doctor. They even blessed me with a name with a unique spelling – Remesh – which is spelled with an 'e' rather than an 'a' – and which has raised many an eyebrow at every occasion I have to spell my name.

In conclusion, I thank every member, friend and colleague who has enabled me to attain this coveted position. The staff of IAP central office has been most cooperative and are the pillars of strength to any President. I thank them all. I have no words to thank my wife Dr. Jayalakshmy and son Arjun who by themselves have been like co opted IAP members and were always positive in their thoughts for IAP, and allowed me to spare much more time and effort for the organization. My special gratitude to my immediate colleagues in Pediatrics and management of Apollo Adlux Hospital, Cochin, especially Medical Director Dr Anil, CEO Mr Neelkannan, and my colleague, Senior Consultant in Pediatrics, Dr Saju, for their constant encouragement and support.

On this occasion, my thoughts go out to my respected teacher at Government Medical College, Kottayam and IAP President 2011, Dr TU Sukumaran who handheld me to IAP 2½ decades back, and Dr. MKC Nair and Dr. Sachidananda Kamath, Past National Presidents of IAP, who ably guided me at the organizational level. I am very much indebted to Dr. Santhosh Soans and Dr. Diganth Shastri, who, as my Presidents, nurtured my organizational aptitude in my tenure as Honorary Secretary General of CIAP in 2018 and 2019. If I am to come this far as the President of IAP, the credit should truly be placed at the feet of my Friends at IAP Kerala who always cared and inspired me by their warmth and affection.

I am very much thankful to the OB and EB of 2022 for the whole hearted support in their proactive commitment to the Academy. My HSG, Dr Vineet Saxena, is my pillar of support and as always is a perfect task master at the back office. It is well said that *"The best preparation for tomorrow is doing your best today."* The organizing team of PEDICON 2022 has strived every day for the last two-and-a-half years, even in the face of a raging pandemic, to make today a reality. With this TEAM at the helm, we all are sure to have the life time toast of an academic, gastro-nomic and social feast at India Expo Mart, Greater Noida in the week ahead.

Dears, the Covid pandemic makes it pertinent to reflect on a famous saying "*This too shall pass.*" Life is like a road, there are bumps, cracks, U turns, road blocks, but the only important thing is life goes on. I end by quoting the Chandogya Upanishad:

yovaibhûmâ, tatsukhaC, nâlpesukhamasti,
bhûmaivasukha Cbhûmâtvevavijijñâsitavyaiti

"There is no joy in the finite; there is joy only in the infinite."

Friends, we have been through the terrible experience of a Pandemic. It was a situation of despair and no hope, yet life is now returning to normal. Let us all orient ourselves to this healing process of humanity and contribute our mite to the emerging world of peace and prosperity for all. I wish you all a safe, healthy and most enjoyable post-COVID era coming up. I will and shall always remain as your humble servant and friend in IAP!

Jai Hind! Jai IAP!

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

INVITED COMMENTARY

Breast Milk Monthly D-livery

Sara S Oberhelman-Eaton, Tom D Thacher
Department of Family Medicine, Mayo Clinic, Rochester MN 55905
Correspondence to: Dr. Tom D Thacher, Professor of Family Medicine, College of Medicine, Mayo Clinic, Rochester, USA.
thacher.thomas@mayo.edu

Nutritional rickets continues to have serious consequences in infants and children worldwide, and it remains prevalent in African and South Asian countries, like India. Bone pain, skeletal abnormalities, stunted growth, developmental delays, and life-threatening hypocalcemic seizures and cardiomyopathy are entirely preventable outcomes with adequate calcium intake and vitamin D supplementation.

Vitamin D can either be ingested or synthesized cutaneously following ultraviolet light exposure. An estimated 70-100% of the general population of India is vitamin D deficient, likely secondary to limited vitamin D food fortification, restricted sunlight exposure and darkly pigmented skin [1]. Vitamin D deficiency is common among lactating women and human milk contains low amounts of vitamin D, increasing the risk of nutritional rickets in Indian infants.

The Indian Academy of Pediatrics [2] and a Global Consensus Group [3] recommend that all infants receive 400 IU/day of vitamin D for the first year of life for prevention of rickets. However, adherence with this recommendation is low. In a study of vitamin D adherence in India, 41.5% of infants received vitamin D at any point during the study, but only 8.8% received routine appropriate vitamin D dosing [4]. Similar findings of low adherence have been reported worldwide, despite a multitude of recommendations for infant supplementation to reduce rates of rickets. The inconvenience of providing supplemental drops to an exclusively breastfed infant may be one reason parents do not routinely provide the recommended supplementation. Therefore, maternal supplementation for a breastfeeding dyad has been utilized for improved ease of administration.

Ramot and colleagues [5] compared two monthly vitamin D doses for 12 months in lactating mothers and found that 12,000 IU monthly did not result in sufficient infant vitamin D status, but 120,000 IU monthly achieved vitamin D sufficiency (25(OH)D>20 ng/mL) in the majority (95%) of infants. Their findings are important for two reasons. First, this is the first study of maternal bolus dosing of vitamin D to span the infant's entire first year and demonstrated both maternal and infant safety. Second, this study provides new data to establish the ideal maternal dose for monthly administration. Previous studies of maternal supplementation with 100,000 IU or less monthly did not assure infant vitamin D sufficiency [6]. This study showed that 120,000 IU monthly provided sufficient vitamin D in most but not all infants. Another study of 150,000 IU resulted in sufficiency for all infants after one month [7]. Thus, the optimal monthly maternal dose for lactating mothers is likely between 120,000 and 150,000 IU.

Daily maternal supplementation with vitamin D 5000-6400 IU safely achieves sufficient serum 25(OH)D concen trations in breastfed infants [7-9]. Maternal supplemen-tation was preferred over infant supplementation by mothers in Minnesota, USA: 88.4% of the surveyed mothers preferred to supplement themselves rather than their infants [10]. Among family medicine clinicians, 87.5% would recommend either maternal supplementation (37.5%) or allow parents to choose between maternal or infant supplementation (50%) [11]. Vitamin D supplementation of lactating mothers has the additional advantages of protecting the infant from vitamin D toxicity related to dosing errors, promoting the completeness of breast milk nutrition, and simpler adherence than infant drops.

From a public health perspective, the option to provide maternal monthly administration of vitamin D for infant benefit is quite important. With proper infra-structure and oversight, maternal vitamin D adminis-tration could theoretically be coupled with well-baby examinations and/or public health initiatives focusing on women and children. Large proportions of mothers (43%) [10] and clinicians (30%) [11] in a single community in the United States would prefer a monthly regimen. Similar investigations have not been done in India, but one could hypothesize a similar willingness to accept a monthly administration schedule.

Nutritional rickets can be eradicated, and Ramot and colleagues [5] demonstrate a feasible way to prevent vitamin D deficiency through maternal monthly supple-mentation. Given the safety and efficacy of maternal vitamin D supplementation for infant vitamin D sufficiency, national

and global recommendations should be updated to reflect maternal supplementation as a viable option. Public health initiatives should explore local opportunities to include monthly maternal supplementation in already established mother/child interventions. These initiatives could prevent vitamin D deficiency and decrease the incidence of nutritional rickets in India and globally.

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

REFERENCES

1. Ritu G, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. Nutrients. 2014;6:729-75.
2. Gupta P, Dabas A, Seth A, et al. Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets. Indian Pediatr. 2021 Dec 29:S097475591600382. Epub ahead of print.
3. Munns CF, Shaw N, Kiely M, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016;101:394-415.
4. Meena P, Saran AN, Shah D, et al. Compliance to prescription of routine vitamin D supplementation in infants. Indian Pediatr. 2020;57:1067-9.
5. Ramot R, Yadav S, Vishnoi SK, Sharma P, Khadgawat R, Jora R. Effect of maternal supplementation with two different doses of vitamin D during lactation on vitamin D status, anthropometry and bone mass of infants: a randomized controlled trial. Indian Pediatr. 2022;59:276-82.
6. Wheeler BJ, Taylor BJ, Herbison P, et al. High dose monthly maternal cholecalciferol supplementation during breast-feeding affects maternal and infant vitamin D status at 5 months postpartum: a randomized controlled trial. J Nutr. 2016;146:1999-2006.
7. Oberhelman SS, Meekins ME, Fischer PR, et al. Maternal vitamin D supplementation to improve the vitamin D status of breastfed infants: a randomized control trial. Mayo Clinc Proc. 2013;88:1378-87.
8. Hollis BW, Wagner CL, Howard CR, et al. Maternal versus infant vitamin D supplementation during lactation: a randomized controlled trial. Pediatrics. 2015;136:625-34.
9. Wagner CL, Hylsey TC, Fanning D, et al. High dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med. 2006;1:59-70.
10. Umaretiya PJ, Oberhelman SS, Cozine EW, et al. Maternal preferences for vitamin D supplementation in breastfed infants. Ann Fam Med. 2017;15:68-70.
11. Oberhelman SS, Cozine EW, Umaretiya PJ, et al. Vitamin D and the breastfeeding infant: family medicine clinicians' know-ledge, attitudes and practices. J Hum Lact. 2018;34:331-6.

CLIPPINGS

Whole-exome sequencing and variant spectrum in children with suspected inherited renal tubular disorder: The East India Tubulopathy Gene Study (Pediatr Nephrol. 2022 Jan 10. doi: 10.1007/s00467-021-05388-y)

A multicenter, descriptive cross-sectional study was performed in 77 children (73% male) in Eastern India. Children less than 18 years with clinically suspected tubulopathy were enrolled in the study and whole exome sequencing (WES) was performed in all the cases. Sanger sequencing and Multiplex ligation-dependent probe assay (MLPA) were also done when indicated. The variants were classified as pathogenic/likely pathogenic (P/LP) in accordance with American College of Medical Genetics and Genomics, 2015. Fifty five (24 novel) P/LP variants were identified and genetic diagnosis was established in 54 children (70%). Clinically, distal renal tubular acidosis (32.4%) was the most commonly identified tubular disorder but the diagnostic yield of WES was highest for nephrogenic diabetes insipidus (100%). Barakat syndrome and Renal cyst with diabetes syndrome were the rare disorders identified. WES led to revision of clinical diagnosis in 14 children (26% of those with a confirmed genetic diagnosis and 18% of the overall cohort) and detection of unidentified co-morbidities (sensorineural deafness *n*=5, hemolytic anemia *n*=2, dental changes *n*=1). The authors suggested that WES is an essential tool in the diagnosis and management of inherited tubulopathies in India.

Evaluation of daily low-dose prednisolone during upper respiratory tract infection to prevent relapse in children with relapsing steroid-sensitive nephrotic syndrome - The PREDNOS 2 randomized clinical trial (JAMA Pediatr. 2022;176:236-43)

A number of studies including, randomized controlled trials, have established that increasing the maintenance dose of corticosteroids during upper respiratory tract infections (URTI) for 5-7 days can reduce the risk of relapse in nephrotic syndrome. PREDNOS 2 is a phase 3, double blind, placebo-controlled randomized clinical trial which evaluated the efficacy of daily (for 5-7 days) low dose prednisolone (15 mg/m^2/day) during an episode of URTI in reducing the risk of relapse among 365 children with or without background immunosuppressive treatment in the United Kingdom. The primary outcome was the incidence of first upper respiratory tract infection-related relapse (URR). Secondary outcomes were overall rate of relapse, changes in background immunosuppressive treatment, cumulative dose of prednisolone, rates of serious adverse events, incidence of corticosteroid adverse effects, and quality of life. In intention to treat analysis, the number of patients experiencing URR was 56 of 131 (42.7%) in the prednisolone arm and 58 of 131 (44.3%) in the placebo arm (adjusted risk difference, 0.02; 95% CI, 0.14 to 0.10; *P*=0.70). No significant differences were observed in secondary outcomes as well between the treatment arms. It was concluded that daily short course of low dose prednisolone at the time of URTI does not reduce the risk of relapse in children with nephrotic syndrome.

DR PRAJAL AGARWAL
prajal.agarwal@gmail.com

RESEARCH PAPER

Effect of Maternal Supplementation With Two Different Doses of Vitamin D During Lactation on Vitamin D Status, Anthropometry and Bone Mass of Infants: *A Randomized Controlled Trial*

Rekha Ramot,[1] Swati Yadav,[2] SK Vishnoi,[2] Pramod Sharma,[2] Rajesh Khadgawat,[1] Rakesh Jora[2]

From [1]Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi; [2]Department of Pediatrics, Dr S N Medical College, Jodhpur, Rajasthan.

Correspondence to: Prof Rakesh Jora, Department of Pediatrics, Dr SN Medical College, Jodhpur, Rajasthan. jorarakesh@gmail.com

Received: March 10, 2021; Initial review: June 09, 2021; Accepted: December 18, 2021.

Background: There is a high prevalence of vitamin D deficiency (VDD) in exclusively breast-fed infants in the absence of appropriate vitamin D supplementation.

Objective: To evaluate the efficacy of two doses of maternal vitamin D supplementation on vitamin D levels of mother-infant pairs and to assess its effect on growth parameters (weight, length and head circumference) and bone mass of infants.

Study design: Randomized controlled trial.

Participants: Lactating mother-infant pairs (*n*=220).

Intervention: Maternal oral vitamin D supplementation in two doses (group 1: 1,20,000 IU/month and group 2: 12,000 IU/month) for 12 months.

Main outcomes: Maternal and infant serum 25OHD levels, and infants' growth and bone mass.

Results: There was high prevalence of VDD at baseline in mothers (94%) as well as infants (98.5%), which was reduced to 43.1% in (mothers) and 46.5% in infants after 12 months. Significantly higher median (IQR) serum 25OHD levels (ng/mL) were observed among mothers in group 1 compared to group 2 [46 (17-159) vs 18 (6-64); *P*<0.01] and in infants [36.5 (15-160) vs 17 (7-32); *P*<0.01]. No significant association was observed between growth parameters or bone mass and serum 25OHD levels of mother or infant between the two groups. Four mothers (3.6%) and two infants (1.8%) in group I had serum 25OHD>100 ng/mL, but without hypercalciuria or hypercalcemia.

Conclusion: Bolus vitamin D supplementation in the dose of 1,20,000 IU/month was more efficacious in improving maternal and infant vitamin D status at 12 months, as compared to 12,000 IU/month.

Keywords: *Bone densitometry, DXA, Lactating mothers, Vitamin D deficiency.*

Published online: January 09, 2022; ***PII:*** S097475591600396

Vitamin D deficiency (VDD) in infancy and childhood is a serious public health concern in Asia, Middle East, and North Africa [1]. A high prevalence of VDD is reported among infants, depending on the definition and the latitude of the population studied [2]. The prevalence of VDD among nursing mothers and their breast-fed infants has been widely reported from India [3,4].

Breast milk is a poor source of vitamin D (~5-80 IU/L) [5], which predisposes exclusively breast-fed infants to an increased risk of developing rickets as compared to vitamin D fortified formula-fed infants [6]. A strong positive correlation has been reported between vitamin D intake of lactating mothers and serum 25-hydroxy vitamin D (25OHD) levels of infants. A sufficient maternal vitamin D intake is associated with optimal vitamin D transfer via breast milk which is adequate to meet infant needs [7]. The Indian Academy of Pediatrics recommends oral supplementation of 400 IU/day of vitamin D to all breastfed infants up to one year of age [8]. However, the practical applicability of this recommendation is questionable as adherence was found to be less than <20% [9]. Therefore, high-dose vitamin D supplementation to lactating mothers seems to be a better approach to address the dual problem of VDD in lactating mother-infant pairs [5].

Invited Commentary: Pages 274-75

Indian data on optimal dose of vitamin D supplementation among lactating mothers to improve vitamin D status of infants is scarce. Therefore, the present study was planned with the primary objective to evaluate the efficacy of two vitamin D supplementation doses (1,20,000 IU/month vs 12,000 IU/month) to lactating mothers on serum 25OHD levels of mother-infant pairs. The effect of maternal vitamin D supplementation on infant's anthropometry and whole body bone mass were also studied as secondary objectives.

METHODS

The present randomized controlled trial was conducted from December, 2014 to December, 2017 after ethical approval. The subjects were enrolled after written informed consent.

Healthy breast-fed mother-infant pairs within one month of delivery, willing to follow-up for 12 months were included. Mothers with pre-existing type 2 diabetes, hypertension, chronic renal or liver disease, antipsychotic drug exposure, clinical osteomalacia or severe vitamin D deficiency or exposure to medications known to affect vitamin D metabolism were excluded. Infants with congenital malformations and birth asphyxia were excluded. Additionally, mothers with serum calcium >11mg/dL, serum 25OHD level >100 ng/mL, liver enzymes elevated >3 times upper limit of normal (ULN) and serum creatinine above ULN for age at screening were also excluded.

The mothers were randomized (using computer-generated simple random code) into two groups (1:1 ratio) of oral vitamin D supplementation: 1,20,000 IU/month (group 1) and 12,000 IU/month (group 2) for 12 months. The vitamin D dose 400 IU/day (group 2) was chosen considering high prevalence VDD in India and ICMR-NIN recommendation [10], while the dose of 4000 IU/day (group I) was chosen based on recommendations of the Endocrine Society to maintain serum 25OHD ≥30ng/mL in exclusively breast-fed infants not on vitamin D supplements [11]. The vitamin D supplements were administered as telephonically supervised monthly bolus doses for better compliance. All the subjects were advised to regularly go-out in sun on a daily basis (the city where study was conducted has abundant sunshine throughout the year). Vitamin D preparations were provided as oral tablets (strength 12,000 IU and 1,20,000 IU); unlabelled for dose and identical in all aspects of colour, taste, and external appearance (Torrent Pharmaceuticals).

The safety of intervention was assessed by measurement of corrected total serum calcium and urinary calcium: creatinine ratio (non-fasting, second void sample) at baseline, six months, and 12 months. Hypercalcemia was defined as a total serum calcium level of >11 mg/dL and hypercalciuria as urinary (spot urine sample) calcium: creatinine ratio >0.4 [12]. Subjects with urinary calcium: creatinine ratio of >0.4 without hypercalcemia were re-evaluated with a timed 24-hour urine calcium excretion and 4 mg/kg excretion was considered as abnormal. Any subject, who developed both hypercalcemia and hypercalciuria was excluded from further intervention.

The biochemical parameters (complete blood counts, liver and renal function tests, total serum calcium, phosphate, total alkaline phosphatase, and blood glucose) were measured using Roche Hitachi 912 Chemistry Analyzer (GMI, Inc.), serum 25OHD was assessed using chemiluminescent assay using LIASON (DiaSorin Inc.) auto analyzer. The reproducibility of the assay ranged from 6% to 12%, and the laboratory was registered with UK-DEQAS vitamin D assay external quality control assessment program (*www.deqas.org*). The vitamin D status was categorized as: severe deficiency, deficiency, insufficiency, and sufficiency based on serum 25OHD levels (ng/mL) of <10, <20, 20-29, and ≥30, respectively [13].

The whole body bone mass of infant was assessed by dual-energy *X*-ray absorptiometry (DXA) using GE Lunar Prodigy Advance instrument 8743 (GE Medical systems) at 12 months (±15 days). The scans were conducted with uniform swaddling of infants in fed and sleeping state without sedation. In order to obtain artefact-free scans, appropriate positioning of infants was achieved by securing the infant's upper extremities away from the trunk region and gently binding of both the upper and lower extremities using a cotton blanket. The scans with movement artefacts were excluded.

The birthweight of infants was measured to the nearest 10 g using an electronic weighing scale, length to nearest 0.5 cm using an infant measuring board, and head circumference to the nearest 0.1 cm using a non-stretchable tape.

The sample size was calculated based on the presumption that 10% subjects in the control arm and 40% subjects in the intervention group would achieve maternal serum 25OHD >30 ng/mL after one year. Hundred subjects in each arm were required to detect the above difference with 90% power and 97.5% confidence levels. Anticipating 20% dropouts, 110 subjects were required to be enrolled in each arm.

Statistical analysis: This was carried out using STATA14.2 (StataCorp LLC). The appropriately coded data were entered in Microsoft Excel from case record forms, and extreme values (beyond 1.5 times of inter-quartile range below Q1 or above Q3) were excluded. Continuous variables were compared by independent *t*-test (normally distributed) or Wilcoxson rank sum test (non-normally distributed) and within group comparison was assessed using paired *t*-test (normally distributed). The linear regression was applied to assess the association between maternal and infant vitamin D status as well as the association of infant vitamin D status with bone mass.

RESULTS

A total of 220 mother-infant pairs (138 multiparaous

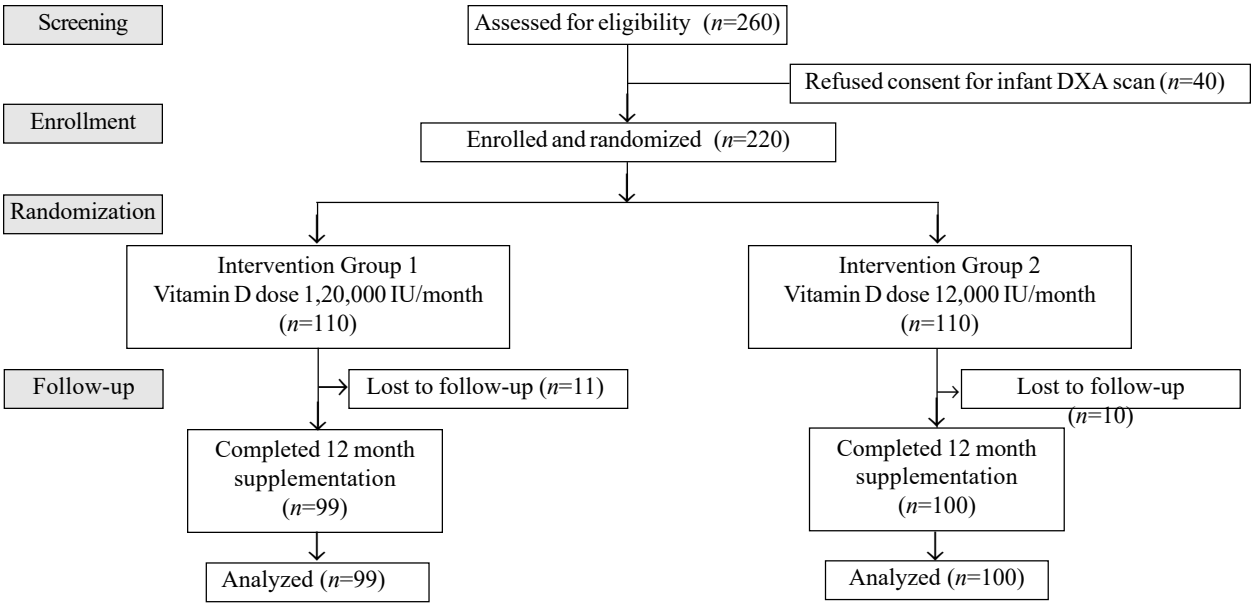


Fig. 1 Flow chart of study participants.

Table I Baseline Maternal and Infant Characteristics

Variable	*Group 1*	*Group 2*
Maternal characteristics	(*n*=110)	(*n*=110)
Age, y	25.3 (4.6)	24.8 (4.3)
Height, cm	156.05 (6.4)	157.6 (5.7)
BMI, kg/m^2	23.07 (3.9)	23.6 (4.3)
Gestational age, wk	38.6 (1.01)	38.2(1.3)
Infant characteristics		
Normal birthweight	*(n=90)*	*(n=95)*
Weight, kg	2.8 (0.4)	2.9 (0.4)
Length, cm	48.4 (1.66)	48.4 (1.96)
Head circumference, cm	33.3 (1.10)	33.1 (1.18)
Low birthweight	*(n=20)*	*(n=15)*
Weight, kg	2.3 (0.13)	2.20 (0.19)
Length, cm	46.9 (2.7)	44.5 (1.8)
Head circumference, cm	32.1 (1.38)	32 (1.26)

Data expressed as mean (*SD*). *BMI: body mass index.*

mothers; 114 male infants) were randomized into two groups (**Fig. 1**). Baseline demographic characteristics of the study population are presented in **Table I**.

The median (range) of maternal and infant serum 25OHD levels of entire group at baseline were 8.3 (0.4-30.1) and 5.8 (0.2-33.8) ng/mL, respectively, which was not significantly different between the two groups (**Table II** and **III**). There was a high prevalence of VDD in mothers (94%) and infants (98.5%) at baseline (**Web Table I**).

Maternal serum 25OHD levels of ≥30 ng/mL and >20-30 ng/mL were seen in 73 (73.7%) and 18 (18.2%) in group 1, and 5 (5%) and 17 (17%) in group 2 at 12 months. Among infants, 75 (75.7%) and 19 (19.2) had serum 25OHD ≥30 and >20-30 mg/mL in group 1, while in group 2, only 5 and 13 infants had ≥30 and >20-29 ng/mL serum 25OHD levels, respetively. The proportion of infants with serum 25OHD <20 ng/mL reduced to 5 (5%) in group I but increased to 82 (82%) in group 2 (**Web Table I**). The comparison of vitamin D status of mothers and infants with respect to supplementation groups is presented in **Fig. 2**.

Increased (mean) urinary calcium:creatinine ratio (>0.4) was observed in 3 (0.63), 5 (0.73), and 1 (0.88) mother at baseline, six months, and 12 months, respectively. However, none of these subjects developed hypercalcemia (symptomatic or asymptomatic) and hypercalciuria, or both. Only two infants had serum 25OHD levels >100ng/mL after 12 months of supplementation (both belonged to group 1); however, none of them developed hypercalciuria or hypercalcemia.

There was no significant difference in anthropometric growth parameters (length, weight and head circumference) of infants between the two groups at baseline as well as at one year (P>0.05) (**Table IV**).

The vitamin D status of mother and infant was significantly correlated at baseline as well as at 12 months. With each ng/mL increase in maternal serum 25OHD, infant serum 25OHD increased by 0.55 ng/mL (95% CI 0.36 to 0.74) after 12 months of supplementation.

Table II Maternal Biochemical Parameters at Baseline and 12 Months in the Two Groups

Parameter	*Group I*			*Group II*		
	Baseline (n=110)	*Follow-up (n=99)*	*Mean diff (95% CI)*	*Baseline (n=110)*	*Follow up (n=100)*	*Mean diff (95% CI)*
Calcium; mg/dL	9.2 (0.88)	8.7 (0.87)	-0.46 (-0.71, -0.21)[b]	9 (0.92)	8.8 (0.87)	-0.25 (-0.51, 0.02)
Phosphate; mg/dL	4.8 (0.59)	4.5 (0.87)	-0.35 (-0.56, -0.14)[b]	5.01(0.62)	4.5 (0.85)	-0.46 (-0.66, 0.26)[b]
ALP, IU/L	214.9 (69.95)	170.6 (39)	-44.3 (-58.6, -29.9)[b]	226.6 (78.54)	163.6 (36.48)	-62.3 (-79.9, 44.6)[b]
25OHD, ng/mL[a]	9.2 (6.3, 12.5)	46 (29, 69)	44.9 (39.4, 50.4)[b]	7.8 (4.1,12.2)	18 (16, 20)	9.9 (8.1, 11.8)[b]
Albumin, g/dL	2.9 (0.36)	3.6 (0.74)	0.69 (0.52, 0.85)[b]	2.9 (0.38)	3.5 (0.74)	0.66 (0.51, 0.81)[b]
Urinary calcium/ creatinine[a]	0.07 (0.04, 0.13)	0.09 (0.04, 0.16)	-	0.07 (0.03,0.15)	0.07 (0.04, 0.14)	-

Data represented as mean (SD) or [a]median (IQR). Maternal vitamin D supplementation Group I- 120000 IU/mth and Group II- 12000 IU/mth. [b]P<0.05. ALP-alkaline phosphatase; 25OHD-25-hydroxy vitamin D.

Table III Infant Biochemical Parameters at Baseline and 12 Months in the Two Groups

Serum levels	*Group I*			*Group II*		
	Baseline (n=110)	*Follow-up (n=99)*	*Mean diff (95% CI)*	*Baseline (n=110)*	*Follow up (n=100)*	*Mean diff (95% CI)*
Calcium, mg/dL	9.2 (1.0)	8.8 (0.89)	-0.48 (-0.74, -0.21)[b]	9.3 (0.9)	8.8 (0.88)	-0.43 (-0.66, 0.19)[b]
Phosphate, mg/dL	4.9 (0.85)	4.9 (0.84)	0.006 (-0.23, 0.24)	5.01 (0.73)	5.09 (0.80)	0.07 (-0.16, 0.31)
ALP, IU/L	259.2 (113.09)	280 (112.2)	20.9 (-9.16, 50.9)	252.1 (108.53)	296 (105.85)	43.9 (15.9,71.9)
Albumin, g/dL	3.03 (0.49)	3.6 (0.67)	0.56 (0.39, 0.73)[b]	3.1 (0.45)	3.6 (0.80)	0.47 (0.28, 0.66)[b]
25OHD, ng/mL[a]	7.1 (4.3, 9.2)	36.5 (30.5, 56)	36.9 (32.7, 41.2)[b]	4.8 (2.7 to 9.2)	17 (14.2,19)	12.05 (10.6, 14.4)[b]

Data represented as mean (SD) or [a]median (IQR). Maternal vitamin D supplementation Group I-120000 IU/mth and Group II-12000 IU/mth. [b]P<0.05. ALP: alkaline phosphatase; 25OHD: 25-hydroxy vitamin D.

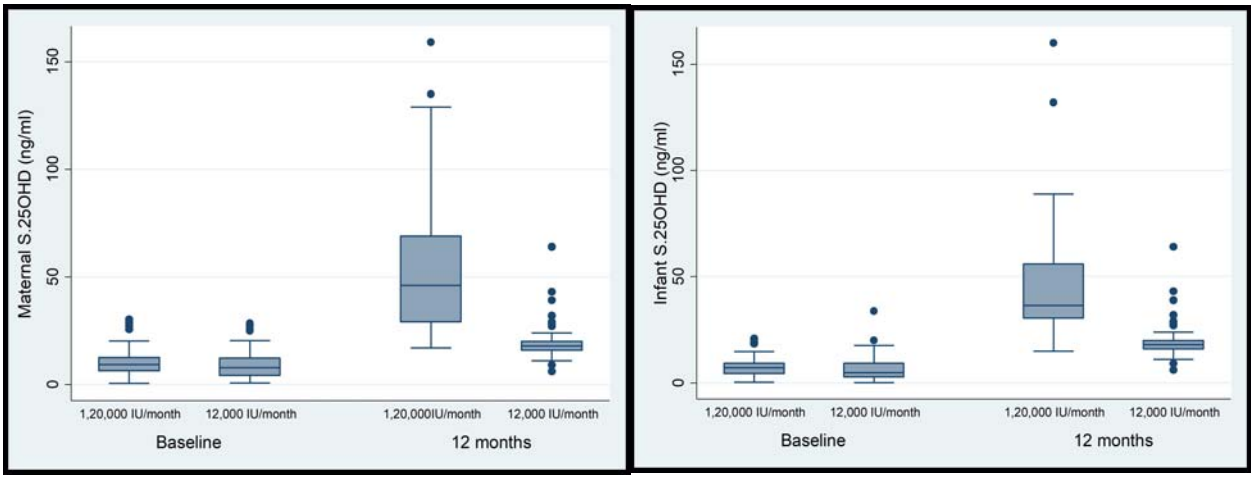
There was no significant difference in infant bone mass parameters between the two groups after one year of supplementation (**Table IV**). The mean BMC, BMD, and bone area of LBW infants were significantly lower as compared to the corresponding values of normal birth weight infants ($P<0.05$). The infant bone mass was not significantly associated with maternal age, BMI, and maternal serum 25OHD parameters (baseline, at 12 months and delta-change) in both the groups. Similarly, the infant's vitamin D level at baseline, at 12 months, and delta-change in serum 25OHD levels were also not significantly associated with bone mass parameters (**Web Table II**).

The infant's weight at birth as well as 12 months was significantly associated with bone mass parameters in both the groups (all $P<0.05$). Each 100 g increase in birth weight was associated with a mean (95% CI) increase in BMC, BMD and bone area by 0.004 (0.001 to 0.004) g, 0.26 (0.79 to 4.61) g/cm^2 and 0.0002 (0.0016 to 0.002) cm^2, respectively for group 1, and for group 2, 0.005 (0.001 to 0.006) g, 0.28 (0.35 to 5.17) g/cm^2 and 0.0002 (0.0005 to 0.003) cm^2, respectively. Similar increases were also observed irrespective of the groups without any significant difference between the groups.

DISCUSSION

The present study assessed the effects of vitamin D supplementation of two doses (1,20,000) IU/month vs 12,000 IU/month) for 12 months on serum 25O HD levels of lactating mothers and infants, and reports a significant improvement in vitamin D status of both mothers and infants. The serum 25O HD levels of mothers and infants randomized to higher dose were significantly higher as compared to the lower dose group.

In comparison to the global data, a higher prevalence of VDD has been reported across all age groups in the Indian population [3,4,14,15]. Exclusively breastfed infants



a *b*

Fig. 2 Vitamin D status in the two treatment groups (*a*) mothers and (*b*) infants.

are at higher risk of developing VDD as breastmilk has insufficient vitamin D content (10 to 20% of maternal blood vitamin D levels) [16]. This is further compromised by a high prevalence of VDD in the mother. Daily maternal vitamin D supplementation of 4000-6400 IU/day to mothers is recommended to maintain serum 25OHD concentration >30 ng/mL in exclusively breastfed infants not on vitamin D supplements [7,17]. The cholecalciferol readily passes to breast milk by simple diffusion across the cell membranes into the milk while 25OHD requires the presence of vitamin D binding proteins (megalin-cubilin endocytotic system) [18]. It has been suggested that for every 1000 IU per day cholecalciferol intake by mother, milk antirachitic activity would increase by <80 IU/L [19].

Table IV Comparison of Anthropometry and Bone Mass of Infants in the Two Groups

Parameter	*Group 1*	*Group 2*	*P value*
Anthropometry			
Normal birthweight	*n=90*	*n=95*	
Weight, kg	8.5 (0.98)	8.4 (0.97)	0.47
Length, cm	74 (3.19)	74 (2.80)	0.98
Head circumference, cm	44.2 (1.51)	44.1 (1.41)	0.78
Low birthweight	*n=20*	*n=15*	
Weight, kg	8.1 (0.9)	7.8 (0.9)	0.38
Length, cm	72.8 (3.61)	72.9 (2.72)	0.92
Head circumference, cm	43.4 (1.22)	43.9 (1.24)	0.29
Bone mass parameters			
Normal birthweight	*n=90*	*n=95*	
BMC, g	126.3 (29.67)	123.2 (23.65)	0.42
BMD, g/cm^2	0.323 (0.04)	0.320 (0.03)	0.57
Area, cm^2	387.6 (53.46)	383.5 (47.58)	0.56
Low birthweight	*n=20*	*n=15*	
BMC, g	110.2 (27.09)	*106.4 (19.73)*	0.65
BMD, g/cm^2	0.297 (0.04)	0.297 (0.03)	0.97
Area, cm^2	366.8 (49.9)	*355.3 (34.77)*	0.45

Data expressed as mean (SD). P<0.05 for intragroup comparison between normal birthweight and low birthweight infants. BMC: bone mineral content, BMD: bone mineral density. Maternal vitamin D supplementation Group I- 1,20,000 IU/mth and Group II- 12,000 IU/mth.

The MAVID randomized controlled trial compared vitamin D supplementation of 1200 IU/day to mothers with 400 IU/day given to babies and reported a similar increase in serum 25OHD level of infants in both groups. However, mothers in the first group had significantly higher serum 25OHD levels [20]. Similarly, another study, using a higher dose of cholecalciferol supplementation (6400 vs 300 IU/day to mothers for six months) showed significantly higher serum 25OHD levels in mothers and breast milk, but not in infants [19]. Similar results have also been reported in other studies [17,21,22]. Our study also reported similar results, with a significant increase in serum 25OHD levels of mothers as well as infants in both the groups. These differences with earlier studies (VDD in <30% subjects) could be because of a large difference in baseline vitamin D status.

Supplementation of vitamin D in daily dose is more physiological; however, the bolus dose (weekly or monthly) is equally effective in terms of improving vitamin D status with a higher adherence rate [23]. Comparison of daily vs bolus dose of vitamin D supplementation in lactating mothers showed equal efficacy [24]. We used bolus doses of vitamin D for supplementation, which gave us a very high compliance rate with minimal dropouts (<5% in both groups). Maintaining a high compliance rate for the study population, which is not highly educated (~60% of the study population was educated up to middle school

WHAT IS ALREADY KNOWN?

- Maternal vitamin D supplementation improves maternal and infant vitamin D status, and may be given in higher doses than those currently recommended.

WHAT THIS STUDY ADDS?

- Maternal vitamin D supplementation with a dose of 1,20,000 IU per month is more efficacious and safe than 12,000 IU per month in Indian population.

only, data not presented), is a significant advantage for countries with limited health resources.

There is limited evidence on whether maternal vitamin D supplementation during lactation improves infant growth. No effect on infant's weight, length, and head circumference was reported earlier even after controlling for confounding factors, similar to the present study. However, the majority of subjects did not have VDD [21]. Studies from regions where VDD is common have also shown similar results [25]. The present study also had a high proportion of maternal VDD but did not show any significant difference in infant's anthropometry.

The effects of maternal vitamin D supplementation on infant bone mass parameters have not been clearly evaluated. The MAVID trial reported no significant differences in infant whole-body BMC or BMD between the intervention (1200 IU/day) vs the control group (400 IU/day) of maternal vitamin D supplementation for six months [20]. Likewise, greater than 90% of the study subjects in the present study had VDD at baseline, but significant difference was not seen in whole body bone mass parameters between the two groups.

Due to logistic issues, we could not carry out estimation of vitamin D content in breast milk, which would have given an insight regarding the appropriate dose of maternal vitamin D supplementation. The details of supplementary feeding, which might have contributed to additional vitamin D intake by the infant, were not captured. Similarly, the details of sun exposure by mothers-infants and seasonal variability were not captured. However, we presume these variables would have affected both the groups similarly as subjects were randomized. It would have been better if infants were supplemented directly (like 400 IU/day) and compared with supplementation of lactating mother in improving vitamin D status of infant. However, in view of poor compliance of direct vitamin D supplementation in infant [9], this was not planned. The estimation of serum PTH was not planned due to logistic reasons (storage and transportation).

In conclusion, the present study shows that bolus vitamin D supplementation of lactating mothers (starting from the first postpartum month) in the dose of 1,20,000 IU/month was more efficacious to improve maternal and infant vitamin D status in comparison to 12,000 IU/month. However, vitamin D supplementation did not affect growth and bone mass parameters of infants.

Ethics clearance: Ethics Committee, Dr SN Medical College; No. F.1/Acad/MC/JU/13/ 16276, dated August 21, 2013.
Contributors: RK, RJ: contributed in conceptualising, planning and design of the study, data collection, analysis and interpretation of results and writing of manuscript; RR: involved in data collection, analysis and manuscript writing; SKV,PS,SW: involved in data collection. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India (Grant No-GIA/68/2014-DHR).
Competing interests: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets around the world: causes and future directions. Ann Trop Paediatr. 2006;26:1-16.
2. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: A review of the current evidence. Arch Pediatr Adolesc Med. 2008;162: 513-19.
3. Bhalala U, Desai M, Parekh P, et al. Subclinical hypovitaminosis D among exclusively breastfed young infants. Indian Pediatr. 2007;44:897-901.
4. Seth A, Marwaha RK, Singla B, et al. Vitamin D nutritional status of exclusively breast fed infants and their mothers. J Pediatr Endocrinol Metab. 2009;22:241-6.
5. Food and Nutrition Board. Standing Committee on the scientific evaluation of dietary reference intakes. Dietary Reference Intakes for Vitamin D and Calcium. National Academy Press; 2010.
6. Widdowson EM. Food intake and growth in the newly-born. Proc Nutr Soc. 1971;30:127-35.
7. Thiele DK, Senti JL, Anderson CM. Maternal vitamin D supplementation to meet the needs of the breastfed infant: A systematic review. J Hum Lact. 2013;29:163-70.
8. Khadilkar A, Khadilkar V, Chinnappa J, et al. Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics

(IAP) Guidelines. Indian Pediatr. 2017;54:567-73.
9. Perrine CG, Sharma AJ, Jefferds ME, et al. Adherence to vitamin D recommendations among US infants. Pediatrics. 2010; 125:627-32.
10. Indian Council of Medical Research. Nutrient Requirements and Recommended Dietary Allowances for Indians 2010. Accessed December 02, 2021. Available from: *https://www.icmr.nic.in/content/nutrient-requirements-recommended-dietary-allowances-indians*
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:1911-3.
12. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nut. 2001;73:288-94.
13. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266-81.
14. Khadgawat R, Marwaha RK, Garg MK, et al. Impact of vitamin D fortified milk supplementation on vitamin D status of healthy school children aged 10-14 years. Osteoporos Int. 2013;24:2335-43.
15. Jain V, Gupta N, Kalaivani M, et al. Vitamin D deficiency in healthy breastfed term infants at 3 months and their mothers in India: Seasonal variation and determinants. Indian J Med Res. 2011;133:267-73.
16. Hollis BW, Frank NE. Quantitation of vitamin D2, vitamin D3, 25-hydroxyvitamin D2, and 25-hydroxyvitamin D3 in human milk. Methods Enzymol. 1986;123:167-76.
17. Hollis BW, Wagner CL, Howard CR, et al. Maternal versus infant vitamin D supplementation during lactation: A randomized controlled trial. Pediatrics. 2015;136:625-34.
18. Hollis BW, Wagner CL. The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes. J Clin Endocrinol Metab. 2013;98:4619-28.
19. Wagner CL, Hulsey TC, Fanning D, et al. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: A 6-month follow-up pilot study. Breastfeed Med. 2006;1:59-70.
20. Czech-Kowalska J, Latka-Grot J, Bulsiewicz D, et al. Impact of vitamin D supplementation during lactation on vitamin D status and body composition of mother-infant pairs: A MAVID randomized controlled trial. PLoS One. 2014; 9:e107708.
21. Hollis BW, Wagner CL. Vitamin D requirements during lactation: High-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004;80:1752S-58S.
22. Dawodu A, Salameh KM, Al-Janahi NS. The effect of high-dose postpartum maternal vitamin D supplementation alone compared with maternal plus infant vitamin D supplementation in breastfeeding infants in a high-risk population: A randomized controlled trial. Nutrients. 2019;11:1632.
23. Meekins ME, Oberhelman SS, Lee BR, et al. Pharmacokinetics of daily versus monthly vitamin D3 supplementation in non-lactating women. Eur J Clin Nutr. 2014; 68:632-34.
24. Oberhelman SS, Meekins ME, Fischer PR, et al. Maternal vitamin D supplementation to improve the vitamin D status of breast-fed infants: A randomized controlled trial. Mayo Clin Proc. 2013;88:1378-87.
25. Roth DE, Morris SK, Zlotkin S, et al. Vitamin D supplementation in pregnancy and lactation and infant growth. N Engl J Med. 2018; 379:535-46.

CLIPPINGS

C3 Glomerulopathy and related disorders in children - Etiology-phenotype correlation and outcomes (Clin J Am Soc Nephrol. 2021;16:1639-51)

Membranoproliferative glomerulonephritis (MPGN) is a histopathological entity characterized by increased mesangial matrix and cellularity along with thickening of glomerular capillary walls, resulting from dysregulation of the alternative complement pathway. It is broadly classified into C3 glomerulopathy [C3 glomerulonephritis (C3GN) and Dense deposit disease (DDD)] and immune complex MPGN. This multicenter observational cohort study enrolled 80 pediatric (2-15 years) patients with MPGN/C3 glomerulopathy to determine the phenotype and were followed up for a median of 5.18 (IQR, 2.13-8.08) years within the National Registry of Rare Kidney Diseases (RaDaR). C3GN was more common than immune complex MPGN (39 vs 31 patients) while 10 patients were identified with immune complex GN. Acquired (anticomplement autoantibodies) alternate pathway dysregulation was detected in 46% patients across all groups while genetic alterations contributed to only 9% of patients. Hematuria was the most common presentation (91%) and low estimated glomerular filtration rate (eGFR) was detected in 44% patients at recruitment. Importantly, severe kidney dysfunction (eGFR <30 mL/min per 1.73 m^2) was observed only in patients with C3GN. On follow up, complete or partial remission was observed in 28 patients (71%) with C3GN and 36 patients (88%) with immune complex MPGN. Eleven patients (14%) progressed to renal failure and histopathologic evidence of >50% crescents was found to be the only risk factor for renal failure in multivariate analysis (hazard ratio, 6.2; 95% confidence interval, 1.05 to 36.6; $P<0.05$). Nine transplants were performed in eight patients but 2 of these failed due to recurrent disease. The authors concluded that presenting eGFR and crescentic disease are important prognostic markers of C3GN in pediatric patients, and even though acquired complement pathway abnormalities are common among these patients, they do not contribute to renal failure.

DR PRAJAL AGARWAL
prajal.agarwal@gmail.com

Web Table I Vitamin D Status of Mother and Infants

Serum 25OHD, ng/mL	*Group 1[#] n(%)*		*Group 2[#] n(%)*	
	Baseline (n=110)	*Follow-up (n=99)*	*Baseline (n=110)*	*Follow-up (n=99)*
Mother				
<10	58(58.6)	-	63(63)	5(5)
10-20	35(35.3)	8(8.1)	31(31)	73(73)
21-30	5(5.05)	18(18.2)	6(6)	17(17)
≥30	1(1.01)	73(73.7)	-	5(5)
Infant				
<10	78(78.7)	-	78(78)	5(5)
10-20	19(19.2)	5(5.05)	21(21)	77(77)
21-30	2 (2.02)	19(19.2)	1(1)	13(13)
≥30	-	75(75.7)	-	5(5)

[#]Represents dose of maternal vitamin D supplementation ;Group I- 120000IU/month and Group II- 12000IU/month 25OHD – 25 – hydroxyl vitamin D

Web Table II Variation in Bone Mass Based on Maternal and Infant Vitamin D Status

Serum 25OHD, ng/mL	*BMC (g)*			*BMD (g/cm^2)*			*Area (cm^2)*		
	Group 1	*Group 2*	*P Value*	*Group 1*	*Group 2*	*P Value*	*Group 1*	*Group 2*	*P Value*
Maternal baseline[a]									
<10	123.5(28.27)	121.6(22.6)	0.68	0.320(0.04)	0.317(0.03)	0.71	383(54.54)	381.5(44.39)	0.86
10-20	131.7(32.6)	126.6(27.45)	0.47	0.329(0.05)	0.325(0.03)	0.68	395.7(53.61)	385.9(57.12)	0.47
21-29	121.5(26.14)	125.4(11.08)	0.75	0.317(0.04)	0.319(0.01)	0.91	381.2(47.40)	392.2(25.26)	0.63
Maternal 1 year									
<10	-	103.7(17.45)	-	-	0.292(0.03)	-	-	352.7(32.98)	-
10-20	110.9(22.13)	124.5(22.53)	0.11	0.322(0.06)	0.319(0.03)	0.81	346(46.84)	388(43.06)	0.05
21-29	126.3(19.91)	126.8(28.62)	0.95	0.322(0.03)	0.330(0.04)	0.50	391.4(36.62)	382.7(58.11)	0.59
≥30	128(32.16)	112.2(20.10)	0.28	0.323(0.04)	0.321(0.01)	0.91	391.2(56.32)	351.4(72.13)	0.14
Infant baseline[a]									
<10	126.4(29.88)	122.3(22.45)	0.33	0.325(0.04)	0.319(0.03)	0.37	385.9(55.33)	381.9(45.67)	0.62
10-20	126.8(31.65)	126(30.44)	0.94	0.319(0.04)	0.322(0.04)	0.83	392.5(51.33)	386.8(59.4)	0.76
21-29	#	#	-	#	#	-	#	#	-
Infant 1 **year[b]**									
10-20	126.6(30.1)	123.1(24.53)	0.39	0.323(0.04)	0.320(0.03)	0.56	387.9(54.25)	382.7(49.35)	0.50
21-29	126.5(30.25)	126.1(17.74)	0.96	0.322(0.04)	0.320(0.03)	0.91	388.9(53.05)	393.3(40.06)	0.77
≥30	127.3(29.94)	#	-	0.322(0.04)	#	-	390.9(52.67)	#	-

Data expressed as Mean(SD); # Represents single observation, so Mean(SD) could not be calculated. [a]None had value >30ng/mL.
[b] None had value <10ng/mL

RESEARCH PAPER

Pediatric Hemophagocytic Lymphohistiocytosis - A Single Center Study

Tanusree Paul, Manas Kalra, Arun Danewa, Pallavi Sachdeva, Kasi Bharathi Thatikonda, Divij Sachdeva, Anupam Sachdeva

From Department of Pediatric Hematology Oncology and BMT Unit, Institute of Child Health, Sir Ganga Ram Hospital, Delhi.

Correspondence to: Dr Anupam Sachdeva, Director Pediatric Hematology Oncology and BMT, Institute of Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110 060. anupamace@yahoo.co.in
Received: June 02, 2020; Initial review: July 07, 2020; Accepted: April 01, 2021.

Objective: To describe the epidemiological features, outcomes and prognostic factors in diagnosis of pediatric hemophagocytic lymphohistiocytosis (HLH). **Methods**: 118 children fulfilling the inclusion criteria for HLH were identified from review of hospital records for period January, 2010 to December, 2019. **Result**: Median age at diagnosis was 4 years (range13 days-15 years). Presenting features were fever (100%), hepatosplenomegaly (91%), neurological symptoms (23%), bicytopenia (76%), transaminitis (67.3%), increased soluble interleukin-2 receptor) (sIL-2R) (78%) and hemophagocytosis on bone marrow (75%). Median follow-up duration was 13.5 months (3 days to 102 months). Primary HLH was identified in 27 (23%) patients. Etiology of secondary HLH was infections in 53 (45%), rheumatologic illnesses in 21 (18%) and malignancies in 8 (6%) children. Treatment modalities were steroid only (25%), anti-infectious agent (58%), multi-agent chemotherapy (43%) and HSCT (40%); mortality among above treatment groups were 25%, 58%, 43% and 40%, respectively. 15 patients (13%) had relapsed/refractory HLH who were treated with salvage chemotherapy and hematopoietic stem cell transplantation (HSCT). The overall mortality rate was 39%; mortality within 30 days seen in 23%. Estimated overall survival (OS) and event free survival (EFS) at 3 years were 62% and 61%, respectively. **Conclusion**: Pediatric HLH is an aggressive disease with high mortality. Hyponatremia, hyperbilirubinemia, coagulopathy and increased sIL2 receptor level at diagnosis predicts poor outcome.

Keywords: *Management, Outcome, Prognostic factor, Soluble IL-2 receptor.*

Published online: May 20, 2021; ***PII***: S097475591600325

Hemophagocytic lymphohistocytosis (HLH) is an aggressive and frequently fatal hyper-inflammatory syndrome, characterized by excessive activation of lymphocytes and macrophages that produce high level of cytokines. Primary form includes familial HLH (FHL) and immune deficiency-associated HLH [1]. Secondary HLH is associated with infections, autoimmune diseases and malignant disorders without an identifiable underlying genetic trigger [1]. The diagnosis of HLH is usually made as per the HLH 2004 diagnostic criteria laid down by the Histiocytic society [1].

In India, there is limited data on pediatric HLH [2-12]. This study describes the clinical features, outcomes and prognostic factors in a large sample of pediatric HLH from a single center.

METHODS

This is a retrospective analysis of data on children aged less than 16 years, diagnosed with HLH between January, 2010 and December, 2019 in the department of pediatrics of our tertiary care center. Patients fulfilling five out of the eight criteria i.e., fever, splenomegaly, bi- or pan-cytopenia, hypertriglyceridemia and/or hypofibrino-genemia, hemophagocytosis, low/absent NK-cell activity, hyperferritinemia, and high soluble interleukin-2-receptor (sIL-2R) levels, family history or confirmed molecular mutation were diagnosed as HLH [1]. Bone marrow examination was performed in patients presenting with cytopenias and other clinical and laboratory parameters suggestive of HLH. After the availability of next generation sequencing (NGS) in 2016, it was used for diagnosis for patients who fulfilled the criteria or where index of suspicion of HLH was very high. A double sandwich ELISA technique was used to measure sIL-2r after its standardization in 2014.

Remission was defined as no fever, no splenomegaly, no cytopenia (hemoglobin ≥90 g/L, platelets ≥100×109/L, neutrophils >0.5×109/L), no hypertriglyceridemia (triglyceride <3 mmol/L), no hyperferritinemia (ferritin <500 ng/mL), and a normal cerebrospinal fluid (CSF) examination [14]. Refractory HLH was defined as failure to achieve at least a partial response two weeks following standard HLH therapy. Central nervous system (CNS) involvement was labelled when neurological symptoms were present or pleocytosis and/or proteinosis was found in CSF, or abnormalities on magnetic resonance imaging were documented. Overall survival (OS) was measured as the

time from HLH diagnosis to the date of death from any cause or the last follow-up. Event free survival was defined as the probability of being alive and in conti-nuous complete remission at last follow up. Relapse, graft failure or refractory disease was considered as an event.

Statistical analysis: The Mann-Whitney U test was performed to find the risk factors for mortality. A Kaplan-Meir curve was used to describe mortality. All analyses were performed using SPSS 15.0. A P value < 0.05 was considered significant in the multiple regression analysis.

RESULTS

Of the 122 children diagnosed with HLH, data of 118 patients (66% boys) were included in the analysis. Median (13 days -15 year) age at diagnosis was 4 years; 7 patients were <28 day in age. Of these, 89 patients fulfilled the HLH diagnostic criteria. In 29 patients, the criteria were not fulfilled. However, based on high clinico-pathological suspicion, they were managed as per HLH treatment strategy after a multi-disciplinary team discussion. Median follow up duration was 13.5 months (3 days to 102 months). The median (range) serum ferritin was 6504 ng/mL (44-297,000 ng/mL); ferritin >500 ng/mL and >10,000 ng/mL were observed in 72% and 42% patients, respectively. Three patients presented with serum ferritin>100,000 ng/mL at the time of diagnosis.

Neurological presentation was seen in 28 patients (23%), but only 66.7% (12/18) patients had CSF pleocytosis. Neuroimaging was done in 25 patients; 8 of these had brain parenchymal changes. Intrathecal methotrexate was administered as per protocol in 12 patients. The etiology of primary and secondary HLH are described in **Table I**.

Most patients (42%) were treated only with steroids; dexamethasone being the drug of choice. Another 24 patients (20%) were treated with anti-infectious agents and intensive supportive care. Thirty five patients (29%) were treated with multi-agent chemotherapy including etoposide and steroids, of which 13 children completed 40 weeks therapy as per HLH protocol. Cyclosporine and IVIG were given to 36 (30%) and 32 (27%) patients, respectively. Thirty-two patients (27%) (20 primary HLH, 9 refractory HLH and 3 relapse) were advised HSCT out of which, 10 patients (9%) underwent the procedure after disease remission. The overall mortality rate was 38% (n=45) and among them early mortality within 30 days was seen in 23% (n=28). Mortality among above treatment groups were 25% (12/49) in steroid only, 58% (14/24) in anti-infectious therapy, 43% (15/35) in chemotherapy and 40% (4/10) in HSCT group. Aggressive supportive care including blood products with or without intensive care was given to all the groups. The outcome is shown in **Web Fig. I**.

Eight patients with primary HLH and two patients of refractory HLH underwent allogeneic HSCT. Genetic diagnosis was FHLH 2 (n=2), FHLH 3 (n=3), recurrent EBV triggered HLH (n=2) and in the remaining three patients NGS did not reveal any abnormality. Donors for transplant were HLA-matched, non-affected siblings in two patients and unrelated matched donor in four patients. The decision to perform haploidentical HSCT was made in four patients when a suitable unrelated donor was not available. Transplant-related mortality was seen in four patients, the etiology being veno-occlusive disease and acute GvHD in one patient each, and sepsis in another two. The remaining six patients are alive and in remission. Stable mixed chimerism with disease free survival was observed in six patients till median (range) 14 (4.8-64) months follow-up.

Table I Etiology of Pediatric Hemophagocytic Lymphohistiocytosis (N=118)

Etiology	*No (%)*
Primary HLH	
FHLH 2	10 (9)
FHLH 3	7 (6)
Griselli syndrome (type 2)	3 (2.5)
Mutation not identified	7 (6)
Secondary HLH	
IAHLH	
Virus AHLH[a]	
Dengue	19 (16)
EBV	10 (9)
Dengue/EBV coinfection	1 (1)
CMV	5 (4.5)
HSV	2 (1.5)
Pyogenic infection[b]	
Salmonella typhi	4 (3)
Scrub typhus	3 (2.5)
E.coli sepsis	2 (1.5)
Others	
Leishmaniasis	1 (1)
Not identified	2 (1.5)
Autoimmune disease[c]	
Systemic onset juvenile idiopathic arthritis	15 (13)
Systemic lupus erythematosus	4 (3)
MAHLH at the time of diagnosis	3 (2.5)
Anaplastic large cell lymphoma	2 (1.5)
Hodgkin lymphoma	1 (1)
During chemotherapy	5 (4.5)
Etiology not detected	6 (5)

[a]Parvovirus and influenza virus infection in 1 each; [b]Pseudomonas sepsis and disseminated tuberculosis in 1 each; [c]Kikuchi disease and Kyasanur forest disease were associated with SLE in 1 each. IAHLH: infection associated HLH, MAHLH: malignancy associated HLH.

Fifteen patients (13%) had relapsed/refractory HLH. Out of which, 11 patients (9%) died and the remaining four patients (3%) are disease free. Six patients died within one months of diagnosis. They were unresponsive to chemo-immunotherapy. Three patients relapsed on continuation therapy of HLH 2004 protocol and were started on salvage chemotherapy using L-DEP chemo-therapy [13]. They were refractory to L-DEP protocol and died. One patient had CNS relapse while on HLH 2004 protocol and died due to refractory seizures and prog-ressive CNS worsening. Out of the four patients who survived, two patients underwent HSCT. One patient underwent haploidentical HSCT and another matched sibling donor HSCT after disease remission. They are now disease free. One patient on LDEP protocol is disease free and is awaiting HSCT, and another patient who was refractory to steroid initially achieved disease remission after receiving to cilizumab.

The estimated overall survival (OS) and event free survival (EFS) at 3 years were 62% and 61%, respectively. We did not find hyperferritinemia at presentation as a statistically significant prognostic factor for mortality (P=0.39). The common causes of mortality were sepsis in 58% (26/45) and refractory disease in 25% (11/45). Other causes of mortality were refractory shock (n=3), seizure (n=1), acute GvHD (n=1), VOD (n=1) and pulmonary hemorrhage (n=1).

The odds of death were higher for patients with hyponatremia [OR (95% CI) 3.48 (1.35-8.99); P=0.008] hyperbilirubinemia [OR (95% CI) 2.04 (0.88-4.75); P=0.002], coagulopathy [OR (95% CI) 2.92 (1.15-7.38); P=0.02] and sIL-2r levels ≥2400 U/mL [OR (95% CI) 9.05 (1.06-77.5); P=0.03).

DISCUSSION

In this retrospective study, we report on clinicoetiological factors and outcome of 118 pediatric patients with HLH. The median age at diagnosis in this study was similar to a previous Indian study [7] but higher than other studies [8,9], possibly due to lesser number of familial HLH cases in our study. We suspect that most primary HLH patients succumb to their illness because of lack of early recognition of this entity. Hyperferritinemia, increased LDH, bicytopenia and increased sIL-2R were the most common laboratory abnormalities in patients with HLH, as also reported previously [2,10].

We found that with rising ferritin values, the chances of mortality also increases. Lin, et al. [11] reported that patients with <50% drop in ferritin level after starting treatment had a 17-fold increased chance of dying as compared with a 96% decline in ferritin. High ferritin levels (>50,000 ng/mL) have also been reported to correlate with 30-day mortality [19]. In another pediatric HLH study from India [5], repeat ferritin levels at or near discharge fell significantly (from admission values) in survivors but not in non-survivors.

Among the patients with secondary HLH, infections were the most common cause of HLH, which was consistent with previous reports from India [2,7] and outside [10]. In a case series by Oguz, et al. [10], EBV-triggered HLH consisted one third of the patients and in one Chinese study, almost 75% of HLH patients were associated with EBV [8]. This vulnerability to EBV infection in Chinese pediatric patients with HLH may be related to different genetic backgrounds. A Japnese study [13] reported that survival rate was significantly lower for the group with elevated blood sIL-2R levels (>10,000 U/mL) than for the group without elevated levels of this cytokine. However, no association was found in an adult study [14]. In 95 Chinese patients with HLH, hypoalbu-minemia, increased LDH and IL10 at diagnosis were independent prognostic factors of early death within 30 days [9]. Qiong, et al. [13] described hyperbilirubinemia, severe neutropenia and hypoalbuminemia as poor prog-nostic factors for mortality. However, Ramchandran, et al. [2] did not find any factor signifi-cantly associated with mortality.

In 1993, a study of 122 patients reported an estimated overall 5-year survival of 22% [16]. Patients with secondary HLH treated with chemotherapy-based protocols have had only a 55% survival at 3 years, and early mortality was related to hemorrhages and infections [17]. We report a higher (62%) overall survival at three years. Some studies have reported a higher overall survival rate (76%). The difference in the overall survival in various studies may be attributed to the difference in proportions of patient with secondary HLH and the treatment protocol used [2].

Limitations of our study include lack of genetic testing for all patients with HLH. We have not evaluated children with a secondary HLH for an underlying primary HLH mutation. Also, this is a retrospective study limiting the known advantages of a prospectively done trial. We report hyponatremia, hyperbilirubinemia, coagulopathy and increased sIL-2r as poor prognostic markers of HLH in Indian children. Prompt intervention in such patients may prevent early mortality and improve outcomes.

Acknowledgments: Mrs. Parul Chugh for her assistance with the statistics used in this study.
Ethics clearance: IEC, Sir Ganga Ram Hospital, New Delhi; No. EC/10/20/1739, dated March 24, 2021.
Contributors: TP, MK, AD: designed the study; TP, PS, KBT: collected the data; KBT, DS, PS: did the data analysis and interpretation; TP, AD, PS: wrote the first draft; MK, AS: critically reviewed the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related

WHAT THIS STUDY ADDS?

- Hyponatremia, hyperbilirubinemia, coagulopathy and increased sIL-2r were poor prognostic markers at diagnosis in children with hemophagocytic lymphohistiocytosis.

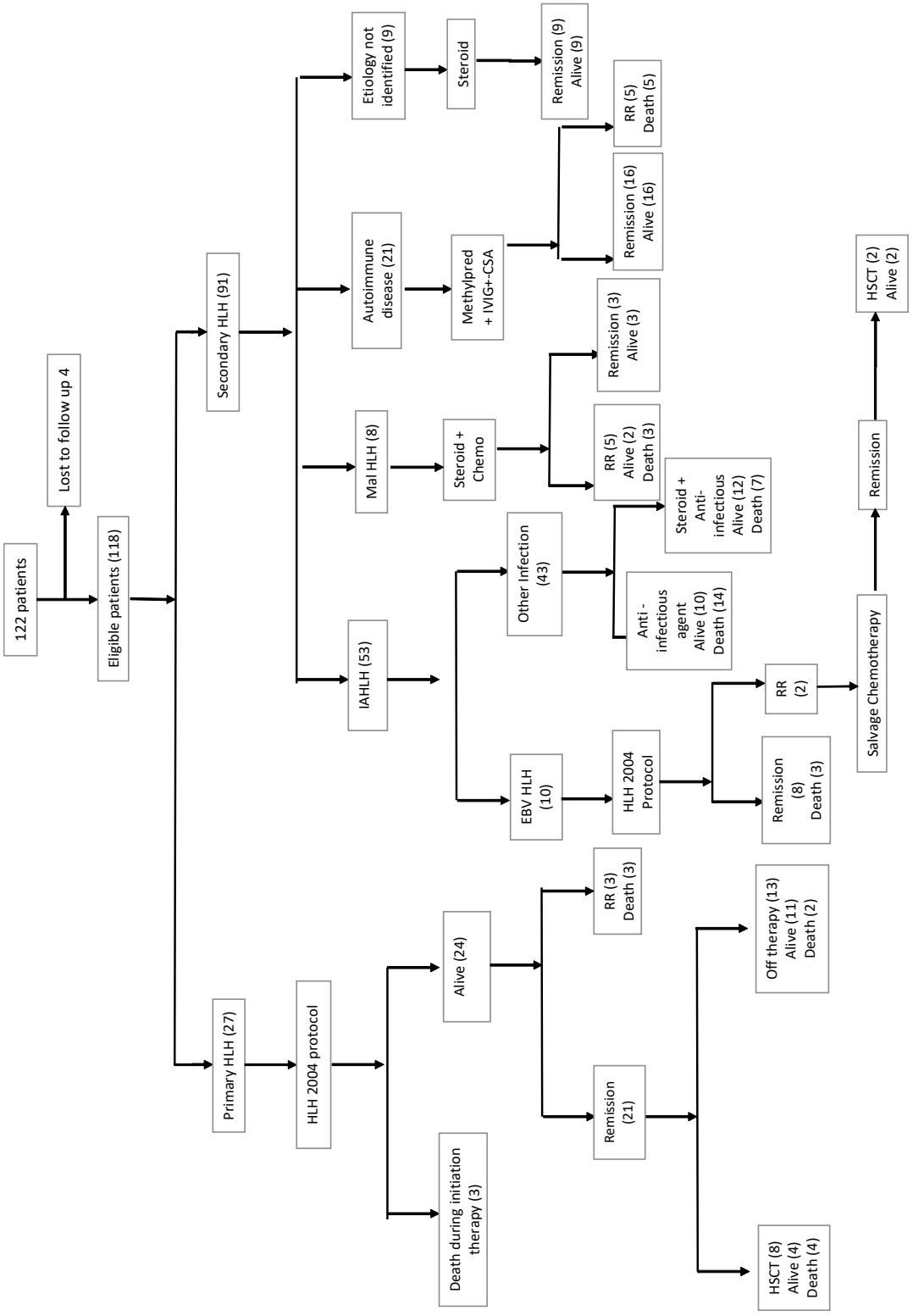
to the study.

Funding: None; *Competing interest*: None stated.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Henter JI, Horne A, Aricó M, et al. HLH 2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.
2. Ramchandran B, Balasubranian S, Abhishek N, et al. Profile of haemophagocytic lymphohistiocytosis in children in a tertiary care hospital. Indian Pediatr. 2011;48:31-5.
3. Rajajee S, Ashok I, Manwani N, et al. Profile of hemophagocytic lymphohistiocytosis; Efficacy of intravenous immunoglobulin therapy. Indian J Pediatr. 2014;81:1337-41.
4. Ramzan M, Yadav SP, Kharya G, et al. Hemophagocytic lymphohistiocytosis in infants: a single center experience from India. Pediatr Hematol Oncol. 2014;31:285-92.
5. Basu S, Maji B, Barman S, Ghosh A. Hyperferritinemia in hemophagocytic lymphohistiocytosis: A single institution experience in pediatric patients. Indian J Clin Biochem. 2018;33:108-12.
6. Bhattacharya D, Angurana SK, Nallasamy K, et al. Severe dengue and associated hemophagocytic lymphohistiocytosis in PICU. Indian J Pediatr. 2019;86:1094-98.
7. Nandhakumar D, Loganatha A, Sivasankaran M, et al. Hemophagocytic lymphohistiocytosis in children. Indian J Pediatr. 2020;87:526-31.
8. Xu XJ, Wang HS, Ju XL, et al. Clinical presentation and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in China: A Retrospective multicenter study. Pediatr Blood Cancer. 2017;64:e26264.
9. Luo ZB, Chen YY, Xu XJ, et al. Prognostic factors of early death in children with hemophagocytic lymphohistio-cytosis. Cytokine. 2017;97:80-5.
10. Oguz MM, Sahin G, AltinelAcoglu E, et al. Secondary hemophagocytic lymphohistiocytosis in pediatric patients: A single center experience and factors that influenced patient prognosis. Pediatr Hematol Oncol. 2019;36:1-16.
11. Lin TF, Ferlic-Stark LL, Allen CE, et al. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011;56:154-5.
12. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophago-cytic lymphohistiocytosis. Am J Hematol. 2015;90: 220-4.
13. Imashuku S, Hibi S, Todo S. Hemophagocytic lymphohistiocytosis in infancy and childhood. J Pediatr. 1997; 130: 352-7.
14. Hayden A, Lin M, Park S, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood Adv. 2017;1:2529-34.
15. Bin Q, Gao JH, Luo JM. Prognostic factor of early outcome in Pediatric HLH an analysis of 116 cases. Ann Hematol. 2016;95:1411-18.
16. Arico M, Janka G, Fischer A, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. Leukemia. 1996;10:197-203.
17. Henter JI, Samuelsson-Horne A, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002;100:2367-73.



RR-Relapse/Refractory, CSA-Cyclosporin, IVIG-Intravenous Immunoglobulin

Web Fig. 1 Outcome in Pediatric Hemophagocytic Lymphohistiocytosis.

RESEARCH PAPER

Profile of Functional Constipation in Children at a Referral Hospital

VIKAS ARVINDBHAI MAKHWANA, KAKOLI ACHARYYA, SAUGATA ACHARYYA
From Department of Pediatrics, Calcutta Medical Research Institute, Kolkata, West Bengal.

Correspondence to: Dr Saugata Acharyya, Senior Consultant and Head, Department of Pediatrics, Calcutta Medical Research Institute, Kolkata 700 027, West Bengal. acharyyasaugata@yahoo.com
Received: June 10, 2021; Initial review: July 08, 2021; Accepted: September 21, 2021.

Objective: To study the social, demographic and clinical profile of functional constipation (FC) in children. **Methods:** A cross-sectional study was performed in a tertiary-care hospital to assess prevalence and profile of functional constipation among children (1-18 years) using Rome IV diagnostic criteria. **Results:** Children with FC constituted 5.56% (87/1565) of hospital attendees. 64.4% were between 2-6 years old and 48.3% had a past history of use of laxatives. Painful defecation was the commonest (62.1%) presenting symptom, while avoidance to school toilet was the commonest (25.3%) precipitating factor. Fecal impaction was present in 70.1% children. **Conclusion:** Functional constipation was the commonest cause of constipation, and a majority of these children had associated fecal impaction.

Keywords: *Fecal impaction, Functional gastrointestinal disorder, Painful defecation*.

Published online: January 09, 2022; ***PII***: S097475591600399

Constipation is a frequently encountered problem in pediatric age group. Constipation is usually defined as infrequent defecation, painful defecation, or both. Acute constipation persists for less than 4 weeks, beyond which it become chronic. The diagnosis of functional constipation is mostly by exclusion of organic etiology. The Rome IV criteria provide a symptom-based diagnostic tool for functional gastrointestinal disorders (FGID) in children and adolescents [1].

There is very little Indian data on the clinical profile of childhood functional constipation (FC), diagnosed as per the newer Rome IV criteria. Hence, the present study was conducted to evaluate the proportion of children with FC using Rome IV diagnostic criteria, along with assessment of their demographic and clinical profile.

METHODS

A questionnaire-based cross-sectional study was undertaken at the pediatric department of Calcutta Medical Research Institute between April, 2019 and March, 2020, after obtaining approval from the institutional ethics committee. From the children and adolescents aged 1-18 years who attended our hospital outpatient department during the study period, those with infrequent and/or painful defecation were referred to the constipation clinic for further evaluation. Children with potential alarm features for organic causes of constipation and those with irritable bowel syndrome-constipation variant (IBS-C), as per Rome IV criteria, were excluded. Children with recurrent abdominal pain and those receiving analgesic/antispasmodic medi-cation for their symptoms were also excluded. A trained pediatric gastroenterologist evaluated all children attending the constipation clinic to identify those with FC. A symptom-based clinical diagnosis of children with FC was made on the basis of history and physical examination. Following the consensus guidelines of European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition [2], a digital rectal examination was performed only to confirm the diagnosis of fecal impaction and to exclude underlying medical conditions. A plain abdominal radio-graph was performed in children with suspected fecal impaction, in whom a digital rectal examination was either unreliable or not possible. None of the children had barium enema and manometry, as these do not constitute essential first line investigations in constipation. Likewise, routine allergy testing for cow milk allergy or laboratory screening tests for hypothyroidism, celiac disease and hypercalcemia were not undertaken, as we had already excluded those children with potential alarm features.

A detailed clinical and demographic profile of children with FC were noted. These included mean age at presentation, sex, duration of symptoms at the time of enrolment, nutritional and socioeconomic status (Kuppuswamy scale), treatment history, common clinical presentations and precipitating factors. The data were collected using direct interview by a single investigator to minimize subjective bias. Diagnosis of behavioral problems like temper tantrum or school phobia was made as per standard guidelines [DSM-5].

Statistical analysis: Categorical variables are expressed as number (percent), and continuous variables as mean (SD).

RESULTS

Out of a total of 1565 children aged 1-18 years presenting in the outpatient department (OPD) during the study period, 176 (11.25%) were referred to the constipation clinic. Out of them, 23 declined to participate in the study. Of the remaining 153 children, 19 (12.4%) had alarm features suggesting organic etiologies for constipation, hence were excluded. Of these 19 children, six had Hirschprung disease, three had neurodevelopmental disorder, two had neural tube defects, and one each had congenital hypothy-roidism, celiac disease and cystic fibrosis. Another 14 children (9.2%) were suspected to have IBS-C and were excluded from the study. Thirty three (21.6%) children with constipation had presented with recurrent abdominal pain, and of these 13 had used oral paracetamol, 11 had used oral drotaverin and 9 had used a combination of oral dicyclo-mine and simethicone, without long-lasting relief of their symptoms. Since these medications had the potential to contribute to their symptom of constipation, these were excluded. Thus, 87 (56.9%, 49 females) were diagnosed to have FC (5.6% of those attending the OPD).

The mean (SD) age at presentation of the children with FC was 58.3 (26.5) months, with a mean (SD) duration of symptoms of 74.5 (25.4) days. The commonest age range of children with FC was between 2-6 years (64.4%). Among children with FC, 79.3% had urban residence; and 42.5% (37/87), 25.3% and 13.8% were from upper middle, lower middle and upper lower socio economic class.

Amongst the 48 (55.2%) children with FC aged 1 to 5 years, Out of the 39 (44.8%) children and adolescents between 5-18 years, 25 (64.1%) had normal BMI and 9 (23.1%) children were either overweight or obese.

Out of the 87 children with FC, 42 (48.3%) had a past history of using oral laxatives (26 oral lactulose, 16 oral polyethylene glycol), without any long term relief of symptom severity. The mean (SD) duration of oral laxative use was 45.4 (10.08) days. Sixty one (70.1%) had fecal impaction; of these, 32 (52.5%) had impaction confirmed by digital rectal examination, 18 (29.5%) had palpable fecolith on abdominal palpation, and 11 (18.0%) had it verified by abdominal *X*-rays. Painful defecation (62.1%) was the commonest clinical presentation (**Table I**). Aversion to use school toilet was the commonest precipitating factor (25.3%) for FC (48.7% in those aged 5-18 years).

Table I Clinical Presentation and Associated Factors of Functional Constipation (*N*=87)

Parameters	*No. (%)*
Presenting features	
Fecal impaction	61 (70.1)
Painful defecation	54 (62.1)
Fecal incontinence	23 (26.4)
Withholding behavior	21 (24.1)
Blood streaked stool	12 (13.8)
Urinary symptoms	9 (10.3)
Associated factors	
Aversion to use school toilet	22 (25.3)
School/playgroup phobia	19 (21.8)
Temper tantrum/separation anxiety	17 (19.5)
Sibling rivalry	14 (16.1)

DISCUSSION

The proportion of children with FC in our study (5.6%) is lower than the pooled prevalence of 9.5% reported previously [3]. This is despite the fact that we had used the Rome IV criteria (with a lower symptom duration for diagnosis) than previous studies using Rome III criteria. This may be due to the exclusion of those children with 'potential alarm features' and those with constipation and recurrent abdominal pain, who were treated with anal-gesics and antispasmodics. In our study, FC was the commonest cause among all constipated children, which is in concurrence with other studies from India using Rome III criteria [4,5]. The median age of children at the time of enrolment in our study was more than the median age reported in a previous larger Indian study using the Rome III criteria [6]. We have found that children between 2-6 years age group are the ones affected most with FC, which is similar to a previous study [7]. In our study the commonest presenting clinical symptom of FC was painful defecation (62.1%), this is similar to studies done in Sri Lanka [8] and US [9] and but higher than studies done in India [10]. Proportion of fecal incontinence [10,11] and fecal impaction on abdominal and digital rectal examination [11] are similar to previous Indian studies. We found aversion to use the school toilet as the commonest precipitating factor for FC, which was also reported in a previous study [11].

Use of Rome IV criteria for diagnosis and direct interview by a single investigator for data collection are the main strengths of our study. However, FC was diag-nosed on the basis of recall of symptoms over past one month, which might lead to a recall bias. Profile of FC from different regions using recent criteria would further inform the pediatrician for early diagnosis and management.

Ethics clearance: IEC. Calcutta Medical Research Institute; No. PROT/DNB/96/PED/10/2019, dated Sep 10, 2019.
Contributors: SA, KA: conceived and planned the study, supervised the conduct of the study; MV: data collection by interviewing the participants/parents. All the authors were involved in preparation and drafting of the manuscript along with literature search. All authors approved the final version of the manuscript.
Funding: None; *Competing interest*: None stated.

WHAT THIS STUDY ADDS?

- We report the profile of children with functional constipation diagnosed using the Rome IV criteria.

REFERENCE

1. Hyams SJ, Lorenzo DC, Saps M et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroentero-logy. 2016;150:1456-68.
2. Tabbers MM, Benninga MA, Di Lorenzo c, et al. Evalua-tion and treatment of functional constipation in infants and children: Evidence based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014; 58: 258-74.
3. Koppen IJN, Vriesman MH, Saps M, et al. Prevalence of functional defecation disorders in children: A systematic review and meta-analysis. J Pediatr. 2018;198: 121-130.e6.
4. Kondapalli CS, Gullapalli S. Constipation in children: incidence, causes in relation to diet pattern and psycho-social aspects. Int J Contemp Pediatr. 2018;5:6-13.
5. Raju BB, Sumathi B. Constipation in children. Indian Journal of Practical Pediatrics. 2008;10:201-07.
6. Poddar U, Singh S, Pawaria A, et al. Aetiological spectrum, clinical differentiation and efficacy of polyethylene glycol over lactulose in children with constipation: Experience of 316 cases. J Paed Child Health. 2019;55.2:162-67.
7. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3-18.
8. Rajindrajith S, Devanaryana NM, Adhikari C, et al. Constipation in children: An epidemiological study in Sri Lanka using Rome III criteria. Arch Dis Child. 2012; 97:43-5.
9. Borowitz SM, Cox DJ, Tam A, et al. Precipitants of constipation during early childhood. J Am Board Fam Pract. 2003;16:213-8.
10. Bansal R, Agarwal AK, Chaudhary SR, et al. Clinical manifestations and etiology of pediatric constipation in North India. International Journal of Scientific Studies. 2016;4:185-90.
11. Khanna V, Poddar U, Yachha SK. Etiology and clinical spectrum of constipation in Indian children. Indian Pediatr. 2010;47:1025-30.

RESEARCH PAPER

Hepatitis B Vaccination Coverage of Preschool Children in Libreville, Gabon: Prevalence and Determining Factors

S MINTO'O,[1] E KUISSI KAMGAING,[1] U BISVIGOU,[2] FC LOEMBE,[1] D ZOUANZE,[1] E NGOUNGOU,[2] SJ ATEGBO[1]

From [1]Department of Pediatrics, Faculty of Medicine, University of Health Sciences; [2]Department of Public Health and Biostatistics, Faculty of Medicine, University of Health Sciences, Libreville, Gabon.

Correspondence to:
Dr Steeve Minto'o,
Faculty of Medicine,
P.O. Box 4009 Libreville,
Gabon.steeve.mintoo@hotmail.fr
Received: November 10, 2020;
Initial review: November 14, 2020;
Accepted: October 08, 2021.

Objective: We aimed to assess hepatitis B vaccination coverage (vaccine coverage) among preschool children in Libreville, Gabon, and determine associated factors. **Methods**: A cross-sectional study was done evaluating hepatitis B vaccination records, by cluster random sampling of children aged 4 months to 5 years from 5 medical centres **Results**: Of the 500 children (243 males) included, we found a hepatitis B vaccine coverage of 78.6% (95% CI 75% to 82.2%). Factors significantly associated with vaccine coverage included parental confidence in the vaccine (OR=2.2;95% CI 1.4-5.5), the number of children at home lower than the median (aOR=1.6; 95% CI ; 1.3-3.7). and working mothers/fathers. **Conclusion**: Hepatitis B vaccine coverage in Libreville is lower than WHO objectives. Healthcare providers have a crucial role in building up confidence among parents.

Keywords: *pre-school children, national immunization, Africa, WHO, vaccination coverage.*

Published online: January 09, 2022; ***PII***: S097475591600395

As per the World Health Organization (WHO) 2015 estimates, the worldwide prevalence of Hepatitis B (HBV) infection in under-5 children has declined to 1.3% from 4.7% in the pre-vaccination era.The Pacific region with 6.2% and the African Region with 6.1% of their people infected, are areas of high endemicity [1]. Hepatitis B vaccination is the most effective interventional strategy available to achieve the WHO objective of eliminating HBV as a public health threat by the year 2030 [2,3].

To reduce the burden of chronic HBV infection, HBV was introduced in the Gabonese Expanded Program on Immunization (EPI) in 2004, as a 3-dose schedule, combined with Diphtheria-Tetanus-Pertussis-Haemophilus influenzae b vaccines at 6, 10, and 14 weeks of life, without a birth dose [4], similar to many countries in the WHO African Region [5]. In Libreville, healthcare is free in the public sector, unlike the private sector. As per WHO 2015 report, the coverage of three-doses of the HBV vaccine administered in all 47 member states was 77%. A low coverage of 11% was reported in the few countries where hepatitis B birth-dose was introduced [8].The absence of an institutional surveillance system for hepatitis B infection presents a challenge for the estimation of HBV vaccine coverage (vaccine coverage). In 2010, a study conducted in Libreville showed a prevalence of the third dose of the hepatitis B vaccine of 71.3% [6].

METHODS

We conducted a multi-center cross-sectional study, from April to December, 2019 in Libreville, Gabon in five randomly selected medical centres. Taking the target population of children from 0 to 6 years as 170000, expecting a prevalence of complete vaccine coverage at one year of 36 % [4] in Gabon, an acceptable margin of error of 5% and 95% CI, factor mitigating our design effect as 1.3, we included five clusters (5 randomly selected hospitals and medical centers of Libreville, Gabon) resulting in a cluster size of 92 cases and a total sample size of 460 subjects. Participants included children aged four months to six years, coming for consultation, having a vaccination booklet and being accompanied by either parent or current guardian, who gave informed consent for participation. Vaccination coverage (vaccine coverage) was calculated as subjects having received at least 3 doses of hepatitis B vaccine. Data regarding socio-demographic settings, education and employment status of parents, acceptance of parents for HBV vaccination as well as the number of HBV vaccine doses, were recorded. To prevent bias, investigation days were fixed and investigators could meet the same practitioner no more than two times and a maximum number of five subjects could be included in a day by an investigator. This survey received clearance from Gabon EPI National Directorate, the directions of university hospitals, and participating health centers. As

per the directors' instructions, information concerning the religion or the ethnicity was not collected.

Statistical analysis: The prevalence of vaccine coverage was expressed as percentage with 95% CI. Univariate and multivariable logistic regression analysis were done to assess the association between parent's parameters and vaccine coverage. Statistical significance was taken at $P<0.05$. The analysis was carried out using Epi Info 7.2.2 from CDC.

RESULTS

A total of 500 children from 500 different households (243 (48.6%) males), with a median age of 11 months (IQR), were included. The median birth order of the children was second and the median number of children at home was 2 (min=1; max=13). The socio-demographic characteristics of the parents are summarized in **Table I.**

A significant proportion of parents [107 (21.4%) had relocated ($P<0.001$) and had a job loss [16 (3.2%)] within the first 6 months of the child's life ($P<0.001$). A total of 393 (78.6%; 95% CI 75% to 82.2%) children had received at least three doses of vaccine, while 107 (21.4%; 95% CI 19.6%-23.2%) children had received between 0 and 2 doses of vaccine. **Table II** shows the factors associated with hepatitis B vaccination coverage. Unemployed father vs others was associated with a lack of hepatitis B vaccination [aOR 3.7 (95% CI 2.2-5.9); $P<0.001$].

DISCUSSION

We found a vaccine coverage of 78.6%, which is not an appreciable improvement over a vaccine coverage of 71.3% in 2010 [6], falling far short of the WHO target of 90% intended for 2020 [1]. The vaccine coverage of Libreville matches with urban areas of Senegal (76.5%) [11], while the nearby country of Cameroon reported a prevalence of 66.7% in 2018 [12]. On the other hand, French Polynesia reported a vaccine coverage of 98% in six-year-old children [7]. Also, Southeast Asian countries have shown a consistent improvement in hepatitis B vaccine coverage [13]. Our study showed that parents' confidence in vaccines was an important factor favouring vaccine coverage. The importance of the role of counsell-ing by health care providers and parents' knowledge about the disease and the vaccine has been reported in India, as well as in a systematic review on the factors influencing vaccine coverage [14,15]. In the Zhejiang province of China, fixed residence of the child was associated with better vaccine coverage compared to migrant children [19]. This data corroborates with our results.

Other studies have demonstrated associations of vaccine coverage with tribal groups and religion. Christian children showed better vaccine coverage compared to muslims in Cameroon [12]. Severe ethnicity compared to Poular and residence in the western region compared to the southern region were associated with better vaccine coverage rates in Senegal [11]. However, we could not analyze these factors because the medical committees of the hospitals did not distinguish ethnicity or religion of the patients. Further, in our study, unemploy-ment among parents was significantly associated with lack of hepatitis B vaccination.

The random sampling method used in this study, and the sociodemographic and educational characteristics of parents are similar to those of 2012 Demographic and Health Survey (DHS) [4]. Random cluster sampling was also used in Qatar, while in USA, the government uses data from the National Immunization system-Child Monitoring (Nis-Child), which allows real-time vaccination monitoring of children born and living in the USA [9]. In contrast, in France, 85% of vaccination is done by private sector, which is not recorded in a central database. So, vaccine reimbursement data obtained from National Health Insurance Information System has been used to estimate vaccine coverage [10].

To conclude, the prevalence of vaccine coverage in our study is lower than 2020 WHO objectives for our health

Table I Characteristics of the Parents of the Children included in the study

Characteristics	*Mothers (N =500)*	*Fathers (N=500)*
Age (y), mean (SD)	27.2 (6)	33.5 (7.5)
Status of a parent at childbirth		
Pupil or student	225 (45)	69 (13.8)
Unemployed	120 (24)	20 (4)
Liberal	54 (10.8)	138 (27.6)
Employed	101 (20.2)	273 (54.6)

All values are in number (%) unless mentioned otherwise.

Table II Factors Associated With Good Vaccination Coverage

Factors	*aOR (95% CI)*	*P*
Number of children at home (Less than median vs more than median)	1.62 (1.3-3.7)	<0.001
Employed mothers vs unemployed	1.09 (0.9-2.2)	0.02
No change in residence in the first 6 months	1.7 (1.2-3.4)	0.002
Parents' confidence in vaccine	2.2 (1.4-5.50)	<0.001

aOR: adjusted odds ratio.

WHAT THIS STUDY ADDS?

- Hepatitis B vaccination coverage is suboptimal in preschool children in Gabon.

region. Analysis of the determinants of vaccine coverage showed the crucial role of health care providers in educating and counselling parents.

Ethics clearance: Gabon Ministry of Health, EPI National Directorate, University Hospitals and Health Centres participating to the study.

Acknowledgements: Directorates of institution: Centre Hospita-lier Universitaire de Libreville, Centre Hospitalier Mère et Enfant Fondation Jeanne Ebori, Centre de Santé d'Awendjé, Centre de Santé de NzengAyong, Centre de Santé de La Peyrie.

Contributors: SM, UB, EKK, EN, SJA: design of the study was discussed and decided; DNZ, FCL, SM, UB: The data collect was realised; MS, UZN, UB: The data analysis was performed; MS, UB, UZN, FCL, EKK, EN, SJA: The discussion before writing was made unanimously. MS: wrote the draft of the article, and all the members made their comments and inputs. The original article was written in French, and the translation made by SM and checked with Grammarly software.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. World Health Organization. Global hepatitis report; 2017. Accessed September 05, 2021. Available from: *http://app@s.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1*
2. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronichepatitis B infection. 2015. Accessed September 05, 2021. Available from: *9789241549059_eng.pdf (who.int)*
3. Groc S, Abbate JL, Le Gal F, Gerber A, Tuaillon E. High prevalence and diversity of hepatitis B and hepatitis delta virus in Gabon. J Viral Hepat. 2019;26:170-82.
4. DGS (Direction Générale de la Statistique du Gabon) / ICF International. 2012.Gabon Demographic and Health Survey 2012: Synthesis Report. [Enquête Démographique et de Santé du Gabon 2012 : Rapport de synthèse]. Calverton, Maryland, USA: DGS et ICF International. Accessed September 05, 2021. Available from: *https://www.dhsprogram.com/pubs/pdf/SR198/SR198.pdf*
5. Al-Romaihi H, Al-Masri H, Shawky S, et al. Assessment of hepatitis B immunization program among school students in Qatar. East Mediterr Health J. 2018;24:736-44.
6. Ategbo S, Ngoungou EB, Koko J, et al. Étude de la couverture vaccinale chez les enfants de 0 à 5 ans à Libreville (Gabon) [Immunizationcoverage of children aged 0 to 5 years in Libreville (Gabon)]. Sante. 2010;20:215-9.
7. Patel MK, Le Calvez E, Wannemuehler K, Ségalin JM. Hepatitis B vaccination coverage and prevalence of hepatitis B surface antigen among children in French Polynesia, 2014. Am J Trop Med Hyg. 2016;94:1370-75.
8. Abara WE, Collier MG, Teshale EH. Impact of universal infant hepatitis B vaccination in the US- affiliated Pacific Islands, 1985-2015.Vaccine. 2017;35:997-1000.
9. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang. Vaccination coverage among children aged 19-35 months – United states, 2016.US Department of Health Service/Center for Disease Control and Prevention. Morbidity and Mortality Weekly Report. 2017;66:1171-77.
10. Fonteneau L, Ragot M, Guthmann JP, Levy Bruhl D. Use of health care reimbursement data to estimate vaccination coverage in France: example of hepatitis B, meningitis C, and Human papillomavirus vaccination. Rev Epidemol Sante Publique. 2015;63:293-98.
11. Sarker AR, Akram R, Ali N, Chowdhury ZI, Sultana M. Coverage and determinants of full immunization: vacci-nation coverage among Senegalese children. *Medicina.* 2019; 55:480.
12. Dionne-Odom J, Westfall AO, Nzuobontane D, et al. Predictors of infant hepatitis B immunization in Cameroon: data to inform implementation of a hepatitis B birth dose. Pediatr Infect Dis J. 2018;37:103-07.
13. Childs L, Roesel S, Tohme RA. Status and progress of hepatitis B control through vaccination in the South-East Asia Region, 1992-2015. Vaccine. 2018;36:6-14.
14. Steinhoff M, Simon A. Parental attitudes towards inûuenza vaccination for children in South India. World Journal of Pediatrics. 2017;13:84-90.
15. Smith LE, Amlôt R, Weinman J, Yiend J, Rubin GJ. A systematic review of factors affecting vaccine uptake in young children.Vaccine. 2017;35:6059-69.

RESEARCH PAPER

Profile of Girls With Adnexal Torsion: Single Center Experience

PATRYCJA SOSNOWSKA-SIENKIEWICZ, PRZEMYSLAW MANKOWSKI
From Department of Pediatric Surgery, Traumatology and Urology, Poznan University of Medical Sciences, Poland

Correspondence to:
Dr Patrycja Sosnowska-Sienkiewicz, Department of Pediatric Surgery, Traumatology and Urology, Poznan University of Medical Sciences, ul. Szpitalna 27/33, 60-572 Poznan, Poland.
patrycja.sosnowska@outlook.com
Received: July 04, 2021;
Initial review: October 09, 2021;
Accepted: December 15, 2021

Objective: To compare features of pre-menarchal and post-menarchal patients with adnexal torsion. **Methods**: We reviewed hospital records to note examination findings, laboratory work-up, imaging results, operative findings and course during hospital stay for 56 girls aged from 7 days to 17 years with adnexal torsion presenting between January, 2012 and December, 2020. **Results**: 31 girls were pre-menarchal. Pain was the most common symptom. There were significant differences in the volume of the ovary visualized in ultrasound in amenorrheic and menstruating girls [median (IQR) 78234 (39600, 183600) mm^3 vs 243432 (158661, 388800) mm^3; *P*=0.004]. Pain was the most common symptom. Over the years, there was an increase in laparoscopic procedures, and efforts to preserve the ovary after the torsion. **Conclusions**: The differential diagnosis in the case of abdominal pain should include adnexal torsion both in non-menstruating and menstruating girls.

Key words: *Abdominal pain, Laparoscopy, Ovarian torsion, Outcome*.

Published online: January 09, 2022; ***PII***: S097475591600401

Adnexal torsion is the fifth most common gynecological emergency, accounting for approximately 15% of all cases of torsion in the pediatric and adolescent age group. In neonates, torsion is rare, and occurs in only 16% of girls younger than 1 year [1]. Most often the child presents with abdominal pain, nausea, vomiting and fever, although not all of these symptoms always occur [2]. The first imaging examination in the case of suspected adnexal torsion is an abdominal ultrasound (USG), wherein lesions in the ovary may or may not be visible. Furthermore, it is often difficult to assess proper vascularization of the organ [3]. There-fore, if adnexal torsion is suspected, immediate laparo-scopic evaluation is indicated in order to preserve ovarian function and future fertility [1,2,4]. The surgical treatment may include detorsion alone, detorsion with oophoropexy, or oophorectomy [5].

The aim of this study was to analyze and compare pre-menarchal and post-menarchal patients with adnexal torsion, treated surgically at a single pediatric surgery department over 10 years.

METHODS

The study was a retrospective chart review of 56 girls aged from 7 days to 17 years, who had undergone surgical treatment of adnexal torsion at our center between January, 2010 and December, 2020. Medical charts were analyzed for the following data: age at time of surgery, occurrence of menarche, laboratory test results including tumor markers, results of imaging examination, mean volume of the twisted ovary, type of surgical treatment, time of oophoropexy, defects in the structure or pathological lesions of the adnexa, symptoms on admission, median score on the pain scale and the course of hospitalization. Tumor markers were evaluated if a lesion was detected in the ovary during ultrasound examination.

Institutional ethics committee waived-off the need to obtain individual participant's consent.

Statistical analysis: We used Statistica 10 (StatSoft Inc.) for analysis. Statistical significance was set at $P<0.05$. To examine the relationship between the described variables, the Mann-Whitney and Fisher-Freeman-Halton tests were used.

RESULTS

Data of 56 girls (31 premenarchal) were analyzed. Baseline characteristics and the presenting complaints are shown in **Table I**. Ultrasound examination was performed on admission in all patients, which identified adenexal torsion in 72%. In the remaining, the examination was inconclusive and torsion features were not visualized.

Pain was reported in 44 girls (76%), with post-menarchal girls reporting more severe pain than amenorrheic girls (**Fig. 1a**). The volume of the ovary visualized in ultrasound in amenorrheic girls was significantly smaller than menstruating girls [median (IQR) volume 78234 (39600, 183600) mm^3 vs 243432 (158661, 388800) mm^3; *P*=0.004] (**Fig. 1b**).

Laboratory tests were normal in most of the patients, except six girls with increased C- reactive protein (CRP) and

Table I Characteristics of Girls With Adnexal Torsion (*N*=56)

Characteristics	*Pre-menarchal (n=31)*	*Post-menarchal (n=25)*
Age, y[a]	6 (4.75)	13 (2.84)
Ultrasound at admission	31 (53)	27 (47)
Features of ovarian torsion	20 (64)	20 (74)
Inconclusive examination	11 (35)	7 (26)
Ovary volume (mm^3) [b,c]	78234 (39600, 183600)	243432 (158661, 388800)
Chief complaint		
Abdominal pain	20	24
Nausea	14	19
Vomiting	1	7
Restlessness	6	0
Pain score (1-10) [b]	6 (5,9)	7 (5,10)
Laparoscopy	15 (48)	19 (70)
Laparotomy	16 (59)	7 (26)
Coexisting lesion in the ovary	13 (42)	14 (52)
Defect in adnexal structure	9 (29)	5 (19)
Oophoropexy[d]	10 (32)	7 (26)

All values in no. (%) or [a]mean (SD) and [b]median (IQR). [c]Volume of twisted ovary; [d]Done during ovarian torsion surgery in one pre-menarchal and two post-menarchal girls.

elevated leukocyte counts. All these patients had their ovaries removed due to complete necrosis.

Over 10 years, 34 laparoscopies and 33 laparotomies were performed. There was an increase in the use of laparoscopic technique over the years. During laparoscopy, 24% of the patients were diagnosed with an excessively long fallopian tube, elongated mesentery of the fallopian tube and ovary or elongated ligaments of the ovary. Planned, postponed oophoropexy was performed in all of these girls. During the surgery of de-torsion, three patients had oophoropexy performed simultaneously, in two cases due to ovary torsion in the past and in one girl because it was a single ovary.

Twenty-seven girls were preoperatively diagnosed with an accompanying ovarian lesion. A simple ovarian cyst was diagnosed in 23 patients, teratomas in two patients, and granulosa cell tumor and chocolate cyst in 1 patient each. Over the 10 years, there was an increasing tendency to preserve the ovaries (P<0.001).

DISCUSSION

Adnexal torsion is a pediatric condition with symptoms similar to other more common diseases, which causes difficulty in timely recognition [6]. Diagnostic delay can lead to adnexal necrosis and the necessity of its resection [7]. Similar to our data, other centers also report approximately half of the children with ovarian torsion being pre-menarchal [7,8]. Menstruating girls experienced pain more strongly than non-menstruating girls, which may be due to their greater awareness of pain or greater anxiety about loss of an ovary. Trans-abdominal ultra-sonography has a sensitivity of 92% and specificity of 96% in detecting adnexal torsion [9]. The use of Doppler studies in detecting adnexal torsion is limited because of their low sensitivity and dependence on the radiologist's experience. Sasaki, et al. [10] reported that normal Doppler arterial flow was present in 60% of surgically confirmed cases of adnexal torsion. That is why Doppler flow alone cannot guide clinical decision making.

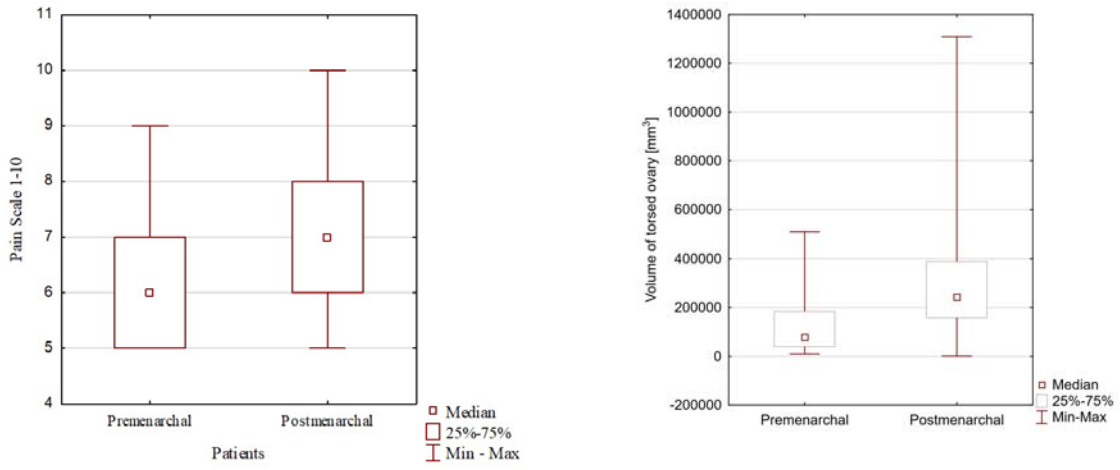


Fig. 1 *a*) Comparison of score on 1-10 pain scale for pre-menarchal and post-menarchal patients, *b*) Comparison of volume of torsed ovaries in pre-menarchal and post-menarchal patients.

WHAT THIS STUDY ADDS?

- The differential diagnosis in the case of abdominal pain should include adnexal torsion both in non-menstruating and menstruating girls and ultrasound examination plays an important role in this differentiation.

A minimally invasive approach involving laparoscopy is preferred as the operating technique. It enables safe access and does not require long, painful healing of extensive postoperative wounds as in the case of laparotomy [11,12]. For this reason, the tendency to increase the number of laparoscopies performed, and to reduce the number of laparotomies in patients due to ovarian torsion has changed over the years; although, it is sometimes limited by access to appropriate equipment and expertise.

Kives, et al. [13] reported that congenitally long ovarian ligaments, excessive laxity of the pelvic ligaments, or a relatively small uterus may be predisposing factors for adnexal torsion, which were seen in a quarter of our patients. Sasaki, et al. [10] reported that adnexal torsion in pediatric and adolescent females involves an ovary without an associated mass or cyst in as many as 46% of cases, as opposed to adult women, where coexistence of ovarian lesions that induce torsion is more frequent.

Based on the available literature, the aims of surgery currently are to detorse the adnexa and to preserve the ovary regardless of its appearance and the timing of presentation [14,15]. A tendency not to remove the ovaries and to leave them in the abdomen for further observation was also seen in our study.

We conclude that the differential diagnosis in the case of abdominal pain should include adnexal torsion both in non-menstruating and menstruating girls. Ultrasound examination plays an important role in the differential diagnosis of abdominal pain in girls, and laparoscopy is the method of choice when ovarian torsion is suspected.

Ethics clearance: Bioethics Committee of Poznan University of Medical Sciences; No. KB-470/21 dated June 09, 2021.

Contributors: PS-S, PM: conceptualization, methodology, validation, formal analysis, data curation, original draft preparation, writing, project administration, funding acquisition; PS-S, software, investigation, resource, visualization; PM: supervision. Both the authors have approved the final version of manuscript, and are accountable for all aspects related to the study.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. Childress KJ, Dietrich JE. Pediatric ovarian torsion. Surg Clin North Am. 2017;97:209-21.
2. ACOG Committee Opinion No, 783. Adnexal Torsion in Adolescents. Obstet Gynecol. 2019;134:e56-e63.
3. Sintim-Damoa A, Majmudar AS, Cohen HL, et al. Pediatric ovarian torsion: Spectrum of imaging findings. Radiographics. 2017;37:1892-908.
4. Schuh AM, Klein EJ, Allred RJ, et al. Pediatric adnexal torsion: not just a postmenarchal problem. J Emerg Med. 2017;52: 169-75.
5. Dasgupta R, Renaud E, Goldin AB, et al. Ovarian torsion in pediatric and adolescent patients: A systematic review. J Pediatr Surg. 2018;53:1387-91.
6. Abes M, Sarihan H. Ooophoropexy in children with ovarian torsion. Eur J Pediatrc Surg. 2004;14:168-71.
7. Oltmann SC, Fischer A, Barber R et al. Cannot exclude torsion-a 15-year review. J Pediatr Surg. 2009;44:1212-17.
8. Oskayli MC, Durakbasa CU, Masrabaci K, et al. Surgical approach to ovarian torsion in children. J Pediatr Adolesc Gynecol. 2015;28:343-7.
9. Casey RK, Damle LF, Gomez-Lobo V. Isolated fallopian tube torsion in pediatric and adolescent females: a retrospective review of 15 cases at a single institution. J Pediatr Adolesc Gynecol. 2013;26:189-92.
10. Sasaki KJ, Miller CE. Adnexal torsion: Review of the literature. J Minim Invasive Gynecol. 2014;21:196-202.
11. Rousseau V, Massicot R, Darwish AA, et al. Emergency management and conservative surgery of ovarian torsion in children: a report of 40 cases. J Pediatr Adolesc Gynecol. 2008;21:201-6.
12. Hubner N, Langer JC, Kives S, et al. Evolution in the management of pediatric and adolescent ovarian torsion as a result of quality improvement measures. J Pediatr Adolesc Gynecol. 2017;30:132-7.
13. £uczak J, Bag³aj M. Selecting treatment method for ovarian masses in children - 24 years of experience. J Ovarian Res. 2017;10:59.
14. Fuchs N, Smorgick N, Tovbin Y, et al.. Oophoropexy to prevent adnexal torsion: How, when, and for whom? J Minim Invasive Gynecol. 2010;17:205-8.
15. Dasgupta R, Renaud E, Goldin AB, et al. Ovarian torsion in pediatric and adolescent patients: A systematic review. J Pediatr Surg. 2018;53:1387-91.

RESEARCH PAPER

Hindi Translation and Validation of Childhood Asthma Control Test (C-ACT)

PRAWIN KUMAR,[1] CHIRAG THAKUR,[1] JAGDISH P GOYAL,[1] JAYKARAN CHARAN,[2] KULDEEP SINGH[1]
From Departments of [1]Pediatrics and [2]Pharmacology, All India Institute of Medical Sciences Jodhpur, Rajasthan.

Correspondence to: Dr Prawin Kumar, Associate Professor, Pediatrics, All India Institute of Medical Sciences, Jodhpur 342 005, Rajasthan. drprawin484@gmail.com
Received: June 22, 2021; Initial review: August 03, 2021; Accepted: December 08, 2021.

Objective: Hindi translation and validation of the Childhood Asthma Control Test (C-ACT). **Methods**: Children aged 5-11 years with newly diagnosed asthma were enrolled and followed every 4-weeks for 12 weeks. Asthma control was assessed with C-ACT and Global Initiative for Asthma (GINA) criteria. **Results**: 60 children (34 boys, 56%) were enrolled. C-ACT showed a statistically significant correlation with GINA criteria at all visits. Cronbach's alpha to assess the internal consistency was 0.74, and the intraclass correlation coefficient to measure test-retest reliability was 0.83. The maximum area under the curve (AUC) for C-ACT was 0.95 (95% CI: 0.89-1.0; P<0.001). At a cutoff score of ≥20, the sensitivity, specificity, positive predictive value, and negative predictive value of C-ACT were 97.9%, 25%, 88.7%, and 87.5%, respectively. **Conclusions**: Hindi version of the C-ACT score is valid, reliable, and correlates well with the GINA criteria for asthma control in children. It has a high sensitivity at a cutoff score of ≥20, but the specificity was poor in differentiating asthma control.

Keywords: *Assessment, Management, Questionnaire*.

Published online: January 09, 2022; ***PII***: S097475591600400

Assessment of symptom control is a crucial step in asthma management in children, which can be assessed either by the clinician or their parents/caregiver [1-3]. The Global Initiative for Asthma (GINA) symptom control tool is simple and widely used in clinical practice [2]. However, it is primarily a clinician-based assessment and may under or overesti-mate asthma control, especially in younger children [4]. Moreover, GINA criteria help clinical decision-making; a more objective tool is desirable for research purposes [2].

Several validated tools are available for the objective assessment of asthma control. The childhood asthma control test (C-ACT) is validated and widely used in children 4-11 years [4]. It was developed by Liu, et al. [5] as a self-administered questionnaire, incorporating input from both children and their caregivers. The major draw-back in the widespread use of these tools is the non-availability in local languages. Therefore, we performed Hindi translation and validation of C-ACT against the GINA criteria in asthmatic children aged 5-11 years.

METHODS

This prospective study was a part of an experimental research designed to assess the role of vitamin D3 in asthma [6]. It was carried out in the pediatric chest clinic of a tertiary care institute from July, 2018 to July, 2019. The study was approved by the institute's ethics committee. We took written, informed consent from the parents or caretakers. Children from 5-11 years with a recent asthma diagnosis requiring step III therapy as per the GINA guideline were included. We excluded children already on asthma medication, unwilling to participate in the study, or having other chronic respiratory diseases. The enrolled children were followed up every four weeks till 12 weeks of therapy.

We used the GINA symptom control tool and C-ACT to assess asthma control at each visit. The GINA symptom control tool classifies asthma control into three groups: well-controlled, partly controlled, and uncontrolled [2]. In this study, we took partly or uncontrolled children together. The C-ACT is a 27-point scale consisting of 7 question items. Children need to respond to item no. 1-4, while parents have to answer item no. 5-7. Asthma was considered to control if the C-ACT score was ≥20, while uncontrolled if the score was ≤19 [5]. We took prior permission from the developer of C-ACT. We followed the International Linguistic Validation Guideline of a Clinical Outcome Assessment (Mapi Research Trust, 2016).

Statistical analysis: We analyzed the data with SPSS v23 software. Cronbach-α was used to measure internal consistency and intraclass correlation at all visits. Criterion validity was assessed with the Spearman correlation coefficient. Wilcoxon ranked sum test was used to determine discriminative validity between C-ACT and GINA criteria at each visit. The responsiveness of C-ACT was evaluated with

the Wilcoxon ranked-sum test and Jonckheere-Terpstra test. A receiver operating character-istics (ROC) curve analysis was performed to assess the diagnostic value of C-ACT against GINA criteria. We used the Youden index for deciding the optimal discriminative threshold (cutoff value) for the C-ACT. A *P* value <0.05 was considered significant.

RESULTS

A total of 60 children (34 boys, 56%) were enrolled (mean (SD) age 8.9 (1.6) years). The baseline demographic characteristics and pulmonary function test (PFT) values are shown in **Table I**. As per GINA criteria, 48 (80%), 49 (81.6%), and 52 (86.6%) children had well-controlled, while 12 (20%), 11 (18.4%), and 8 (13.4%) children had partly or poorly controlled asthma at 4, 8 and 12 weeks, respectively. The median C-ACT score was 17 (15,19), 24 (22,25), 25 (23,26), 25 (24,26) at baseline, 4, 8 and 12 weeks of follow-up, respectively.

The Cronbach's alpha for the C-ACT score was 0.6, 0.67, and 0.74 at 4, 8, and 12 weeks, respectively. The intraclass correlation coefficient of the C-ACT score was 0.41 (*P*=0.02). The criterion validity of C-ACT score was 0.42 (*P*<0.001), 0.47 (*P*<0.001), 0.54 (*P* <0.001) at 4, 8 and 12 weeks, respectively. C-ACT scores showed significant discriminative validity in differentiating asthma control at each follow-up visit (**Web Fig. 1**).

The Jonckheere-Terpstra test showed a moderate correlation (r=0.49, *P*<0.001) between GINA criteria and C-ACT score from the 4 to 12 weeks of follow-up. In the ROC, the maximum area under the curve (AUC) for C-ACT scores against the GINA criteria was 0.95 (95% CI: 0.89-1.0; *P*<0.001) (**Fig. 1**). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy at different C-ACT cutoff values have been shown in **Web Table I**. At a cutoff score of ≥20, the sensitivity was 97.9%, while the specificity was only 25%. The maximum Youden index was 0.79 at a C-ACT cutoff score of 23.

Table I Baseline Demographic Characteristics and Pulmonary Function Test of Children With Asthma Enrolled in the Study (*N*=60)

Characteristics	*Number (%)*
Age (y), mean (SD)	8.9 (1.6)
Male gender	34 (56.7)
BMI *z*-score, mean (SD)	1.9 (0.12)
Family history of asthma	28 (46.7)
History of exclusive breastfeeding	36 (60)
Rural residence	31 (51.7)
Exposure to smoke	35 (58.3)
Pet at home	33 (55)
Cockroach at home	8 (13.4)
Use of mosquito coil	8 (13.4)
Pulmonary function test indices, mean (SD)	
FEV_1	75.5 (21.5)
FVC	75.8 (20.3)
FEV_1/FVC	97.4 (20.3)

Values in no. (%) or as stated. BMI-body mass index, FEV_1-forced expiratory volume in one second; FVC-forced Vital capacity.

DISCUSSION

We validated the Hindi translation of C-ACT against the GINA criteria of asthma control, and observed that the Hindi version of the C-ACT score is a reliable and valid tool for assessing asthma control in children aged 5-11 years. It has a good sensitivity at a cutoff score of ≥20 but has poor specificity in discriminating asthma control.

Of the various translated versions of C-ACT, the sensitivity and specificity at the cutoff point of ≥20 varies across studies [4]. Koolen, et al. [7] reported that the C-ACT scores correlates well with the GINA criteria of asthma control. Moreover, they found that detecting uncontrolled asthma at a cutoff score of ≤19 was 100% specific but only 33% sensitive. In a cross-sectional study, Chen, et al. [3] reported a significant correlation of C-ACT with physician evaluation score (PES) in children with persistent asthma but not for those having intermittent asthma. They reported Chinese version of C-ACT to be a reliable, valid, and responsive tool for assessing asthma control in children from 4-11 years [3]. The Spanish and Brazilian Portuguese versions of C-ACT have also shown good test

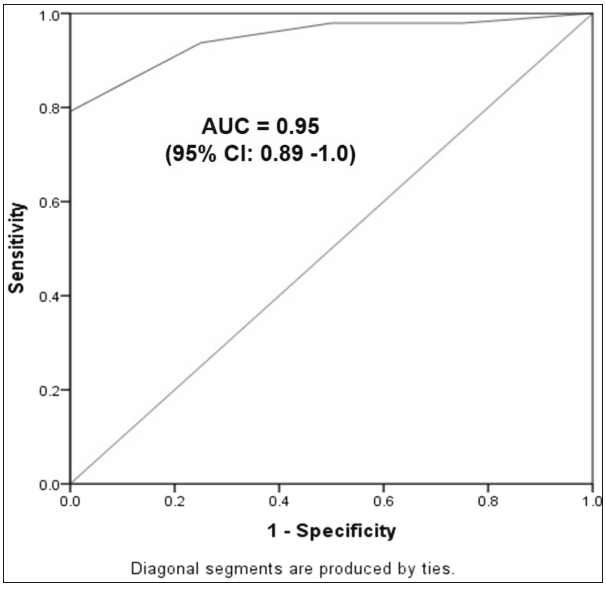


Fig. 1 Receiver operating characteristics (ROC) curve for Hindi version of Childhood Asthma Control Test (C-ACT) scores against the Global Initiative for Asthma (GINA) criteria.

WHAT THIS STUDY ADDS?

- Hindi version of the Childhood Asthma Control Test (C-ACT) is valid, reliable, and correlates with Global Initiative for Asthma (GINA) criteria of asthma control in children 5-11 years of age.

characteristics [8,9]. They also found a good sensitivity, internal consistency (α=0.82), and reliability in assessing asthma control in children 4-11 years [8].

We measured asthma control at 4, 8, and 12 weeks after initiating the ICS therapy. Like other studies, Hindi version of C-ACT also showed an outstanding AUC against the GINA criteria of asthma control. Sommanus, et al. [10], in their study, translated C-ACT into Thai and measured it at 3-time points viz., 3, 6, and 12 months. They found a significant AUC (> 80%) at each visit against the GINA criteria. Sekerel, et al. [11] followed children at three visits of 2-months intervals with Turkish version of C-ACT. They also found a significant AUC (80.3%) in discriminating asthma control as per GINA criteria. Similar results were found with the Arabic version [12].

Although C-ACT was not previously translated in Hindi, Somashekar, et al. [13] validated the English version against GINA criteria. They found a statistically signi-ficant AUC (0.7) in differentiating asthma control. The sensitivity and specificity of the English version at a cutoff score of 20 were 74.1% and 58.6%, respectively. They concluded that C-ACT correlates with GINA criteria and can be used for asthma control [13]. In most studies, a cutoff score of ≥20 indicated adequate asthma control. However, a few authors [10,11,14,15] have suggested different values to differentiate uncontrolled asthma. We also observed higher specificity and PPV at a cutoff score of ≥23 without changing the sensitivity and NPV.

A few studies have also attempted to compare the C-ACT with PFT indices. Sommanus, et al. [10] found a signi-ficant correlation between Thai version of C-ACT and FEV_1 at 3-months and 1-year of follow-up. Similarly, Sekerel, et al. [11] observed a significant correlation between Turkish version of C-ACT scores and FEV_1 at visit-1 but not on visit-2 and 3. Furthermore, in their study, Oliveira, et al. [9] did not find a significant correlation between Bralizion version of C-ACT and PFT indices. Similar to our results, most authors did not find a statistically significant correlation between PFT and C-ACT scores at any visit [9-11].

The major strength of the study is that children with only newly physician-diagnosed asthma were included. Secondly, C-ACT was validated against the GINA criteria, which is the gold-standard test for asthma control. The major limitation of the study was the relatively small sample size; although, we have assessed at multiple time points viz., baseline, 4,8, and 12 weeks of follow-up. Secondly, this was a single-center study and restricted to only one geographical part of India, so results may not be generalizable. It may require subsequent validation from other parts of India.

In conclusion, Hindi version of the C-ACT is a valid and reliable tool for assessing asthma control in children 5-11 years. It has shown maximum AUC in the ROC curve at a cutoff score of ≥20 in differentiating asthma control as defined by GINA criteria.

Acknowledgment: Mapi Research Trust, Lyon, France, for permitting Hindi translation of C-ACT.
Ethics clearance: This study was part of another research, approved by IEC, AIIMS, Jodhpur; No. AIIMS/IEC/2018/1141, dated April 30, 2018.
Contributors: PK: conceptualize and design the study, took permission from the developer, assist in Hindi translation, prepare an initial draft, literature review JPG: conceptualization and assist in Hindi translation, manuscript writing, and literature review. CT: data collection and literature review. JC: Statistical analysis and literature review KS: manuscript edit and literature review. All the authors approved the final version of the manuscript.
Funding: None; *Competing interests*: None stated.
Conference presentation: The study was presented at the European Respiratory Society (ERS) International Congress, 2020. The abstract was published in Eur Respir J. 2020;56:679. *Note*: The Mapi Research Trust has the final copyright for the Hindi version of C-ACT, and permission is needed before using it (*https://eprovide.mapi-trust.org/instruments/childhood-asthma-control-test*). Additional material related to this study is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Cloutier MM, Baptist AP, Blake KV, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol. 2020;146:1217-70.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention Updated 2020 [Internet]. Global Initiative for Asthma. 2020. Accessed December 24, 2020. Available from: *www.ginasthma.org*
3. Chen HH, Wang JY, Jan RL, et al. Reliability and validity of childhood asthma control test in a population of Chinese asthmatic children. Qual Life Res. 2008;17:585-93.
4. Alzahrani YA, Becker EA. Asthma control assessment tools. Respir Care. 2016;61:106-16.
5. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-

sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007;119:817-25.
6. Thakur C, Kumar J, Kumar P, et al. Vitamin-D supplementation as an adjunct to standard treatment of asthma in children: A randomized controlled trial (ViDASTA Trial). Pediatr Pulmonol. 2021;56:1427-33.
7. Koolen BB, Pijnenburg MWH, Brackel HJL, et al. Comparing Global Initiative for Asthma (GINA) criteria with the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). Eur Respir J. 2011;38:561-6.
8. Rodríguez-Martínez CE, Melo-Rojas A, Restrepo-Gual-teros SM, et al. Validation of the Spanish version of the childhood asthma control test (cACT) in a population of Hispanic children. J Asthma. 2014;51:855-62.
9. Oliveira SG, Sarria EE, Roncada C, et al. Validation of the Brazilian version of the childhood asthma control test (c-ACT). Pediatr Pulmonol. 2016;51:358-63.
10. Sommanus S, Direkwattanachai C, Lawpoolsri S, et al. Accuracy of childhood asthma control test among thai childhood asthma patients. Asian Pacific J Allergy Immunol. 2018;36:152-8.
11. Sekerel BE, Soyer OU, Keskin O, et al. The reliability and validity of Turkish version of Childhood Asthma Control Test. Qual Life Res. 2012;21:685-90.
12. Al Saleh Al Teneiji M, AlBlooshi A, Al Kalbani A, et al. Validating the Arabic version of childhood asthma control test among Emirati children aged 4-11 years. 2017;PA1332.
13. Somashekar AR, Ramakrishnan KG. Evaluation of asthma control in children using childhood—asthma control test (C-ACT) and Asthma therapy assessment questionnaire (ATAQ). Indian Pediatr. 2017;54:746-8.
14. Yu HR, Niu CK, Kuo HC, et al. Comparison of the global initiative for asthma guideline-based asthma control mea-sure and the childhood asthma control test in evaluating asthma control in children. Pediatr Neonatol. 2010;51:273-8.
15. Liu AH, Zeiger RS, Sorkness CA, et al. The childhood asthma control test: Retrospective determination and clinical validation of a cut point to identify children with very poorly controlled asthma. J Allergy Clin Immunol. 2010;126:267-73.e1.

NEWS IN BRIEF

A National Emergency In Children's Mental Health!

The American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry has declared a national emergency in children's mental health. Mental health issues have been steadily gaining ground over the last decade, but the COVID pandemic has catapulted it to centre stage. In early 2021, suicide attempts by girls between 12- 17 years rose by 51% compared to 2019. Emergency visits for mental health issues rose by 24% in children between 5-11 years and 31% in children 12-17 years between March and October, 2020.

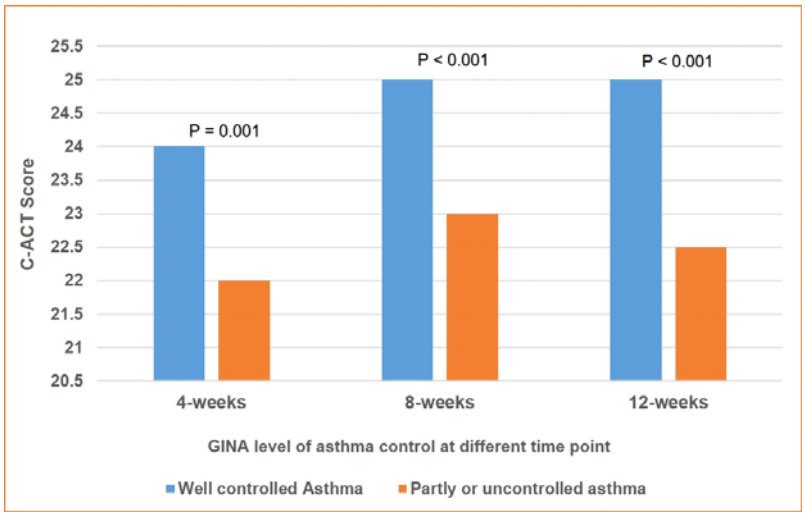
Isolation, lack of social interaction, which had been possible in school, death of family members and excessive exposure to social media and online entertainment are considered some of the possible causes. One possible solution to this complex problem is physical sports. A study comparing the rates of mild to moderate depression in athletes, pre- and post-pandemic found a jump from 10% to 33%. Another study found a whopping 37% incidence of anxiety after the pandemic started. The American Academy of Pediatrics has recommended safe participation in sports and given guidelines for pediatricians to enforce this. They have also suggested that mental health surveillance be integrated into every hospital visit. Techniques to promote resilience like mindfulness, progressive relaxation and meditation are other methods which may be employed. (*www.aap.org*)

Clinician scientists - a new breed

The Indian Institute of Science, Bangalore, which is a premier research institute has now decided to start a Postgraduate Medical College and multi-specialty hospital. They will offer a new kind of course called integrated MD-PhD dual degree. This aims to train physicians in both clinical and research methodology. Students will have access to state of the art medical facilities as well as science and engineering laboratories. It is anticipated to kickstart cutting edge research in several fields such as oncology, neurology, robotics, organ transplant etc.

Philantropists Susmita and Subroto Bagchi as well as Radha and NS Parthasarathy have contributed 425 crores for this. IIT Kharagpur is the second technical institute which will be starting a medical institute. This amalgamation of medical and technical sciences may open the floodgates of research in the biological sciences in India.
(*The Times of India 14 February 2022*)

Gouri Rao Passi
gouripassi@hotmail.com



Web Fig.1 Discriminative validity of Hindi translation of childhood asthma control test (C-ACT) against Global Initiative for Asthma (GINA) criteria at each follow-up visit.

Web Table I Diagnostic Accuracy of Hindi Version of Childhood Asthma Control Test (C-ACT) in Predicting Well-Controlled Asthma

Cut-off score	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
≥ 19	100	0	85.7	85.7	85.7
≥ 20	97.9	25	88.7	66.7	87.5
≥ 21	97.9	37.5	90.4	75	89.3
≥ 22	97.9	37.5	90.4	75	89.3
≥ 23	97.9	50	92.2	80	91.1
≥ 24	79.2	100	100	44.4	82.1

PPV: positive predictive value, NPV: negative predictive value.

Association of Child Neurology (AOCN) Consensus Statement on the Diagnosis and Management of Febrile Seizures

JAYA SHANKAR KAUSHIK,[1] VISHAL SONDHI,[2] SANGEETA YOGANATHAN,[3] RACHANA DUBEY,[4] SUVASINI SHARMA,[5] KOLLENCHERI PUTHENVEETTIL VINAYAN,[6] PIYUSH GUPTA,[7] REKHA MITTAL[8] FOR AOCN EXPERT COMMITTEE*

From [1]Department of Pediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana; [2]Department of Pediatrics, Armed Forces Medical College, Pune, Maharasthra; [3]Department of Pediatric Neurology, Christian College of Medical Sciences, Vellore, Tamil Nadu; [4]Department of Pediatric Neurology, Medanta Hospital, Indore, Madhya Pradesh; [5]Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi; [6]Department of Pediatric Neurology, Amrita Institute of Medical Sciences, Kochi, Kerala; [7]Department of Pediatrics, University College of Medical Sciences, Delhi; [8]Department of Pediatric Neurology, Madhukar Rainbow Children Hospital, Malviya Nagar, Delhi.

**Full list of Committee members provided as Annexure.*

Correspondence to: Dr Rekha Mittal, Additional Director (Pediatric Neurology), Madhukar Rainbow Children Hospital, Malviya Nagar, Delhi. drrekhamittal2008@gmail.com

Justification: Febrile seizures are quite common in children but there are controversies in many aspects of their diagnosis and management. **Methods**: An expert group consisting of pediatric neurologists and pediatricians was constituted. The modified Delphi method was used to develop consensus on the issues of definitions and investigations. The writing group members reviewed the literature and identified the contentious issues under these subheadings. The questions were framed, pruned, and discussed among the writing group members. The final questions were circulated to all experts during the first round of Delphi consensus. The results of the first round were considered to have arrived at a consensus if more than 75% experts agreed. Contentious issues that reached a 50-75% agreement was discussed further in online meetings and subsequently voting was done over an online platform to arrive at a consensus. Three rounds of Delphi were conducted to arrive at final statements. **Results**: The expert group arrived at a consensus on 52 statements. These statements pertain to definitions of febrile seizures, role of blood investigations, urine investigations, neuroimaging, electroencephalography (EEG), cerebrospinal fluid analysis and screening for micronutrient deficiency. In addition, role of rescue medications, intermittent anti-seizure medication and continuous prophylaxis, antipyretic medication and micronutrient supplementation have been covered. **Conclusion**: This consensus statement addresses various contentious issues pertaining to the diagnosis and management of febrile seizures. Adoption of these statements in office practice will improve and standardize the care of children with this disorder.

Keywords: *Complex febrile seizure, Clobazam, Febrile status epilepticus, Simple febrile seizure, Valproate.*

Published online: 10 December, 2021; ***PII***: S097475591600379

Febrile seizures (FS) refer to seizures that occur in association with fever but do not have any other definable cause of the seizure. Febrile seizures are one of the most common neurological complaints in emergency and outpatient units. The most common infection associated with FS is respiratory tract infection [1]. The three most common viral isolates in children with FS include influenza virus, adenovirus, and parainfluenza virus. In India, tropical infections such as malaria and dengue are also important causes of febrile seizures. There have been considerable advances in the understanding of FS in the past decade [2-4]. Considering the difference in ethnicity, demographics, and epidemiology of febrile seizures in Indian children, the Association of Child Neurology (AOCN) proposed to develop a consensus statement for evaluation and management of FS in Indian children.

OBJECTIVE

The objective was to review the literature and develop a consensus statement on evaluating and managing children with FS in India. These recommendations are targeted at general practitioners, pediatricians, emergency physicians, and primary care physicians.

PROCESS

The consensus among the experts was achieved using the Delphi method. A modified Delphi method was adopted with three rounds of Delphi group consensus (**Web Fig. 1**).

Expert group formation: The AOCN formed a core working group of eight members, with six members in the writing group and two senior moderators. The group consisted of seven pediatric neurologists and one clinical pediatrician with a core interest in medical research. Apart from these eight experts, 25 subject experts, pediatric neurologists (AOCN members) and senior pediatricians, were contacted to form the expert group (n=33). All expert members had been in clinical practice for a minimum of 5 years.

Problem identification: The topic of febrile seizures was covered under the following six heads: case definitions, the role of neuroimaging, electroencephalography, lumbar puncture, emergency treatment, and long-term management, including domiciliary management in febrile seizures. Each of the six writing group members were assigned one topic. They were asked to review the literature extensively and identify the questions that remain unaddressed from the literature. A google group was formed of the core group members. The review of literature and questions from each writing member were posted and discussed extensively. Overlaps in the questions were removed, some questions were pruned, and 43 questions were finalized for the first round.

First round of Delphi meeting: These 43 questions were initially circulated to 33 experts through Google forms. Most questions had a closed-ended response, with the last option being open-ended. All 33 experts gave their opinion in the first round of Delphi. Categorical responses, where more than 75% of experts agreed on a single response, were considered to have reached a consensus. [5] Of the initial 43 questions, the questions and the corresponding consensus statements that reached >75% agreement (n=20) in the first-round consensus were presented by the moderator. These were not deliberated further. The contentious statements (n=23, 50-75% agreement) were presented by the moderator one by one, and discussed in the group, followed by online polling (*www.polltab.com*). The open-ended responses (if any) obtained during the first round were qualitatively analyzed using content analysis [6]. The initial statements were further expanded to cover all domains related to febrile seizures, which resulted in a total of 104 question [40 questions on definitions, 11 questions on investigation, 5 questions on neuroimaging, 6 questions on EEG, 37 questions related to management and 9 questions related to vaccination] (**Web Table I**).

Second and third round of Delphi: The second round of Delphi virtual meeting (Zoom video conferencing platform) was conducted; 28 of 33 experts attended this. All the identified questions were discussed over three virtual meetings lasting for a total duration of 4.5 hours. Of the 107 statements, 67 statements (64.4%) reached >75% agree-ment and were considered to have achieved consensus, and not deliberated further. However, the statements where consensus was not reached (50-75% agreement) in the second round (n=28, 26.9%) were discussed again. The statements (n=6, 5.8%) were reframed based on experts' discussion and suggestions and polled again (third round). Those statements which did not reach consensus even after the third round (n=3, 2.9%) were considered to have failed to reach an agreement.

Final statements: The final statements (n=52) were categorized into 13 subheadings: definitions, blood investigation, micronutrient deficiency, urine analysis, neuroimaging, electroencephalography (EEG), cerebro-spinal fluid (CSF) analysis, genetic testing, domiciliary care, acute management of a febrile seizure, intermittent prophylaxis, continuous prophylaxis, antipyretic medication, and role of micronutrient supplementation. Each subheading had one or more consensus statements about that topic, leading to a total of 52 statements. These statements were circulated among all experts for approval.

RECOMMENDATIONS

The final group consensus statements related to definitions (**Table I**), investigations (**Table II** and **III**) and management (**Table IV**) have been outlined. The key messages have been summarized in **Box I.**

Definitions

Definitions of febrile seizure, simple FS (SFS), and complex FS (CFS) are similar to the definitions adopted by other international guidelines. CFS traditionally includes those that are multiple, focal, and/or prolonged (>15 minutes). Literature suggests that children with multiple episodes are defined by some authors as SFS plus and are consi-dered to behave like SFS instead of CFS. However, the group disagreed on the usage of this separate terminology of SFS plus [7]. Other terms like 'fever triggered epilepsy,' 'atypical febrile seizure,' 'febrile seizure alone' used by various authors were considered confusing and not recommended for clinical use by the expert group.

Investigations

Serum electrolyte abnormalities, including hypocalcemia, are uncommon in children with FS. Considering the limited importance of serum ferritin and serum vitamin D levels, these investigations were considered redundant among children with FS unless clinically indicated. As most children do not have a focus of infection, urine analysis may be considered among those younger than 18 months with a febrile seizure. The clinician must consider further evaluation of central nervous system for infection if consciousness has not returned to pre-seizure state within one hour of onset. Lumbar puncture should be considered for children less than 12 months of age, and in children more than 12 months who have been pre-treated with antibiotics.

Routine neuroimaging is not recommended in children with SFS [2,4,8-9]. There is a diversity of opinion on recommending brain CT and/or MRI in children with CFS [8-9]. Emergent non-contrast CT brain may be indicated if there is a history of trauma, status epilepticus, clinical suspicion of raised intracranial pressure or presence of ventriculoperitoneal shunt in a child with fever and seizures

Table I Consensus Definitions of Febrile Seizures

Terminology	*Consensus definition*
Febrile seizures	A seizure accompanied by fever (temperature>38.4° C or 101° F) without central nervous system infection, metabolic disturbances, or a history of afebrile seizure or any acute neurological insult (severe electrolyte imbalance, meningitis, trauma) in children aged 6 months to 6 years.[a]
Simple febrile seizures	Febrile seizures without a focal component, which last less than 15 minutes, and do not recur within 24 hours
Complex febrile seizures	Febrile seizures that are focal and/or prolonged for more than 15 minutes and/or recur within 24 hours
Febrile status epilepticus	Febrile seizure lasting for 30 minutes or more
Febrile seizure plus	Febrile seizures that continue past the usual age where they are expected to resolve (6 years) and/or accompanied by afebrile generalized (tonic-clonic, atonic, myoclonic, myoclonic-atonic, or absence) or focal seizures
Genetic epilepsy with febrile seizure plus (GEFS+)	Febrile seizures plus with a family history of febrile seizures, febrile seizures plus, or afebrile seizures like generalized tonic clonic, myoclonic, absence atonic and focal seizures.

[a]*FS may rarely occur in children younger than 6 months of age.*

[10]. MRI brain with epilepsy protocol was considered the neuroimaging modality of choice by the expert group once the child has been stabilized. The purpose of MRI in the first episode of a CFS would be to look for features of viral encephalitis, acute disseminated encephalomyelitis, virus associated encephalopathy, intra-cranial space occupying lesions, cortical malformations and for hippocampal abnormalities.

In retrospective studies, prolonged FS have been noted as a significant risk factor for the development of mesial temporal sclerosis and consequent temporal lobe epilepsy [11]. The FEBSTAT study is an ongoing pros-pective cohort study planned to follow-up children with febrile status epilepticus to study the development of hippocampal sclerosis and temporal lobe epilepsy. In the first of the reports of MRI abnormalities in the FEBSTAT study, Shinnar, et al. [12] reported 11.5% of children with febrile status epilepticus had increased T2 signal in the hippocampus as compared to none in children with SFS, when imaged within 72 hours of the onset of seizure. Subsequently, Chan, et al. [13] reported the presence of hippocampal malrotation, a likely pathological error in brain development, in 8.8% of children with febrile status epilepticus as compared to 2.1% of the controls. Lewis, et al. [14] performed a follow-up study to see if the abnormal signal abnormalities in the hippocampus resulted in hippocampal sclerosis. MRI obtained after 1 year in 14/22 children with acute T2 hyperintensities in the hippocampus showed hippocampal sclerosis in 10 children. These results indicate that acute stage T2 hyperintensities after prolonged FS may lead to hippocampal sclerosis. However, whether this leads to temporal lobe epilepsy on follow-up remains to be seen. Moreover, the therapeutic implications of finding these abnormalities on the acute stage imaging are not clear at present. With this background, the group consensus was developed on obtaining an early MRI

Table II Group Consensus on Investigations in Febrile Seizure

Blood investigations

Complete blood count (CBC) is not required among all children with simple febrile seizures.

- CBC with C-reactive protein (CRP) could be considered for children with complex febrile seizures and those with febrile status epilepticus.

Routine blood sugar, serum electrolytes (sodium and potassium), and serum calcium testing are not required in children with simple febrile seizures.

- Routine blood sugar, serum electrolytes (sodium), and serum calcium testing may be considered among those brought convulsing to the emergency room, including those with febrile status epilepticus.
- Serum calcium may be considered among infants (<1 year) with simple febrile seizures.

Blood sugar testing and serum calcium testing may be considered among children with complex febrile seizures.

Serum sodium and potassium estimation are not required in all children with complex febrile seizures.

Serum magnesium levels are not indicated among children with simple and complex febrile seizures.

- The group could not reach any consensus on its estimation among children with febrile status epilepticus, considering the paucity of literature.

Micronutrient deficiency

All children with febrile seizures need not be screened for iron deficiency.

- It may be considered among those with clinical pallor on examination.

Routine assessment of serum phosphorus, alkaline phosphatase, and vitamin D is not required in febrile seizures.

- These tests may be performed if the child has clinical features of rickets or if the child has hypocalcemia.

Table III Group Consensus on Specific Investigations in Febrile Seizure

1.	*Neuroimaging*
1.1	In children with simple febrile seizures, neuroimaging is NOT indicated.
1.2	In children with the first episode of complex febrile seizure with prolonged or focal features, MRI brain should be considered within 72 hours.[a,b]
1.3	Routine follow-up imaging is NOT required for those children whose initial neuroimaging did not suggest an alternate diagnosis.
2.	*Electroencephalography (EEG)*
2.1	Routine EEG is NOT indicated among children with simple febrile seizure.
2.2	EEG may be considered in children with complex febrile seizures; however, the prognostic significance of the abnormalities to predict future epilepsy is unclear.
2.3	Additionally, EEG may be considered among those children with focal findings on neuroimaging.
2.4	EEG, where indicated, should be performed within one week of febrile seizure or at the earliest feasibility.
2.5	EEG protocol should include a minimum of 30-minute record and must include both sleep and awake state
3.	*Cerebrospinal fluid analysis (Lumbar puncture)*
3.1	Lumbar puncture should be considered in children less than 12 months of age with first episode of FS, especially if they have not received immunization against *Streptococcal pneumoniae* and *Hemophilus influenzae* type B.
3.2	Lumbar puncture should be considered among children more than 12 months who have been pre-treated with antibiotics.[c]
3.3	CSF analysis is NOT required among children aged 12-18 months who have not received a full course of Hib and pneumococcal vaccination and there are no clinical features of meningitis.
3.4	Lumbar puncture is NOT required for ALL children with complex febrile seizure
3.5	All children with febrile status epilepticus as the first presentation of FS must be subjected to CSF analysis.
3.6	Lumbar puncture is NOT indicated among children brought to emergency services in the sedated state after receiving benzodiazepines. If the child's sensorium continues to be obtunded after sufficient time elapses, then Lumbar puncture should be considered.
3.7	Lumbar puncture should be *preferably* preceded by neuroimaging in children with focal neurological deficits, clinical symptoms, and signs of raised intracranial pressure.
3.8	Routine CSF viral or bacterial panel is NOT indicated for all patients with febrile seizures; it is indicated only if the routine CSF analysis is indicative of meningitis.
3.9	Lumbar puncture should be performed in FS in any age group if there are clinical features of meningitis.
4.	*Genetic testing*
4.1	Genetic testing for Dravet syndrome may be considered in children recurrent febrile status epilepticus, onset of prolonged hemiconvulsive seizures below 1 year age. However, decision to order genetic investigations for screening for SCN1A must be made in consultation with a pediatric neurologist or geneticist with appropriate genetic counselling to understand the implications of these findings

[a]This is to look for features of neuro-infection or ADEM which may have treatment implications. [b]In children with febrile status epilepticus, acute hippocampal changes and structural hippocampal abnormalities have been described but the therapeutic and prognostic significance of these abnormalities is unclear at present. [c]However, the decision is left at the discretion of the treating physician based on duration, route, and type of antibiotic received and the clinical condition of the child.

Brain, preferably within 72 hours, for children with focal, prolonged FS, including those with febrile status epilepticus. However, apart from ruling out the differential diagnoses as men-tioned earlier, the therapeutic and prognostic significance of hippocampal abnormalities seen on MRI in the acute stage is not clear at present.

EEG is not recommended in developmentally normal children with SFS as it does not predict the recurrence of FS or subsequent epilepsy [15]. The role of EEG in CFS is not clear. EEG may be useful in the acute setting if the child remains encephalopathic after the seizure and is not regaining the baseline status, primarily to rule out ongoing electrographic events. Though some guidelines recommend performing EEG in CFS, a Cochrane review concluded that there are no randomized trials to support or refute EEG use and its appropriate timing in children with CFS [8,16]. EEG may show non-specific abnormalities such as slowing or epileptiform abnormalities. But whether such abnormalities predict the future development of epilepsy is not understood. Conversely, a normal EEG does not exclude the development of future epilepsy. Hence, the group consensus was to consider EEG for children with CFS with a rider that the prognostic and therapeutic implications of the EEG findings are not clear at present.

Management

Parental counseling is an important part of treatment, as FS are by and large benign. Many parents are afraid that their child may die, when they witness the first episode of febrile seizure. The pediatrician should educate the family that even

Table IV Group Consensus Statement on Management of Febrile Seizure

1. *Domiciliary care*
1.1 Domiciliary care should be taught to parents of children with febrile seizure, including an explanation of recovery position, dose and route of abortive medication, when to administer repeat dose, and when to bring the child to the hospital.
1.2 Duration of seizure after which abortive medication should be instituted in the non-hospital setting is 3-5 minutes.
1.3 Intranasal midazolam (0.2 mg/kg) is recommended as abortive medication for domiciliary management of acute seizures.
1.4 Intranasal midazolam may be preferred over rectal diazepam or buccal lorazepam[a]
1.5 The abortive medication can be repeated after 5 minutes in case of prolonged seizures.
2. *Intermittent prophylaxis*
2.1 Intermittent prophylaxis is NOT recommended for the first episode of simple febrile seizure.
2.2 Intermittent prophylaxis may be considered among children with frequent recurrent simple febrile seizures with parental anxiety, and residence far from medical facilities and those with complex febrile seizure who have not been started on continuous prophylaxis.
2.3 The drug of choice for intermittent prophylaxis is clobazam (0.5-1 mg/kg/day in two divided doses for 3 days maximum dose 20 mg/day). There is no need to taper the drug while stopping after 3 days.
2.4 Parents should initiate intermittent prophylaxis if the child develops fever (>38 C) or when they administer antipyretic medication.
3. *Continuous prophylaxis*
3.1 Continuous prophylaxis with anti-seizure medication may be considered among children with febrile status epilepticus, febrile seizures in a children with neurodevelopmental delay, frequent complex febrile seizures[b] and children with FS+/GEFS+ with afebrile seizures.
3.2 Continuous prophylaxis is NOT recommended in simple febrile seizures
3.3 Drug of choice for continuous prophylaxis is sodium valproate[c]. Baseline investigations like liver function tests are NOT required in an otherwise healthy child before starting sodium valproate.
3.4 Once initiated, the anti-seizure medication should be considered for a 2 years seizure freedom period or guided individually based on primary syndrome (GEFS+/Dravet syndrome).
3.5 Management of febrile status epilepticus must be similar to management of convulsive status epilepticus. In children who present to emergency services with febrile status epilepticus and who are already diagnosed with Dravet syndrome, FS+, GEFS+, sodium channel blockers (phenytoin) may be avoided.
4. *Antipyretic medication:* Paracetamol 15 mg/kg/dose 6 hourly may be considered for the febrile episode duration. Antipyretic medications administered round the clock for the duration of fever do NOT prevent occurrence or recurrence of seizure but will make the child comfortable.
5. *Micronutrient supplementation:* There is no role of empirical supplementation with oral iron, zinc, or vitamin D among children with a febrile seizure.
6. *Parental education: The parental education and counseling should cover the following aspects:*
   - Explanation about why febrile seizures occur and they do not constitute epilepsy
   - The risk of death during the seizure is negligible
   - Simple febrile seizures do not lead to epilepsy or intellectual impairment
   - Explanation about the risk of febrile seizure recurrence
   - Explanation on what is to be done if the child has fever.
   - Explanation on what is to be done if the child has a seizure
   - Basic first aid and recovery position to be taught to parents.
   - Advice regarding rescue medication to be explained to parents and when to give this medication.
   - Explanation about the danger signs, and when the child should be brought to medical attention.

[a]Buccal lorazepam is not available in India. Rectal diazepam gel also has availability issues, and also there are social issues in rectal administration. [b]There was no group consensus on number of episodes to define "frequent"; thus this was intentionally kept ~~it~~ flexible to enable the treating physician to take a decision. [c]Sodium valproate is not preferred in children with suspected inborn errors of metabolism; the treating physician may consider use of alternative medication in such cases.

though dramatic in appearance, these seizures do not lead to neurological disease or dysfunction. The more parents understand about this condition, the less likely it is that they will rush to the emergency room. However, parents should also be educated on when to bring the child with a seizure to the emergency department because in some cases the cause may be a virus or a bacterial infection of the brain.

Six-hourly paracetamol may be advised for the first 48 hours in case of future episodes of fever. Antipyretic medications administered round the clock for the duration of fever may not prevent occurrence or recurrence of seizures but will make the child less uncomfortable. Parents must be educated and trained in the home management of seizures and the use of abortive medication. Rescue seizure

Box I Key Recommendations for Diagnosis and Management of Febrile Seizures

First episode of suspected febrile seizure: [a]Routine complete blood count, blood sugar, serum electrolytes (sodium), and serum calcium testing are not required among all children with simple febrile seizure but may be considered among those brought convulsing to the emergency room, including those with febrile status epilepticus, or if clinically indicated.

First episode of suspected febrile seizure: [a]Routine assessment of serum calcium, serum phosphorus, alkaline phosphatase, and vitamin D and screening for iron deficiency anemia is not required in febrile seizure.

Magnetic resonance imaging (MRI)[a] brain with epilepsy protocol may be considered within 72 hours among children with complex febrile seizure with prolonged or focal features. If MRI is not available, CT scan can be done.

Electroencephalography (EEG)[a] should be considered in children with complex febrile seizure; however, the prognostic significance of the abnormalities to predict future epilepsy is unclear.

Lumbar puncture[a] should be considered for children less than 12 months of age, and in children more than 12 months who have been pre-treated with antibiotics.

The mainstay of management is parental education and counseling about the overall benign nature of the condition, good prognosis for future neurodevelopment outcome, and low likelihood of developing epilepsy.

Six hourly paracetamol may be advised for the first 48 hours in future episodes of fever. Antipyretic medications administered round the clock for the duration of fever do not prevent occurrence or recurrence of seizures but will make the child comfortable

Parents must be educated and trained in the home management of seizure and the use of abortive medication (intranasal midazolam or rectal diazepam).

Intermittent prophylaxis [clobazam (0.5-1 mg/kg)] may be considered among children with one or more of:

i) frequent recurrent simple febrile seizure,

ii) parental anxiety, and

iii) residence far from medical facilities, complex febrile seizure, including febrile status epilepticus.

Continuous prophylaxis with anti-seizure medication (sodium valproate) may be considered among children with

i) febrile status epilepticus,

ii) febrile seizures in a child with neurodevelopmental delay, and

iii) children with FS+/GEFS+ with afebrile seizure.

[a]*In subsequent episodes, investigations may be considered as per the clinical indications.*

medication should be considered when the febrile seizure lasts longer than 3-5 minutes. The FEBSTAT study team has shown that prolonged FS are unlikely to stop spontaneously [17]. Intranasal midazolam was considered abortive rescue medication of choice for domiciliary management by the expert group. In case this is not available, rectal diazepam gel may be considered; although, it may also have availability issues.

The use of intermittent anti-seizure prophylaxis for simple FS is controversial. Its prescription should be avoided for the first episode of SFS. Given the overall benign nature of a SFS compared with anti-seizure medications' potential toxicities, treatment risks seem to outweigh the benefits. It may be considered for children with frequent recurrent SFS, parental anxiety and residence far from medical facilities, and for children with CFS, if not on continuous prophylaxis. The drug of choice is oral clobazam, considering its easy availability and low cost. The group reviewed reports of intermittent leveti-racetam for FS, but considering the paucity of robust evidence, the group did not consider the same as an alternative [18].

The decision for continuous prophylaxis is based on weighing the benefits of preventing FS recurrence vs risks of possible adverse effects of anti-seizure medi-cation. The indications are limited to those with febrile status epilepticus, FS+, and those with pre-existing neurodevelopmental disorders like cerebral palsy, global developmental delay or autism spectrum disorder. The FEBSTAT study had revealed that 14 of 22 children with acute hippocampal changes on MRI performed within 72 hours, had developed mesial temporal sclerosis on follow up MRI [14]. Considering the risk of hypoxic injury as well as higher chances of future febrile status epilepticus, the group included febrile status epilepticus as one of the indications for continuous prophylaxis other than FS+ and those with neuro-developmental delay. Management of individual episodes of febrile seizures and febrile status epilepticus must be in line with the standard protocols for management of acute seizures and convulsive status epilepticus, except for those already diagnosed with FS+/GEFS+ spectrum where sodium channel blockers like phenytoin may be avoided.

Two topics were considered out of the ambit of this consensus: immunization in children with FS and the role of genetic investigations in FS. Pediatricians are advised to follow the Immunization Schedule (2020-21) recommended by Indian Academy of Pediatrics (IAP) for guidance on immunization [19]. The decision to order genetic investi-

gations for screening for *SCN1A* must be made in consultation with a geneticist, with appropriate genetic counselling to understand the implications of these findings.

CONCLUSION

This consensus statement has been prepared considering the available evidence and expert opinion in situations where (frequently) evidence is lacking. However, there are certain limitations with Delphi method, which include firstly, fatigue among experts who are required to respond to same or similar questions in multiple rounds; second is lack of reliability as the same expert may answer the same question differently when it is administered multiple times; and third that it is a time consuming and laborious exercise for both researcher and participants with participant drop-outs [20]. Despite these limitations, Delphi method is a well-accepted robust method to reach at a consensus among experts. To conclude, the present consensus docu-ment aims to provide some clarity on the diagnosis and management of children with a febrile seizure, which will be useful for office practice. As more evidence is available from ongoing studies, these recommendations will be updated.

Contributors: SS, RM, JSK: conceptualized the idea; JSK, VS, SY, RD, SS, KPV, PG, RM: constituted the writing committee and drafted the manuscript; JSK and VS were involved in administration of Delphi process. All authors approved the final version of manuscript.

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

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

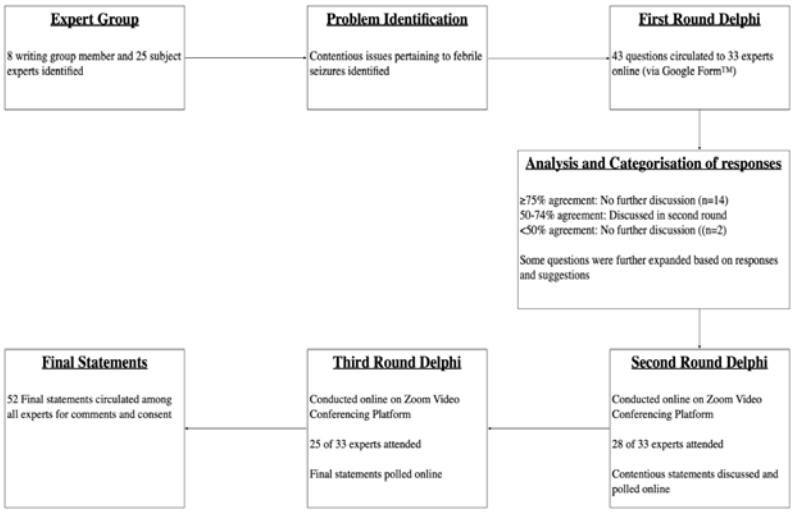
REFERENCES

1. Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. Arch Dis Child. 2007;92:589-93.
2. Subcommittee on Febrile Seizures, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127:389-94.
3. Natsume J, Hamano SI, Iyoda K, et al. New guidelines for management of febrile seizures in Japan. Brain Dev. 2017;39:2-9.
4. Steering Committee on Quality Improvement, Management Subcommittee on Febrile Seizures, American Academy of Pediatrics. Febrile seizures: Clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121:1281-6.
5. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm. 2016;38:655-62.
6. Bengtsson M. How to plan and perform a qualitative study using content analysis. NursingPlus Open. 2016;2:8-14.
7. Grill MF, Ng YT. Simple febrile seizures plus (SFS+)": More than one febrile seizure within 24 hours is usually okay. Epilepsy Behav. 2013;27:472-6.
8. Capovilla G, Mastrangelo M, Romeo A, et al. Recommendations for the management of "febrile seizures": Ad Hoc Task Force of LICE Guidelines Commission. Epilepsia. 2009;50:2-6.
9. DiMario FJ, Jr. Children presenting with complex febrile seizures do not routinely need computed tomography scanning in the emergency department. Pediatrics. 2006;117:528-30.
10. Lyons TW, Johnson KB, Michelson KA, et al. Yield of emergent neuroimaging in children with new-onset seizure and status epilepticus. Seizure. 2016;35:4-10.
11. Theodore WH, Bhatia S, Hatta J, et al. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. Neurology. 1999;52:132-6.
12. Shinnar S, Bello JA, Chan S, et al. MRI abnormalities following febrile status epilepticus in children: The FEBSTAT study. Neurology. 2012;79:871-7.
13. Chan S, Bello JA, Shinnar S, et al. Hippocampal malrotation is associated with prolonged febrile seizures: Results of the FEBSTAT Study. AJR Am J Roentgenol. 2015;205:1068-74.
14. Lewis DV, Shinnar S, Hesdorffer DC, et al. Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol. 2014;75:178-85.
15. Practice parameter: The neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. Pediatrics. 1996;97:769-72.
16. Shah PB, James S, Elayaraja S. EEG for children with complex febrile seizures. Cochrane Database Syst Rev. 2020;4:CD009196.
17. Hesdorffer DC, Shinnar S, Lewis DV, et al. Design and phenomenology of the FEBSTAT study. Epilepsia. 2012;53:1471-80.
18. Hu LY, Shi XY, Li H, et al. Intermittent oral levetiracetam reduced recurrence of febrile seizure accompanied with epileptiform discharge: A pilot study. Ital J Pediatr. 2018;44:70.
19. Kasi SG, Shivananda S, Marathe S, et al. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2020-21) and Update on Immunization for Children Aged 0 Through 18 Years. Indian Pediatr. 2021;58:44-53.
20. Fink-Hafner D, Dagen T, Doušak M, et al. Delphi Method: strengths and weaknesses. Metodoloski Zv. 2019;16:1-9.

ANNEXURE I

List of Expert Members

Anju Agarwal, *Delhi*; Satinder Aneja, *Noida*; Rachana Dubey, *Indore*; Sheffali Gulati, *Delhi*; Piyush Gupta; *Delhi*; Saji James, *Chennai*; Sujata Kanhere, *Mumbai*; Jaya Shankar Kaushik, *Rohtak*; Ajay Kumar, *Patna*; Ravi Kumar, *Bengaluru*; Ranjith Kumar Manokaran, *Chennai*; Devendra Mishra, *Delhi*; Rekha Mittal, *Delhi* (Convenor); Neeta Naik, *Mumbai*; Hansashree Padmanabhan, *Bengaluru*; Debasis Panigrahi, *Bhubaneswar*; Rajniti Prasad, Varanasi; Surekha Rajadhyaksha, *Pune*; Kamer Singh Rana, *Delhi*; Mini Sreedharan, *Trivandrum*; Deepak Sachan, *Delhi*, Abhijeet Saha, *Delhi*; Arushi Gahlot Saini, *Chandigarh*; Suvasini Sharma, *Delhi*; Jigyasha Sinha, *Kolkata*; Vishal Sondhi, *Pune*; Vrajesh Udani, *Mumbai*, Prashant Utage, *Hyderabad;* Kollencheri Puthenveettil Vinayan, *Kochi*; Sangeetha Yoganathan, *Vellore*.



Web Fig. 1 Study methodology.

Web Table I Summary of Responses from Round 1. The Questions That Do Not Need any Further Deliberations and have been Accepted are Shaded Green. The Questions That have been Completely Refuted by More Than 50% of Respondents Have Been Shaded Grey and will not be Deliberated Further. The Questions Where the Responses are Between 50 to 75% Range have been Modified Based on Suggestions Received in the Responses. These have been Shaded Yellow.

Question	*Number of responses*	*Response 1*	*N (%)*	*Response 2*	*N (%)*	*Other responses*	*N (%)*
A. Febrile seizures are defined as seizure accompanied by fever (temperature>38.4 C or 101 F) without central nervous system infection, metabolic disturbances or a history of afebrile seizure or any acute neurological insult (severe electrolyte imbalance, meningitis, trauma) occurring in infants and children aged 6-60 months of age.							
1. Do you perceive the need to define "febrile seizure" as a term?	28	Yes	28 (100%)	No	0		0
2. Do we need to mention "without central nervous system infection"?	27	Yes	21 (77.8%)	No	3 (11.1%)		3 (11.1%)
3. Do we need to mention "without metabolic disturbance"?	28	Yes	22* (78.6%)	No	2 (7.1%)		4 (14.3%)
4. Do we need to mention without a "history of afebrile seizure"?	28	Yes	21^ (75%)	No	7 (25%)		0
5. Do we need to mention "any acute neurological insult (severe electrolyte imbalance, meningitis, trauma)"?	28	Yes	26[#] (92.9%)	No	2 (7.1%)		0
6. Do you want to include "infants and children aged 6-60 months of age"	28	Yes	21 (75%)	No	3 (10.7%)	Other age limits	4 (14.3%)
7. Do you want to revise the upper limit of considering febrile seizures?	28	No	13 (46.4%)	Yes, 6 years	10 (35.7%)	Others	5 (17.9%)
8. Do you want to revise the lower limit of considering febrile seizures?	28	No	20 (71.4%)	Yes, 3months	6 (21.4%)	Others	2 (7.1%)
B1. Simple febrile seizures are defined as febrile seizures that are generalized (without a focal component), duration lasting less than 15 minutes and not recurring within 24 hours							
9. Do you agree with above definition? ¶	28	Yes	8 (28.6%)	No	20 (71.4%)		
B2. Simple febrile seizures are defined with following variables a. Patient aged 6 months to 5 years b. Generalized (without a focal component), c. Spontaneous cessation of convulsion within 15 minutes d. One convulsion within a 24-hour period e. Return to alert mental status after convulsion f. Absence of pre-existing neurological abnormality g. Documentation of fever (>38.4 C)							
10. Do you agree with above definition? ¶	28	Yes	17 (60.7%)	No	11 (39.3%)		
11. In the definition, do we need to mention "Patient aged 6 months to 5 years"	17	Yes	17 (100%)	No	0		
12. In the definition, do we need to mention "spontaneous cessation of convulsion within 15 minutes"	17	Yes	16[*a] (94.1%)	No	1 (5.9%)		
13. In the definition, do you need to include "one convulsion within 24-hour period"	17	Yes	16[*b] (94.1%)	No	1 (5.9%)		
14. In the definition, do you need to include "Return to alert mental status after convulsion"	17	Essential	7 (41.2%)	Describe more	5 (29.4%)	No need to mention	5 (29.4%)

15. In the definition, do we need to include "Absence of pre-existing neurological abnormality"?	17	Yes	14 (82.4%)	No	3 (17.6%)		
16. In the definition, do we need to include "Documentation of fever (>38.4 C)"	17	Yes	8 (47.1%)	No	9 (52.9%)		
C. Complex febrile seizures are febrile seizures that are focal, prolonged (>15 minutes) and/or occurring in a flurry (more than one episode of seizure within first 24 hours of fever)							
17. Are you okay with the term 'focal"?	28	Yes	23 (82.1%)	No, need separate term as "focal febrile seizure"	3 (10.7%)		2 (7.1%)
18. Regarding the terminology "complex febrile seizure", my opinion is:	27	Retain this terminology of complex febrile seizure	14 (51.9%)	Prefer to consider prolonged, recurrent, and focal febrile seizures separately	6 (22.2%)	Prefer to use the term CFS-M (multiple), CFS-P (prolonged), CFS-F (focal) instead of the above two options	7 (25.9%)
19. Regarding the proposed definition of complex febrile seizure, are you okay with the term "prolonged (>15 minutes)"?	28	Yes	26[*b] (78.8%)	No, I would prefer to keep this as a separate entity and call it "prolonged febrile seizure"	1 (3.6%)	No, prolonged should be defined as >30 minutes.	1 (3.6%)
20. Regarding the proposed definition of complex febrile seizure, what is your opinion on "occurring in a flurry (more than one episode of seizure within the first 24 hours of fever)"	28	Yes, but need modifications	22[*c] (78.6%)	No, I think it should be considered as a separate entity	3 (11.1%)	Others	3 (11.1%)
21. Do you want to define what is "multiple"?	28	Anything more than one	22 (78.6%)	No need to define	4 (14.3%)	Others	2 (7.1%)
22. Prolonged febrile seizure (PFS) is defined as a febrile seizure that lasts for more than 15 minutes. What is your opinion about including this as a separate terminology?	28	I want to consider as complex febrile seizures	18 (64.3%)	I agree it's a separate entity	9 (32.1%)	Others	1 (3.6%)
23. Febrile status epilepticus is defined as febrile seizure lasting 30 minutes or more and is considered the extreme end of the complex febrile seizure.	28	I want to consider it, but have suggested modifications	27[*d] (96.4%)	I don't agree to consider as a separate entity. It should be part of complex febrile seizures	1 (3.6%)		

24. Regarding the duration of FSE, the literature mentions it as 30 minutes. What is your suggestion regarding duration herein?	27	It should be like any other status epilepticus with T1>5minutes and T2 >30minutes	16 (59.3%)	I agree with 30 min	10	Include 5 minutes operational definition	1 (3.7%)
25. "SFS+NDD". If a child with pre-existing neurological abnormality develops a simple febrile seizure, we can call it as SFS+NDD	27	Yes, this is good, I agree	10 (37%)	No, there is no need for such terminology	9 (33.3%)	Others	8 (29.6%)
26. If a child has more than two complex features (focal, multiple, prolonged), we can label it depending on the features as CFS-FM, CFS-MP, CFS-FP, CFS-FMP and so on.	27	Yes, this is good, I agree	11 (40.7%)	No, there is no need for such terminology, we can call it as CFS alone	12 (44.4%)	Other	4 (14.8%)
D. Febrile Seizures Plus: Febrile seizures that continue past the usual age where they are expected to resolve and/or are accompanied by afebrile generalized (tonic-clonic, atonic, myoclonic, myoclonic-atonic, or absence) or focal seizures will be considered as febrile seizure plus							
27. Regarding the proposed definition of FS+, what is your overall opinion	28	I completely agree with this ILAE terminology	21 (75%)	I do not agree with this definition proposed	3 (10.7%)	Other	4 (14.3%)
28. Regarding the proposed definition of FS+, what do you think about "that continue past the usual age"?	28	I am okay with above phrase	14[*c] (50%)	why don't we define it as 6 years	10 (35.7%)	Others	4 (14.3%)
29. Regarding the proposed definition of FS+, what do you think about "where they are expected to resolve"?	28	I am okay with above phrase	22 (78.6%)			Others	6 (21.4%)
30. Regarding the definition of FS+, what do you think about the phrase "and/or"	28	I am okay with above phrase	21 (75%)	No, this is not acceptable	7 (25%)	Others	0
31. One of proposed definition of FS+ (by one of the writing member) is as follows: Febrile seizures that continue past the usual age where they are expected to resolve with or without afebrile generalized (tonic-clonic, atonic, myoclonic, myoclonic-atonic, or absence) or focal seizures OR febrile seizures with afebrile generalized (tonic-clonic, atonic, myoclonic, myoclonic-atonic, or absence) or focal seizures.(as in Dravet's syndrome)	27	I completely agree with this definition	7 (25.9%)	I do not agree with this definition proposed	8 (29.6%)	Other comments	12 (44.4%)
E. Genetic epilepsy febrile seizure plus (GEFS+) is defined as a familial epilepsy syndrome in which affected individuals may have variety of epilepsy phenotype, the most common being febrile seizure and febrile seizure plus							
32. What is your opinion on this definition of GEFS+	28	I completely agree with this definition	24 (85.7%)	I do not agree with the definition	3 (10.7%)	Others	4 (14.2%)

33. Can we define GEFS+ simply as "FS+ with positive family history of FS"	28	Yes, this sounds better	10 (35.7%)	I do not agree to this proposal	11 (39.3%)	Others	7 (25%)
F. Other questions related to definitions							
34. What's your opinion on the term "atypical febrile seizure"	28	No need to mention it anywhere	9 (32.1%)	We can mention it that this term is same as CFS and is no longer used	17 (60.7%)	Other	1 (7.1%)
35. What's your opinion on the term "convulsive status epilepticus"	28	I do not think we need to use this terminology	17 (60.7%)	I think we need to define convulsive status epilepticus using standard definition of T1 and T2	11 (39.3%)		
36. What is your opinion on the term "febrile seizure with later epilepsy"? Literature defines it as Individuals where epilepsy (recurrent afebrile seizures) develops after the febrile seizure	27	I do not think we need to use this terminology in this document.	21 (77.7%)	It is okay to retain this term	6 (22.2%)		
37. What is your opinion on the term "fever provoked epilepsy" or "fever triggered epilepsy"?	28	I do not think we need to use this terminology	17 (60.7%)	It is okay to retain this term	10 (35.7%)	Others	1 (3.6%)
G. Duration of seizure for labelling simple/ complex/ febrile status epilepticus							
38. The duration of seizure for defining it as simple febrile seizure should be	31	≤15 min	16 (51.6%)	≤5min	14 (45.2%)	10 min	1 (3.2%)
39. The duration of seizure for defining it as complex febrile seizure should be	31	≥15 min	20 (64.5%)	≥5min	10 (32.3%)	10 min	1 (3.2%)
40. The duration of seizure while labelling it as febrile status epilepticus should be	31	ILAE definition of T1 and T2	24 (77.4%)	≥30 min	7 (24%)		
H1. Investigations: Lumbar Puncture/ CSF analysis							
41. CSF analysis should preferably be performed for							
a) All children ≤12 months	31	Yes	29 (93.5%)	No	2 (6.5%)		
b) All patients with febrile status epilepticus	31	Yes	16 (51.6%)	No	15 (48.3%)		
c) Children who have not received full course of HiB and pneumococcus vaccination	31	Yes	12 (38.7%)	No	19 (61.3%)		
d) All children with complex febrile seizures	31	Yes	7 (22.6%)	Yes	24 (77.4%)		
42. Among children with age >12 months lumbar puncture should be performed for							
a) Children with signs of meningoencephalitis like neck rigidity, positive kernigs/ Brudzinski	31	Yes	31 (100%)	No	0		
b) Children who have received a single dose of IV cephalosporin or amikacin; or children	31	Yes	24 (77.4%)	No	7 (22.6%)		

wo have received >24 hours of oral cephalosporin/ amoxycillin or sulfa drugs							
c) LP decision can be individualized based on clinicians experience	31	Yes	17 (54.8%)	No	14 (41.2%)		
43. CSF in a child with febrile seizures should be analyzed for							
a) Cytology gram stain, proteins and sugar	31	Yes	31 (100%)	-			
b) Viral or bacterial panel should be done only if routine CSF analysis is suggestive of bacterial/ viral meningitis	31	Yes	20 (64.5%)	No	11 (35.5%)		
c) Routine CSF viral panel is NOT indicated for all patients with febrile seizures	31	Yes	27 (87.1%)	No	4 (12.9%)		
44. In a patient needing lumbar puncture,							
a) Lumbar puncture should be *preferably* preceded by neuroimaging wherever feasible	31	Yes	31 (100%)				
b) If neuroimaging is not feasible, then lumbar puncture may be considered if all of following conditions are met: seizure was generalized; there is no focal neurological deficit; there is no papilledema; and there are no clinical features of raised ICP	31	Yes	26 (83.9%)	No	5 (16.1%)		
H2. Laboratory investigations							
45. In children with febrile seizures with no localizing clinical features, the CBC ±ESR±CRP should be considered							
a) For all patients with Febrile status epilepticus	31	Yes	25 (80.6%)	No	6 (19.4%)		
b) For all patients with complex febrile seizures	31	Yes	22 (71%)	No	9 (29%)		
c) For all patients with simple febrile seizures	31	Yes	2 (6.5%)	No	29 (93.5%)		
46. In children with febrile seizures with no localizing clinical features, urinalysis should be considered for							
a) all children ≤18m without any focus of infection	31	Yes	25 (80.6%)	No	6 (19.4%)		
b) Children >18m with clinical features suggestive of UTI (dysuria/ frequency/ urgency)	31	Yes	25 (80.6%)	No	6 (19.4%)		
47. Blood glucose should be checked for							
a) All patients with febrile status epilepticus/ ongoing seizures when seen	31	Yes	29 (93.5%)	No	2 (6.5%)		
b) All patients with complex febrile seizures	31	Yes	24 (77.4%)	No	7 (22.6%)		
c) All patients with simple febrile seizures	31	Yes	24 (77.4%)	No	7 (22.6%)		
48. Serum Ca should be checked for							
a) All patients with febrile status epilepticus/ ongoing seizures when seen	31	Yes	29 (93.5%)	No	2 (6.5%)		
b) All patients with complex febrile seizures	31	Yes	24 (77.4%)	No	7 (22.6%)		
c) All patients with simple febrile seizures	31	Yes	24 (77.4%)	No	7 (22.6%)		
49. Serum Na and K should be checked for all patients with							
a) All patients with febrile status epilepticus/ ongoing seizures when seen	31	Yes	26 (83.9%)	No	5 (16.1%)		
b) All patients with complex febrile seizures	31	Yes	14 (45.2%)	No	17 (54.8%)		

c) All patients with simple febrile seizures	31	Yes	6 (19.4%)	No	25 (80.6%)		
50. Serum Mg should be checked for							
a) All children with febrile status epilepticus	30	Yes	18 (60%)	No	12 (40%)		
b) All children with complex febrile seizures	30	Yes	3 (10%)	No	27 (90%)		
c) All children with simple febrile seizures	30	Yes	3 (10%)	No	27 (90%)		
51. Screening for Fe deficiency							
a) All children with febrile seizures need not be screened for iron deficiency.	30	Yes	27 (90%)	No	3 (10%)		
b) Screening should be done only if child has pallor on clinical examination.	30	Yes	30 (100%)	-			
c) Screening should include CBC and PBS for all patients	30	Yes	27 (90%)	No	3 (10%)		
d) Screening. preferably should include serum ferritin	30	Yes	25 (80.6%)	No	6 (19.4%)		
52. Routine assessment of Serum Phosphorus, alkaline phosphatase and vitamin D is not needed. These tests may be performed if the child has clinical features of rickets or if the child has hypocalcemia	31	Yes	26 (83.9%)	No	5 (16.1%)		
H3. Neuroimaging							
53. Urgent neuroimaging is indicated in							
a) Febrile status epilepticus	31	Yes	26 (83.9%)	No	5 (16.1%)		
b) Simple febrile seizures	31	Yes	2 (6.5%)	No	29 (93.5%)		
c) In complex febrile seizures urgent neuroimaging should be considered if the child has focal seizures	31	Yes	17 (54.8%)	No	14 (45.2%)		
d) Neuroimaging should be considered if the child has focal findings on EEG	31	Yes	22 (71%)	No	9 (29%)		
54. The neuroimaging modality of choice in these children should be MRI Brain epilepsy protocol ± contrast	31	Yes	28 (90.3%)	No	3 (9.7%)		
55. The ideal time to perform neuroimaging should be							
a) in Febrile status epilepticus	31	First 72h	25 (80.6%)	72h to 7 days	6 (19.4%)		
b) in complex febrile seizures	21	First 72h	14 (66.7%)	72h to 7 days	7 (33.3%)		
56. Routine follow up neuroimaging is not needed for these children if the initial neuroimaging did not suggest. An alternate diagnosis	30	Yes	28 (93.3%)	No	2 (6.67%)		
57. If the MRI findings are equivocal	30	Nuclear imaging should be performed to rule out MTS	9 (30%)	Nuclear imaging is not needed	21 (70%)		
H4. EEG							
58. Children with simple febrile seizures do not need a routine EEG	31	Yes	31 (100%)				
59. Routine EEG is indicated for							
a) Febrile status epilepticus	31	Yes	26 (83.9%)	No	5 (16.1%)		
b) Complex febrile seizures	31	Yes	20 (64.5%)	No	11 (35.5%)		

c) EEG should be done for patients focal findings on neuroimaging	31	Yes	19 (61.3%)	No	12 (38.7%)		
60. The ideal time to perform an EEG is							
a) Complex Febrile Seizure	31	1 day to 1 week	23 (76.7%)	Other	8 (25.8%)		
b) Febrile. Status epilepticus	31	1 day to 1 week	13 (41.9%)	First 24h	16 (53.3%)		
61. EEG protocol should include minimum 30 minute record and should include both awake and asleep states	31	Yes	31 (100%)	-			
H5. Genetic Testing							
62. Indications for genetic testing includes							
a) Child aged 12 to 25 months with >1 febrile seizure before age 18 months and myoclonic and/or atypical absence seizures refractory to one or more antiseizure drug	31	Yes	25 (80.6%)	No	6 (19.4)		
b) All children with family history of epileptic encephalopathy	31	Yes	25 (80.6%)	No	6 (19.4)		
c) All children with family history of GEFS+	31	Yes	18 (58.1%)	No	13 (41.9%)		
63. Genetic testing is not indicated for							
a) All children with simple febrile seizures	31	Yes	31 (100%)				
b) All children with complex febrile seizures	31	Yes	30 (96.8%)	No	1 (3.2%)		
c) All children with family history of febrile seizures	31	Yes	30 (96.8%)	No	1 (3.2%)		
64. Genetic testing of choice in these patients should be	30	Targeted exome sequencing	26 (86.7%)	Whole exome sequencing	4 (13.3%)		
I. Domiciliary Care							
65. Domiciliary abortive care should be taught to	31	All patients with febrile seizures	28 (90.3%)	Only patients with complex febrile seizures/ febrile status	3 (9.7%)		
66. Duration of seizure after abortive treatment should be instituted in non-hospital setting is	31	2 min	13 (41.9%)	5 min	16 (51.6%)	Others	2 (6.5%)
67. Which drug do you recommended for domiciliary (non-hospital setting) abortive seizure management	31	Midazolam	31 (100%)				
68. Dose and route of midazolam used for domiciliary abortive seizure management	31	Intranasal midazolam 0.2mg/kg	28 (90.3%)	Buccal midazolam 0.2mg/kg	3 (9.7%)		
69. Preferably, Midazolam should be used for abortive treatment at home instead of diazepam or lorazepam	31	Yes	24 (77.4%)	No	7 (2.6%)		
70. Repeat dose of abortive treatment should be administered	31	Repeat dose after 5 minutes if seizures are not controlled	26 (83.9%)	Do not repeat dose	3 (9.7%)	Others	2 (6.5)

		on ¹rst drug de-livery					
71. Parental education for seizure control should be done by	31	Doctor	25 (80.6%)	Nurse	4 (12.9%)	Others	2 (6.5)
72. The mode of parental education for domiciliary seizure control should be	31	Video	27 (87.1%)	Practical demonstration	27 (87.1%)	Printed leaflets	25 (80.6%)
73. The information about domiciliary seizure control should include Recovery position Drug/ Dose/ route Repeat dose When to bring to hospital	31	Yes	31 (100%)				
J. Intermittent Antiseizure drugs							
74. Intermittent antiseizure drug should be administered to							
a) All children with febrile status epilepticus or seizures lasting for ≥5 minutes	31	Yes	27 (87.1%)	No	4 (12.9%)		
b) Recurrent febrile seizures (≥2 episodes)	31	Yes	25 (80.6%)	No	6 (19.4%)		
c) All patients with complex febrile seizures	31	Yes	25 (80.6%)	No	6 (19.4%)		
d) All patients with febrile seizures including simple febrile seizures	31	Yes	10 (32.2%)	No	21 (67.7%)		
75. Antiseizure drug of choice for intermittent prophylaxis							
Clobazam	31	Yes	31 (100%)	-	-		
76. If intermittent prophylaxis has been advised for a child, in which of following scenarios do you recommend that parents should initiate intermittent prophylaxis							
a) Fever >38.4 C or when they start administering antipyretics	31	Yes	30 (96.8%)	No	1 (3.2%)		
b) With any illness like ARI/ AGE	31	Yes	6 (19.45%)	No	25 (80.6%)		
77. Duration of AED when initiated for intermittent prophylaxis							
	31	3 days	27 (87.1%)	During the complete febrile period	3 (9.7%)	2 days	1 (3.2%)
78. Should ASDs be tapered after intermittent prophylaxis							
	31	No	30 (96.8%)	Over 2-3 days	1 (3.2%)		
79. ASD and dose for intermittent prophylaxis							
	31	Clobazam 0.5 to 1 mg/kg in 2 divided doses	25 (80.6%)	Clobazam 1 mg/kg in 2 divided doses	4 (12.9%)	Others	2 (6.5)
K. Antipyretics							
80. Should antipyretics be administered around the clock prophylactically							
	31	Yes, should be administered for all patients with febrile seizures. They do not prevent seizures, but make the child comfortable	28 (90.3%)	Not recommended	3 (9.7%)		
81. Antipyretic of choice for management of fever in these children is							
	31	Paraceta-	25 (80.6%)	Ibuprofen	4 (12.9%)	PCM +	2 (6.5)

		mol (15mg/kg/ dose q6h)				Ibuprofen/ Others	
82. Minimum duration for use of prophylactic antipyretic should be							
	31	Duration of febrile period	25 (80.6%)	First 2-3 days	4 (12.9%)	not do-main of neurologist to give recom-menda-tions for antipyretic use	1 (3.2%)
L. Continuous Anti-Seizure Drug prophylaxis							
83. In which of following conditions, should continuous antiseizure drugs be administered							
a) Febrile status epilepticus	31	Yes	26 (83.9%)	No	5 (16.1%)		
b) Febrile seizures in a child with neurodevelopmental delay	31	Yes	29 (93.5%)	No	2 (6.5%)		
c) GEFS+	31	Yes	29 (93.5%)	No	2 (6.5%)		
d) Focal seizures/ complex febrile seizures	31	Yes	8 (25.8%)	No	23 (74.2%)		
84. ASD used for continuous prophylaxis should be							
	31	VPA	25 (80.6%)	LEV	3 (9.7%)	Others	2 (6.5)
85. Do you recommend any tests before initiating continuous ASD							
	31	None	25 (80.6%)	Genetic tests	2 (6.7%)	LFT	7 (22.5%)
86. Duration for which. Antiseizure drugs should be continued once initiated							
	31	2 years of seizure free peri-od; has to be guided individu-ally based on prima-ry syn-drome (GEFS+/ Dravet)	27 (87.1%)	Others	4 (12.9%)		
M. Management of Febrile Status Epilepticus							
87. For the management of febrile status epilepticus, the benzodiazepine of choice in hospital setting should be							
	31	Loraze-pam	31 (100%)				
88. The number of doses of benzodiazepines that should be administered before administering second line agent should be							
	2 doses	25 (80.6%)	One dose	6 (19.4%)	2 doses		
89. Should phenytoin be used for management of febrile status epilepticus							
	31	Yes	9 (29%)	No	22 (71%)		
90. In a child with febrile status epilepticus, the second line antiseizure drug should be							
a) Valproate	31	Yes	17 (54.8%)	No	14 (45.2%)		
b) Phenytoin	31	Yes	9 (29%)	No	22 (71%)		
c) Levetiracetam	31	Yes	4 (12.9%)	No	27 (87.9%)		
91. The third line ASD in febrile status epilepticus should be							
	31	Le-vetirace-tam	16 (51.6%)	Phenobar-bitone	8 (25.8%)	Others	8 (25.8%)
N. Primary prevention/ prevention of recurrences							
92. Should iron prophylaxis be used for primary prevention or prevention of recurrences							
	31	Yes (3-6mg/kg/da y)	4 (12.9%)	No	27 (87.1%)		
93. Should Zinc supplementation be recommended for prevention of recurrences							
	31	Yes	1 (3.2%)	No	28 (90.3%)	Others	2 (6.5)
94. Should Vitamin D supplementation be recommended for prevention of recurrences							
	31	Yes, for	4 (12.9%)	No	25 (80.6%)	Others	2 (6.5)

		children on long term ASDs					
95. Should tepid sponging be advised for fever, in a child with febrile seizures							
	31	Yes	19 (61.3%)	No	12 (38.7%)		
96. If a child has a febrile seizure, should the vaccine schedule be changed/ interrupted							
	31	Yes	2 (6.5)	No	29 (93.5%)		
97. If a child has a febrile seizure, after what duration (in months), can we administer vaccines?							
	22	0-3 months	18 (81.8%)	>3m	4 (18.2%)		
98. Can we give MR/ MMR and varicella vaccine at same visit in a child with past history of febrile seizure?							
	31	Yes	25 (80.6%)	No	6 (19.4%)		
99. Should acelluar pertussis/ Pentavalent vaccine be given in a child who has a febrile seizure?							
	31	Yes	30 (96.8%)	No	1 (3.2%)		
100. If a child has a vaccine associated febrile seizure, should the child be administered same vaccine in future?							
	31	Yes, but can avoid whole cell pertussis and if needed then administer clobazam prophylaxis	25 (80.6%)	No	6 (19.4%)		
101. Should prophylactic antipyretics be advised along with vaccines to reduce the risk of febrile seizures?							
	31	Yes	21 (67.7%)	No	10 (32.3%)		
102. Can the following vaccines be administered to patients who had febrile seizures							
a) MMR/ MR	31	Yes	25 (80.6%)	No	6 (19.4%)		
b) PCV	31	Yes	27 (87.1%)	No	4 (12.9%)		
c) Influenza	31	Yes	27 (87.1%)	No	4 (12.9%)		
d) Whole cell Pertussis	31						
e) Acellular pertussis	31	Yes	30 (96.8%)	No	1 (3.2%)		
103. Should routine post vaccination clobazam or diazepam be advised for children with febrile seizures?							
	31	Yes	6 (19.4%)	No	25 (80.6%)		
104. Parental counselling in febrile seizures should included							
a) Reassurance about the overall benign nature of the problem	31	Yes	31 (100%)	No	0		
b) Home management of seizure	31	Yes	31 (100%)	No	0		
c) Risk of recurrence of FS	31	Yes	30 (96.8%)	No	1 (3.2%)		
d) Advice regarding paracetamol	31	Yes	28 (90.3%)	No	3 (9.7%)		
e) Advice regarding vaccinations	31	Yes	28 (90.3%)	No	3 (9.7%)		

* Elaborate what is metabolic disturbance (n=6)
^ Reframe as "prior history of afebrile seizure"
# We can omit meningitis (n=1); omit/ modify bracketed conditions (n=6); elaborate bracketed conditions especially metabolic disturbances (n=1)
¶ Three responders did not agree to both definitions.
*a 11/17 respondents (64.7%) agreed to statement without modifications. Suggestions for modifications were given (n=6): avoid use of term convulsion (n=6); reduce duration of cessation of seizure to 5 min (n=2).
*b 17/28 (60.7%) respondents agreed to statement without modifications. Suggestions for modifications were given (n=9): include any child brought convulsing to casualty (n=4); reduce seizure duration to 5 minutes (n=4); reduce seizure duration to 10-15 minutes (n=1).
*c The definition is fine as it is (n=2). Suggested modifications (n=20): Use multiple instead of flurry (n=16), more than one episode in 24 hours (n=1), cluster instead of flurry (n=1), recurrence rather than flurry (n=1), and clarify and/or (n=1).
*d Agree with the definition as it is (n=5). Suggested changes: remove portion suggesting that it is extreme form of complex febrile seizure (n=10); include child brought convulsing to casualty (n=10); re-assess the time in accordance with recent definitions of status epilepticus (n=2)
*e Six (21.4%) respondents agreed to definition without any modifications. Eight respondents wanted the exact age to be mentioned instead of "past the usual age".

Diagnosis and Management of Pediatric Acute Liver Failure: ESPGHAN and NASPGHAN 2022

Sruti Mishra, Pallavi Pallavi

From Department of Pediatrics, Maulana Azad Medical College and Lok Nayak Hospital (Delhi University), BSZ Marg, Delhi. Correspondence to: Dr Pallavi, Assistant Professor, Department of Pediatrics, Maulana Azad Medical College, BSZ Marg, Delhi. pallavi86.delhi@gmail.com

Guidelines for management of pediatric acute liver failure (PALF) were recently published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). We, herein, update the readers about the diagnosis and management of PALF with emphasis on the changes in assessment and staging of hepatic encephalopathy, administration and goals of supportive therapy, frequency of monitoring, and management of complications.

Keywords: *Hepatic encephalopathy, Liver transplant.*

Pediatric acute liver failure (PALF) is characterized by acute liver dysfunction with heterogenous underlying etiologies and a rapid progression resulting in significant morbidity and mortality. Manage-ment of PALF requires rapid age-based pertinent diag-nostic evaluation, prompt initiation of specific and suppor-tive therapy with monitoring for early identification and management of complications. Recently, guidelines for the diagnosis and management of PALF were released by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Euro-pean Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [1]. We summarize these guide-lines to update the readers on this important entity [2].

Definition

Due to the difficulty in precise assessment of hepatic encephalopathy in infants and children, the current guidelines suggest PALF Study Group (PALFSG) consensus entry criteria for the diagnosis of PALF similar to the previous guidelines (**Fig. 1**). These criteria are intended to identify cases of severe acute liver injury that could cause significant clinical deterioration resulting in either death or liver transplant. However, these criteria do not include pediatric chronic liver diseases that present as ALF. Reconsideration of the criteria for initiation of optimal interventions in such cases has been suggested.

Clinical Presentation and Examination

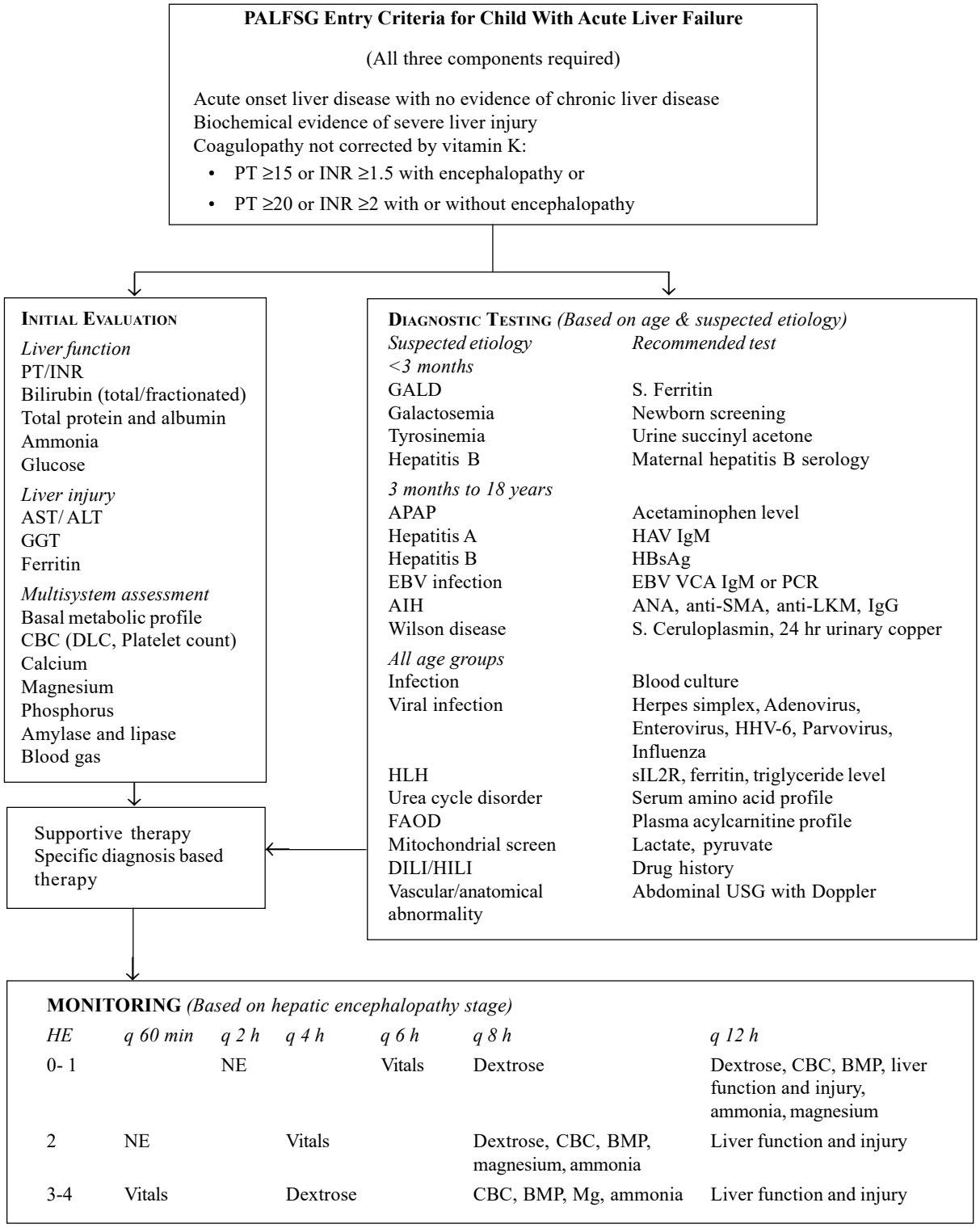
History pertaining to exposure to infectious agents (like recent travel or any contact) or toxins (like chemicals, medications, illicit drugs or wild mushrooms) should be actively asked for. Family history of consanguinity, autoimmune diseases, liver disease, multiple late mis-carriages, early infant death or developmental delay is suggestive of underlying autoimmune or metabolic cause for PALF.

Examination should focus on early identification of features of hepatic encephalopathy: mental (altered sleep-wake cycle, confusion, disorientation) as well as neuro-logical (increased tone, brisk reflexes, positive Babinski sign). Clinical features suggestive of chronic liver disease (like hepatosplenomegaly, ascites, pedal edema, stunting, signs of vitamin D deficiency, spider angiomas etc.) should be ruled out on initial examination.

Diagnostic Evaluation and Management

Current guidelines suggest a 4-step symbiotic diagnostic and management approach for any child meeting PALFSG entry criteria: *i*) Liver function test to assess liver injury, *ii*) Tests for suspected underlying etiology, *iii*) Laboratory tests as well as periodic examination to identify compli-cations of PALF, and *iv*) Baseline hematological, renal, pancreatic and electrolyte assessment.

Once PALF is diagnosed, supportive management should be initiated promptly, irrespective of the underlying etiology. Clinical monitoring at appropriate intervals should also be done in intensive care unit. Early transfer or contact with the liver transplant center must be considered wherever indicated. Laboratory assessment should also be commenced immediately along with supportive treatment. Diagnostic tests for specific etiology should be carried out based on age, and clinical suspicion, with prioritization of investigations to minimize volume of blood drawn for investigations, and reach a diagnosis in the short time



INR: International normalized ratio, LKM: liver-kidney-microsomal antigen, NE: neurological examination, SMA: smooth muscle antigen, PT: prothrombin time, CBC-complete blood count.

Fig. 1 Summary of diagnosis, evaluation, management and monitoring in pediatric acute liver failure (as per Squires, et al. [1]).

allowed by the rapid clinical progression seen in PALF. **Fig. 1** illustrates the approach to a patient meeting PALFSG entry criteria.

In developed countries, acetaminophen toxicity is the most frequently identified cause of PALF accounting for 13.3% of the cases, with no etiology identified in 30-50%. Application of standardized diagnostic test recommendations helped reduce the percentage of Indeterminate PALF from 48% during first two phases of a study to 30.8% in the third phase [5]. However, studies in India show viral infections as the most common cause followed by metabolic liver diseases and drug induced liver injury with only 9-14.6% cases being of indeterminate etiology [3,4]. The diagnostic evaluation should be planned taking into consideration these differences in underlying etiology in different settings. Liver biopsy in indeterminate PALF (IND-PALF) cases can help in identification of a recently defined sub-set, which has dense CD103+ CD8+ T-cell hepatic infiltrates and may benefit from immunosuppressive therapy [6]. The evaluation and management of common causes of PALF in current guidelines is similar to the 2017 NASPGHAN and ESPGHAN guidelines.

Also, all PALF patients need to be assessed for the presence and severity of hepatic encephalopathy; although, identifying it can be quite challenging in infants and young children. Hence, current guidelines have branched hepatic encephalopathy assessment between young children (<4 years) and older children (>4 years) and added neurological signs and EEG [1]. The frequency of monitoring profile in PALF is also now recommended to be based on the HE stage (**Fig. 1**).

Timely initiation of the treatment protocol in PALF can prevent complications and improve the survival. **Table I** summarizes the current guidelines on management of PALF and its complications along with comparison with the prior guidelines. It is recommended to start fluid therapy with 90% of maintenance requirement to prevent over-hydration that can precipitate cerebral edema, pulmonary and peripheral edema; and under-hydration that can cause hepatorenal syndrome [8], hypotension and worsening of encephalopathy. In PALF with cardiovascular dysfunction, noradrenaline is the vasopressor of choice but if requirements escalate, low dose vasopressin can be added [10]. Based on recent evidence demons-

Table I Important Changes in ESPGHAN and NASPGHAN Position Paper on Diagnosis and Management of PALF, 2022 [1]

	2022 Guidelines[a]	*2017 Guidelines*
Etiology and diagnostic evaluation	Specific diagnostic tests based on age suggested Liver biopsy can be performed safely, especially by transvenous (e.g., transjugular) approach & it helps guide management especially in IND-PALF.	Liver biopsy considered if diagnosis unclear. Usually done by transjugular approach.
Fluid and electrolytes	*Fluids*: IVF: Intravenous fluids to be 90% of total maintenance fluids; Initial fluid: one- half normal saline with 10% dextrose with 15 mEq/L potassium; Avoid fluids with predetermined electrolyte concentration (like RL).	Maintain adequate intravascular volume status.
	Glucose: Target serum glucose: 90-120 mg/dL	No specific target glucose range
	Sodium: Target: 145-155 mEq/L, Requirement: 2-3 mEq/kg/day. Treat hyponatremia if: Symptomatic or Na < 120 mEq/L or when fluid restriction is not possible.	Avoid hyponatremia, hypokalemia, hypophosphatemia, hypocalcemia and hypomagnesemia.
	Phosphate: Maintain serum phosphate >3 mg/dL	No target range mentioned.
Hyperammonemia and hepatic encephalopathy (HE)	Staging of hepatic encephalopathy in children < 4 years and > 4 years specified separately. Based on mental status, reflexes, neurological signs and EEG changes.	Hepatic encephalopathy stage 0-5, same for all ages based on mental status and reflexes only.
Arterial ammonia levels are ideal butfree flowing venous blood is convenient.	Restrict protein intake to 1gm/kg/dayLactulose: 0.5 to 30 mL/kg/dose, adjusted to produce 2-4 loose stools per day. Rifaximin: Efficacy in paediatrics is unknown Empiric antibiotics and Extracorporeal support devices to be considered.	Use of lactulose and non-absorbable antibiotics
Cerebral edema[b]	ICP monitoring is recommended in patients with: Stage III or IV encephalopathy; CT scan suggestive of edema; EEG with slowing; Hyperammonia; Mechanical ventilation.	Data insufficient to recommend routine use of ICP monitoring in PALF.

Table contd.

Contd. from pre-page

	2022 Guidelines[a]	*2017 Guidelines*
	No recommendation on prophylactic antiseizure medication Therapies specific for raised ICP: Hyperosmolar therapy: Mannitol: at 0.5-1.0 g/kg; Hypertonic saline 2%-23.4% to maintain S. Na 145-155 mEq/L. Forced hyperventilation: Brief (20 min.) bursts to reduce pCO2<34 [b]Additional targets for raised ICP provided.	*Continuous EEG: Useful as a screening tool* *No role of prophylactic antiseizure medication.* *Therapy for raised ICP: Mannitol: 0.25 mg/kg/dose for acute rise in ICP (Insufficient evidence); Hypertonic saline 3% to 30% to maintain S. Na 145-150 mEq/L*
Coagulopathy (Deranged INR and decreased fibrinogen, factor V and factor VII)	IV Vitamin KPlatelet and/or FFP: Only in active bleeding or invasive procedureAvoid transfusion only to improve platelet or INR. Cryoprecipitate transfusion in low fibrinogen state (<100 mg/dL) Recombinant factor VII: Used before ICP monitor placement only. Its expensive with risk of thrombosis.	Vitamin K FFP transfusion: Only in active bleeds or before invasive procedure Platelet transfusion: If Platelet <50,000 with bleed or < 10,000 irrespective of bleed Recombinant VII: Preferred before invasive procedure in patient with associated renal insufficiency. Carries risk of venous thrombosis.
Kidney injury	Continuous veno-venous hemofiltration or renal replacement therapy (CRRT) is recommended in AKI	Insufficient data to recommend renal replacement therapy in PALF.
Infection	In patients with clinical suspicion or biochemical changes, broad spectrum antibiotics should be started after obtaining blood and tracheal cultures.Discontinue when cultures turn negative.	Prophylactic antibiotics or antifungals: Not recommended. Start antibiotics in patients with SIRS or stage 3/4 HE.
Nutrition	Enteral feeding is preferred over TPN TPN (maximum calories with minimum volume): Restrict protein to 1 gm/kg/day if hyperammonemia present Lipids to be used except if FAOD or mitochondrial disease is suspected.	Enteral feeding preferred as far as possible. Ensure adequate calorie provision, euglycemia, adequate protein without causing hyperammonemia.
Monitoring	Frequency of monitoring specified based on stage of encephalopathy.	No specific frequency suggested.
Neuroimaging	CT recommended in HE.	Head CT scan: Other causes of acute deterioration of sensorium (like ICH)
Plasmapheresis/plasma exchange	Evidence in PALF sparse. Recommended with other extra-corporeal therapy as a bridge to liver transplant	No significant change in survival.
Prognostic markers	KCHC and LIU not valid if LT and death outcomes are separated.	Predictors of outcome provided Serum bilirubin, Prothrombin time, Ammonia, WBC count, onset of hepatic encephalopathy.

Prepared from Squires JE, et al [1] and Lutfi R, et al [2]. [a]No major changes in recommendations for cardiovascular dysfunction, sedation, role of N-acetyl cysteine, liver support therapies and liver transplant. CRRT-Continuous Renal Replacement Therapy, GIR Glucose Infusion Rate; FAOD- Fatty Acid Oxidation Defects, FFP-Fresh Frozen Plasma, ICH-Intracranial Hemorrhage, ICP-Intracranial pressure, IND-PALF Indeterminate Pediatric Acute Liver Failure, IVF- Intravenous Fluids, KCHC- Kings College Hospital Criteria, NIRS- Near-Infrared Spectroscopy, PELD- Pediatric End-stage Liver Disease, SIRS- Systemic Inflammatory Response Syndrome, TCD-Trans-cranial Doppler, TMD-Tympanic membrane displacement, RL- Ringer lactate; TPN-Total Parenteral Nutrition.

trating beneficial effect of lactulose in prevention and management of hepatic encephalopathy [9], it is now recommended in pediatric ALF. There is limited data on role of invasive intracranial pressure (ICP) monitoring in PALF and decision regarding ICP-monitoring needs to be case specific. The conditions where ICP monitoring can be considered and the goals of the monitoring have been added to facilitate the decision.

The recent guidelines emphasize on prompt identification of PALF, age-appropriate evaluation for hepatic encephalopathy, timely institution of supportive therapy and laboratory evaluation coupled with careful monitoring at adequate intervals for identification and management of complications. Investigations to establish an etiological diagnosis should be based on age of the child and clinical features. Liver transplantation can be lifesaving and plan for the same should be established, whenever indicated.

Outlining these essential components, the 2022 guidelines are envisioned to improve patient survival and prompt further studies for better non-invasive diagnostic techniques, neuromonitoring and new therapeutic modalities.

Contributors: SM: drafted the manuscript; PP: reviewed and edited the manuscript with important intellectual inputs. The final draft of the manuscript was approved by both the authors.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. Squires JE, Alonso EM, Ibrahim SH, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. J Pediatr Gastroenterol Nutr. 2022;74:138-58.
2. Lutfi R, Abulebda K, Nitu ME, et al. Intensive care management of pediatric acute liver failure. J Pediatr Gastroenterol Nutr. 2017;64: 660-70.
3. Alam S, Khanna R, Sood V, et al. Profile and outcome of first 109 cases of paediatric acute liver failure at a specialized paediatric liver unit in India. Liver Int. 2017;37:1508-14.
4. Kaur S, Kumar P, Kumar V, et al. Etiology and prognostic factors of acute liver failure in children. Indian pediatr. 2013;50:677-9.
5. Narkewicz MR, Horslen S, Hardison RM, et al. A learning collaborative approach increases specificity of diagnosis of acute liver failure in pediatric patients. Clin Gastroenterol Hepatol. 2018; 16:1801-10.
6. Chapin CA, Burn T, Meijome T, et al. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103+ CD8+ T cell infiltrate. Hepatology. 2018;68:1087-100.
7. Chapin CA, Mohammad S, Bass LM, et al. Liver biopsy can be safely performed in pediatric acute liver failure to aid in diagnosis and management. J Pediatr Gastroenterol Nutr. 2018;67:441-5.
8. Lui PMF, de Carvalho ST, Fradico PF, et al. Hepatorenal syndrome in children: A review. Pediatr Nephrol. 2021;36:2203-15.
9. Gludd LJ, Vilstrup H, Morgan MY. Nonabsorbable disaccharides for hepatic encephalopathy: a systematic review and meta-analysis. Hepatology. 2016;64:908-22.
10. Wendon J, Panel M, Cordoba J, et al. EASL Clinical Practical guidelines on management of acute (fulminant) liver failure. J Hepatol. 2017;66:1047-81.

Short Course of Daily Prednisolone During Upper Respiratory Tract Infection for Children With Relapsing Steroid Sensitive Nephrotic Syndrome

***Source Citation*:** Christian MT, Webb NJA, Mehta S, et al. Evaluation of daily low-dose prednisolone during upper respiratory tract infection to prevent relapse in children with relapsing steroid-sensitive nephrotic syndrome: The PREDNOS 2 randomized clinical trial. JAMA Pediatr. 2021: e215189.

SUMMARY

PREDNOS 2 was a double blind placebo controlled trial done to investigate the use of daily low-dose prednisolone for the treatment of upper respiratory tract infection –related relapses. It evaluated 365 children with relapsing steroid-sensitive nephrotic syndrome with and without background immunosuppressive treatment at 122 pediatric departments in the UK from February 1, 2013, to January 31, 2020. At the beginning of an upper respiratory tract infection, children received 6 days of prednisolone, 15 mg/m^2 daily, or matching placebo preparation. Those already taking alternate-day prednisolone rounded their daily dose using trial medication to the equivalent of 15 mg/m^2 daily or their alternate-day dose, whichever was greater. The primary outcome was the incidence of first upper respi-ratory tract infection-related relapse. The modified intention-to-treat analysis population comprised 271 children (mean (SD) age, 7.6 (3.5) years; 64.2% male), with 134 in the prednisolone arm and 137 in the placebo arm. The number of patients experiencing an upper respiratory tract infection-related relapse was 56 (42.7%) in the predniso-lone arm and 58 (44.3%) in the placebo arm (adjusted risk difference, 0.02; 95% CI, 0.14 to 0.10; *P* =0.70). No evidence was found that the treatment effect differed according to background immuno-suppressive treatment. A post hoc subgroup analysis assessing the primary outcome in 54 children of South Asian ethnicity (risk ratio, 0.66; 95% CI, 0.40-1.10) vs 208 children of other ethnicity (risk ratio, 1.11; 95% CI, 0.81-1.54) found no difference in efficacy of intervention in those of South Asian ethnicity (test for interaction *P*=0.09). The authors concluded that, results of PREDNOS 2 suggest that administering 6 days of daily low-dose prednisolone at the time of an upper respiratory tract infection does not reduce the risk of relapse of nephrotic syndrome in children in the UK and further work is needed to study the inter-ethnic differences in the study response.

COMMENTARIES

Evidence-Based Medicine Viewpoint

A group of researchers in the United Kingdom conducted a randomized controlled trial (RCT) to evaluate whether a short course of daily prednisolone administered to children with steroid sensitive relapsing nephrotic syndrome, at the onset of upper respiratory infection (URI) episodes, would reduce the occurrence of URI associated relapses [1]. Although, they did not specify a clinical question in the PICOT format, it can be deduced from the information provided, as follows. Population (P): Children (1-18y old) with relapsing nephrotic syndrome (irrespective of current treatment); Intervention (I): Oral prednisolone (dose at least 15 mg/m^2) for six days, started at the onset of a URI episode; Comparison (C): Placebo taken at the onset of a URI episode; Outcomes (O): URI-associated relapse, other relapses, cumulative dose of steroid, adverse events, behavior and quality of life indices; Timeframe of outcome measurement (T): 12 months from enrolment. The RCT is summarized in **Table I**.

Critical Appraisal

Overall, the trial was well designed and meticulously conducted. The investigators chose an appropriate study design, used a placebo for comparison of the trial intervention, and minimized common sources of bias. There were several refinements in the RCT, notably the use of strict definitions for frequently used concepts such as relapse, URI episode, and adherence. This diminishes subjective variations and fosters confidence. The investigators paid particular attention to the ethnic background of the RCT participants, given that all the previous four trials were conducted in Asian countries. A detailed critical appraisal of the trial methodology using the currently applicable Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2) [3], is summarized in

Table I Summary of the Trial

Study setting	A total of 122 Pediatrics departments across the United Kingdom were involved, 13 of which offered specialist Pediatric Nephrology services.
Study duration	February 2013 to January 2020. Follow-up was conducted for 12 months after enrolment.
Inclusion criteria	Age 1-18y, with steroid sensitive nephrotic syndrome (not defined further), with ≥2 relapses during the preceding year.
Exclusion criteria	Steroid resistant nephrotic syndrome (no definition specified), cyclophosphamide or rituximab therapy (current or within the previous 3 months), daily steroid therapy, or alternate day steroid therapy if the dose exceeded 15 mg/m^2.
Recruitment procedure	A Participant Information Sheet (PIS) was posted to families of potentially eligible children, approximately 1-2 weeks before scheduled clinic visits. Eligibility criteria were assessed (although it is not mentioned when and where), and participants were recruited when they visited the clinic.
Execution of the Intervention (and Comparison)	Participants were provided trial medication (as 5mg prednisolone or placebo tablets) by post. They were instructed to start treatment as per the number of tablets prescribed, for a total of 6 days. The dosage was calculated as follows. Those not already taking prednisolone received 15 mg/m^2 (upper limit 40 mg) per day; those already taking prednisolone received their alternate day dosage, or 15 mg/m^2 (upper limit 40 mg) per day, whichever was greater. Those in the Comparison group received placebo tablets in an identical fashion. Participants were instructed to identify an upper respiratory infection on the basis of presence for >24 hours of ≥2 among: sore throat, ear ache, ear discharge, runny nose, cough, hoarseness, or fever (tympanic temperature >37 deg C). Those with URI were instructed to start the trial medication.Participants were taught to identify a relapse defined as ≥3+ proteinuria on dipstick on 3 consecutive mornings, or the combination of generalized edema with proteinuria ≥3+ on dipstick. The relapse was deemed to be caused by the URI, if it occurred within 14 days of the URI episode. Relapses were treated with the usual (standard-of-care) treatment for relapses, with cessation of the trial medication if required. Current therapy was escalated in those who experienced >2 relapses within 6 months, or unacceptable side effects of steroids; these participants received a new immune-modulator agent. Therapy was reduced by omitting any ongoing immune-modulator medication in those who experienced remission for 6 months, or unacceptable adverse effects of current therapy.
Outcomes	The primary outcome was the proportion of participants with a URI-related relapse. Other outcomes were the overall rate of relapses, need for escalation of current therapy, reduction in current therapy, cumulative prednisolone dosage during 12 months, serious adverse events, adverse events, adherence to trial medication, behaviour and quality of life indices, and cost.
Follow-up protocol	Participants made 3-montly clinic visits. At each visit, they underwent clinical examination, and outcomes were recorded.
Sample size	The researchers assumed that URI was associated with a 50% relapse rate in children with relapsing steroid sensitive nephrotic syndrome. In order to detect a 35% relative reduction to 32.5%, 250 participants were required allowing for 80% power, and 5% Type I error. They planned to enroll at least 300 participants, making allowance for 15% drop-out. The sample size had to be increased to 360 during the trial because several enrolled participants did not qualify to receive the intervention (or placebo) throughout their participation in the trial.
Data analysis	Intention-to-treat analysis was planned, however rather than including all those who were randomized, data were analysed only in those who qualified to receive the trial medication. Thus, children who did not experience a URI episode during the 12 months following enrolment (hence were ineligible to receive trial medication) were excluded. Appropriate statistical methods were used to analyze the data.
Comparison of groups at baseline	Mean age, gender distribution, multiple anthropometric parameters, age at diagnosis, and duration from previous relapses to randomization, and mean dose of current prednisolone therapy, were comparable between the groups. The groups also had similar proportions of children taking no treatment, long-term prednisolone, combination of prednisolone with immune-modulator, and only immunomodulator. Ethnic background of participants was also comparable.
Summary of results	Intervention vs Comparison *Primary outcome*: • Proportion with URI related relapse: 56/134 vs 58/137

Contd...

from pre-page

Secondary outcomes:

- Number of single, double, triple and quadruple 'URI related relapses': 36 vs 41, 15 vs 10, 4 vs 7, and 1 vs 0, respectively.
- Proportion with any relapse: 91/134 vs 98/137
- Number of 1, 2, 3, 4, 5 and ≥6 relapses: 28 vs 39, 24 vs 24, 2 vs 11, 11 vs 14, 6 vs 5, and 0 vs 5, respectively.
- Proportion with escalation of current immunomodulator therapy: 72/130 vs 71/128
- Proportion with reduction in current immunomodulator therapy: 55/128 vs 62/129
- Median (IQR) cumulative prednisolone dosage in mg: 2060 (1128, 3355) vs 1880 (1115, 3295)
- Serious adverse events: No difference reported (data in a Supplementary file)
- Adverse events: No difference reported (data in a Supplementary file)
- Adherence to trial medication:
  - Timely initiation of trial medication during URI episodes: 328/384 vs 363/407
  - Median (IQR) time to starting trial medication: 0 (0,1) vs 0 (0,1)
  - Rate of adherence (at 3 monthly intervals): Reported as similar, but data not shown.
- Behavior score: No difference reported (data in a Supplementary file)
- Quality of life score: No difference reported (data in a Supplementary file)
- Cost: GBP 252 vs GBP 254 (reported in another publication) [2]

None of the differences was statistically significant.

Table II. Other than lack of clarity about blinding of outcome assessors, there were no other major concerns.

Although, there are no major lacunae in the RCT, some aspects merit consideration. The investigators chose trial medication dosages based on body surface area, but did not report the surface area of the participants at baseline or at any of the follow-up visits. The basis for choosing a prednisolone dose of 15 mg/m^2 for six days, was not explained.

It is unclear why the investigators defined a 'URI related relapse' as occurring within 14 days of a URI episode. On the one hand, this wide interval is beneficial, as it would presumably not miss any URI-related relapse. On the other hand, most URI episodes resolve within the first week of onset, suggesting that some of the relapses counted as URI-related relapses, may not have been so. It can also be argued that the duration of trial therapy i.e., six days may have been chosen to coincide with the usual upper limit of a URI episode. Therefore, it may be worth re-examining the data to check whether there was any difference in the proportion of children experiencing relapse within the first week of a URI episode.

In this RCT, 30% of participants in the intervention group, and 25% in the comparison group, were receiving long-term maintenance prednisolone at the time of enrolment. Considering the anthropometric parameters reported, this would translate to fairly robust dose of steroids. Since the maintenance doses were not ceased during the trial, it is somewhat surprising that the cumulative median dosage of prednisolone over the entire 12-month trial period was just around 2g in both the groups. In fact, a table in the publication reported that the mean pre-trial prednisolone dose was only 0.3 mg/kg on alternate days, which was lower than in other trials. One wonders if this could be a reason that 55% children in either group in this trial required escalation of therapy.

The investigators reported that the trial concluded on 31 January, 2020. Presumably, this means that the last follow-up visit of all children was concluded before that date. If yes, then there would be no COVID-19 related URI in the study population. However, if recruitment ended in January, 2020 with a further 12-month follow-up, then COVID-associated URI could be a cause for some relapses, in which case the short course of low dose prednisolone may make no difference.

The investigators' assumption that 50% URI episodes lead to relapses did not hold, as only about 20% of these episodes led to relapse in the non-intervention arm. Some experts may contend that a much larger sample size would be required to detect clinically meaningful differences with this relatively infrequent background event rate.

In the study population, more than 50% participants were overweight or obese. The situation may be quite different in other population settings, which should be kept

Table II Critical Appraisal of the Study

Criteria	*Response*	*Comments*
Domain 1: Risk of bias arising from the randomization process		
Was the allocation sequence random?	Yes	An internet-based randomization program was used to generate the allocation sequence, although no details were specified. Randomization was stratified on the basis of current treatment.
Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	The allocation sequence was not available to investigators enrolling trial participants. At the time of enrolment, allocation was done wither using the internet program, or by a phone call to the coordinating centre.
Did baseline differences between intervention groups suggest a problem with the randomization process?	No	As shown in Table 1, the groups were comparable. However, body surface area of participants was not reported.
Domain 2: Risk of bias due to deviations from the intended interventions.		
Were participants aware of their assigned intervention during the trial?	Unclear	It was reported that families of participating children, as well as the investigators were blinded to the allocation. However, it is unclear whether they were (or remained) blinded to the intervention after allocation.
Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Unclear	This was not reported in the trial.
Were there deviations from the intended intervention that arose because of the trial context?	No	
Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	The investigators used a modified intention to treat analysis (as described in Table 1).
Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were rendomized.	No	There were no protocol deviations reported i.e., participants received the medications as per the allocation sequence.
Domain 3: Risk of bias due to missing outcome data		
Were data for the outcomes available for all, or nearly all, participants randomized?	Yes	All randomized participants who qualified to receive the trial intervention (or comparison) were included in the analysis (of all outcomes), whereas those who remained in the trial without receiving the intervention (or comparison) were not included in the analysis. There was a very low drop-out rate.
Is there evidence that the result was not biased by missing outcome data?	No	Although there was low attrition, no additional analyses were performed to ensure that the overall result was not biased by missing data.
Could missingness in the outcome depend on its true value?	No	The attrition rate appears to be too low to influence the overall result.
Is it likely that missingness in the outcome depended on its true value?	No	
Domain 4: Risk of bias in measurement of the outcome		
Was the method of measuring the outcome inappropriate?	No	However, all the outcomes were patient/family reported outcomes. Although the determination of these outcomes is not complex, a moderate level of education/ empowerment may be necessary for reliable ascertainment and reporting.
Could measurement or ascertainment of the outcome have differed between intervention groups?	Unclear	The baseline literacy level of parents/children was not described.
Were outcome assessors aware of the intervention received by study participants?	Unclear	This was not specifically reported.
Could assessment of the outcome have been influenced by	Yes	Although fairly objective criteria were used to define

Contd...

from pre-page

knowledge of intervention received?		concepts like URI, relapse, and URI related relapse, these could have been influenced by knowledge of the allocation.
Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Unclear	No data were provided to interpret whether participants could guess their allocation.
Domain 5: Risk of bias in selection of the reported result		
Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	There were no apparent deviations in the analysis plan from that reported in the Trial registration.
Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements	No	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No	

in mind, if trial results are extrapolated to other settings.

Conclusion: This well-designed RCT did not demonstrate any benefit of administering a short course of prednisolone (6 days at 15 mg/m^2) at the onset of URI episodes, in children with frequently relapsing steroid sensitive nephrotic syndrome.

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

JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

REFERENCES

1. Christian MT, Webb NJA, Mehta S, et al. Evaluation of daily low-dose prednisolone during upper respiratory tract infection to prevent relapse in children with relapsing steroid-sensitive nephrotic syndrome: The PREDNOS 2 randomized clinical trial. JAMA Pediatr. 2022; 176:236-43.
2. Christian MT, Webb NJ, Woolley RL, et al. Daily low-dose prednisolone to prevent relapse of steroid-sensitive nephrotic syndrome in children with an upper respiratory tract infection: PREDNOS2 RCT. Health Technol Assess. 2022; 26:1-94.
3. Higgins JPT, Savoviæ J, Page MJ, Sterne JAC. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Accessed March 13, 2022. Available: *https://drive.google.com/file/d/1Q4Fk3HCuBRwIDWTGZa5oH11OdR4Gbhdo/view*

Contemporary Researcher's Viewpoint

Idiopathic nephrotic syndrome, characterized by heavy proteinuria, hypoalbuminemia and edema, is the most common chronic kidney disease of childhood [1]. Steroid sensitive nephrotic syndrome, constituting the majority of cases, is a self-limiting disease with favorable long-term outcomes. However, the occurrence of frequent relapses is associated with significant morbidities due to the illness and the toxicity of medications. Even short-term use of high dose corticosteroids has significant implications: every 1 mg/kg increment in dose increases the risk of adverse events 2.5-fold, comprising of 1.4- to 3.6-fold risk of hypertension, obesity, diabetes and fractures [2]. Therefore, preventing frequent relapses is a major goal when managing nephrotic syndrome [1]. Therapy with prednisolone in low doses on alternate days (AD) is usually the first strategy; however, breakthrough relapses are common, and corticosteroid adverse effects may necessitate use of steroid-sparing agents [3].

Almost one-half of disease relapses are precipitated by minor infections, usually of the upper respiratory tract (URTI). Encouraging findings from a prospective study [1] were confirmed by two randomized controlled trials (RCTs) from South Asia that found that giving the AD dose of prednisolone daily for 5-7 days, beginning with the onset of infection, reduces the risk of relapses in patients with frequently relapsing nephrotic syndrome managed on AD prednisolone. The placebo-controlled cross-over trial from Sri Lanka on 48 patients [4], and the open-label RCT from India on 100 patients [5], formed the basis for the Kidney Disease Improving Global Outcomes (KDIGO) 2012 [6] and Indian Society of Pediatric Nephrology 2021 [1] recommendations that, in patients receiving long term alternate-day prednisolone, the same dose should be administered daily for 5-7 days during fever or respiratory tract infections. Based on additional evidence from another placebo-controlled cross-over RCT from Sri Lanka on 48 patients not on corticosteroids at the time of a similar intervention [7], the KDIGO 2021 extended the recommendation to use prednisone at 0.5 mg/kg daily for 5-7 days during episodes of URTI and other infections to reduce the risk of relapse in all patients, whether on or off corticosteroids [8].

Results from the recent PREDNOS 2 have cast doubt over the utility of this strategy in preventing infection-associated relapses of nephrotic syndrome. This multi-

center, prospective, double-blind, placebo-controlled RCT randomized 365 patients with relapsing nephrotic syndrome (≥2 relapses/year) during 2013-2020 at 122 centers across the United Kingdom to receive either prednisolone or matching placebo at 15 mg/m^2 daily for 6 days, beginning at the start of an URTI. Baseline characteristics and outcomes are presented only for the 271 patients who reported experiencing an URTI during the 1-yr follow-up. Almost half of these patients were on non-steroidal immunosuppression, and 23% were off immuno-suppressive medications; one-fifth of patients reported South Asian ancestry. Similar proportions of patients in the prednisolone and placebo groups experienced an infection-associated relapse (42.7% vs 44.3%) or any relapse (68.9% vs 74.2%). Post hoc analysis ruled out any influence of ethnicity or concomitant immunosuppression on the direction and size of intergroup differences. Strengths of the PREDNOS 2 include its large size, placebo-controlled design, inclusion of diverse ethnic groups, and generalizability to all patients with steroid-sensitive nephrotic syndrome.

The reasons for differences in results between this and the prior RCTs are unclear, and may reflect variations in patient characteristics and study methodologies. The prior RCTs have been criticized for being single-center small studies that were at high risk of bias due to either cross-over or open-label design. The inclusion of participants on levamisole in the Indian study might have introduced heterogeneity and/or attenuated efficacy estimates [5]. However, relapse is an objective outcome that is unlikely to be influenced by biased assessment, and the finding of statistically significant differences despite the small study sizes, supports the use of the intervention. PREDNOS 2 included patients with infrequent relapses as well as patients with frequent relapses managed on other immunosuppressive agents [9]. While this strategy improved its generalizability, it may have attenuated the impact of the intervention since both category of patients may be inherently less prone to develop relapses following infections. Other concerns, stemming from pragmatic choices made when planning study methods, include a high (34.7%) proportion of post-randomization exclusions, and dependence on patient reporting for both the intervention and assessment of outcome.

Infection-associated relapses are as relevant in developed as developing countries, as was illustrated by the reduced incidence of relapses during lockdowns imposed during the SARS-CoV-2 pandemic [10]. Differences in climate, hygiene and ethnicity are unlikely to influence corticosteroid efficacy in suppressing relapses following infections. While awaiting consensus, it appears prudent to continue to recommend the use of daily prednisolone during episodes of URTI in patients with frequently relapsing or steroid-dependent nephrotic syndrome who are using altenate day prednisolone as maintenance therapy. Prednisolone use should not be advocated during infections in patients not on mainte-nance therapy with altenate day prednisolone, nor in those receiving other immuno-suppressive agents. Future trials should either focus on, or examine in adequately-sized subgroups, participants with frequent or infrequent relapses, and those receiving altenate day prednisolone, other agents and no therapy.

Funding: None; *Competing interests*: None stated

ARVIND BAGGA, ADITI SINHA
Department of Pediatrics,
AIIMS, New Delhi, India.
aditisinhaaiims@gmail.com

REFERENCES

1. Sinha A, Bagga A, Banerjee S, et al. Expert Group of Indian Society of Pediatric Nephrology. Steroid Sensitive Nephrotic Syndrome: Revised Guidelines. Indian Pediatr. 2021; 58: 461-81.
2. Oh GJ, Waldo A, Paez-Cruz F, et al. Steroid-associated side effects in patients with primary proteinuric kidney disease. Kidney Int Rep. 2019; 4: 1608-16.
3. Mattoo TK, Mahmoud MA. Increased maintenance cortico-steroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. Nephron. 2000; 85: 343-45.
4. Abeyagunawardena AS, Trompeter RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial. Arch Dis Child. 2008; 93:226-28.
5. Gulati A, Sinha A, Sreenivas V, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011; 6: 63-69.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012; 2:139-274
7. Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, et al. Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. Pediatr Nephrol. 2017; 32: 1377-82.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021; 100 (4S): S1–S276.
9. Christian MT, Webb NJA, Mehta S, et al. Evaluation of daily low-dose prednisolone during upper respiratory tract infection to prevent relapse in children with relapsing steroid-sensitive nephrotic syndrome: The PREDNOS 2 randomized clinical trial. JAMA Pediatr. 2022; 176: 236-43.
10. Crane C, Bakhoum C, Ingulli E. Rates of idiopathic childhood nephrotic syndrome relapse are lower during the COVID-19 pandemic. Pediatr Nephrol. February: 24, 2022. *P*.1-7.

Pediatric Nephrologist's Viewpoint

Globally nephrotic syndrome remains the most common glomerular disease encountered by pediatricians with higher incidence reported among South Asians [1]. Corticosteroids remain the first line therapy but although over 80% are

steroid sensitive (SSNS), 50% -70% of SSNS may evolve into frequent relapsers (FRNS) or steroid dependent (SDNS) requiring multiple courses of steroids and predisposing them to short- and long-term complications of steroid therapy [2]. Trial of long-term alternate day steroid (LTAD) at low dose has been advocated to avoid steroid toxicity while keeping these children in remission. If this strategy fails then the child is usually tried on various steroids sparing agent which includes levamisole, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors and rituximab [3, 4]. Despite use of these strategies, breakthrough relapses are common and studies have shown that nearly 50% of relapses are triggered by viral upper respiratory infections (URTI) and vis-à-vis over half of URTI may precipitate a relapse [4-8]. Although the mechanism by which infections result in relapses is not clear, it is postulated that viral URTI results in T lymphocyte up-regulation which results in cytokine release which plays a key role in inducing relapse [9, 10]. Few studies have also shown that LTAD steroid increases the risk of adreno-cortical suppression and children with suppressed adreno-cortical axis are at increased risk for relapse [11]. Hence increasing the dose of steroid at onset of viral URTI seems rational as this may attenuate the up regulation of T cells and prevent infection associated relapses [12]. Previous studies [13-16] primarily from Asian continent have consistently supported this hypothesis (**Web Table I**) and this strategy has also been endorsed by recent guideline updates [3,4]. Kidney Disease Improving Global Outcome (KDIGO) glomerular disease guideline 2021 recommends single dose daily glucocorticoids at 0.5 mg/kg/day for episodes of upper respiratory tract and other infections for 5-7 days [4] whereas Indian Society of Pediatric Nephrology (ISPN) guideline recommends switch to daily steroid for a similar duration if on alternate day steroid regime at onset of infection [3]. Despite this, one needs to remember that most of the previous studies on which these endorsements are based had various methodological flaws including lack of blinding, small sample size, post-randomization exclusions and crossover design as highlighted by the Cochrane report [17]. Additionally, these studies did not explore the usefulness of increasing steroid dose for URTI among those on other steroid sparing agents' particularly potent agents such as mycophenolate mofetil or calcineurin inhibitors. Lastly, these studies were done among Asians, making their extrapolation to multi-ethnic populations tricky. With this perspective, the pediatric nephrology community was eagerly awaiting the outcome of the PREDNOS 2 trial wherein they re-examined whether increasing steroids during viral URTI decreases relapse rates in a multi-ethnic population [18].

PREDNOS 2 had multiple strengths. It was a well conducted study with robust trial design and their cohort strength far exceeded the combined number of children recruited in the four previous studies (**Web Table I**). This large cohort size is likely to have significant influence in any future meta-analysis. Additionally, unlike previous studies, the cohort was multi-ethnic, included children on all type of background treatment and systematically recorded corticosteroid adverse events including effects on behavior. Evidence based medicine has always been a rapidly changing paradigm and newer evidence through well conducted studies with robust methodology negating previously accepted notions is not uncommon. A recent example in pediatric nephrology being the various RCTs over the last decade questioning the utility of prolonged tapering of steroids after first episode nephrotic syndrome in reducing subsequent relapse rates [19].

Keeping these in perspective, should we in India change our practice of switching to daily steroid at onset of viral URTI among FRNS/SDNS which has been advocated even in the recent ISPN guideline [3]. While acknowledging the robust clinical design of PREDNOS 2 and its large cohort size, it might be still too hasty for us to change our Indian guidelines. Even in PREDNOS 2, lower rate of URR was noted among South Asian population; and although this was not statistically significant, South Asians only comprised a fifth of the total cohort and the trial was not powered enough to show significant difference among various ethnic sub groups. Moreover, the PREDNOS 2 trial was done in UK, which has a temperate climate which is quite different to the mostly tropical climate of Indian subcontinent and might explain their significantly lower URTI episodes than those reported from the Indian sub-continent. Etiology of the underlying viral URTI was also not explored and one can argue this to be a confounding factor as the etiologies might differ between Asia and UK. Lastly, although URR are common, some children do relapse without any evidence of URTIs [5,7]. PREDNOS 2 did not attempt to differentiate between these two groups at onset and it may be argued that steroids might be more useful among those children who have frequent URR than those who usually relapse without any URTIs. Hence, a repeat of PREDNOS 2 among a South Asian population with a high incidence of URTI and URR in a tropical country might give different results. We always have a tendency to generalize our findings but unfortunately one size fits all formula hardly works in medical science and personalized medicine is increasingly been recognized as the optimum goal [20].

In conclusion, a pragmatic approach might be to identify the sub group of children who have high URR and implement the strategy of increasing steroids during URTI attacks among them. As the PREDNOS 2 trial did not show any difference in side effects between the steroid and the placebo group, it might be justified to continue the current

recommendation of increasing steroid during URTI in our sub-continent till availability of robust trials focusing on the sub population likely to show more benefit from such strategy.

Funding: None; *Competing interests*: None stated

RAJIV SINHA
Department of Pediatric Nephrology, Institute of Child Health, Kolkata, India.
rajivsinha_in@yahoo.com

REFERENCES

1. Chanchlani R, Parekh RS. Ethnic differences in childhood nephrotic syndrome. Front Pediatr. 2016; 4:39.
2. Hodson EM, Craig JC, Willis NS. Evidence-based manage-ment of steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2005; 20:1523-30.
3. Sinha A, Bagga A, Banerjee S, et al; Expert Group of Indian Society of Pediatric Nephrology. Steroid Sensitive Nephrotic Syndrome: Revised Guidelines. Indian Pediatr. 2021; 58:461-81.
4. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int. 2021; 100:753-79.
5. Alwadhi RK, Mathew JL, Rath B. Clinical profile of children with nephrotic syndrome not on glucorticoid therapy, but presenting with infection. J Paediatr Child Health. 2004; 40:28-32.
6. Arun S, Bhatnagar S, Menon S, et al. Efficacy of zinc supplements in reducing relapses in steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2009; 24:1583-86.
7. MacDonald NE, Wolfish N, McLaine P, Phipps P, Rossier E. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. J Pediatr. 1986;108(3):378-82.
8. Moorani KN, Khan KMA, Ramzan A. Infections in children with nephrotic syndrome. J Coll Physicians Surg Pak. 2003; 13:337-39.
9. Yap HK, Cheung W, Murugasu B, et al. Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. J Am Soc Nephrol. 1999; 10:529-37.
10. Bruneau S, Dantal J. New insights into the pathophysiology of idiopathic nephrotic syndrome. Clin Immunol. 2009;133: 13–21.
11. Leisti S, Hallman N, Koskimies O, et al. Association of postmedication hypocortisolism with early first relapse of idiopathic nephrotic syndrome. Lancet. 1977; 2:795-96.
12. Leisti S, Koskimies O, Perheentupa J, et al. Idiopathic nephrotic syndrome: prevention of early relapse. Br Med J. 1978;1(6117):892.
13. Mattoo TK, Mahmoud MA. Increased maintenance cortico-steroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. Nephron. 2000; 85:343-45.
14. Abeyagunawardena AS, Trompeter RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomized controlled trial. Arch Dis Child. 2008; 93:226-28.
15. Gulati A, Sinha A, Sreenivas V, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011; 6:63-69.
16. Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, et al. Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. Pediatr Nephrol. 2017;32(8): 1377-82.
17. Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2015 Mar 18;2015(3):CD001533.
18. Christian MT, Webb NJA, Mehta S, et al. Evaluation of daily low-dose prednisolone during upper respiratory tract infection to prevent relapse in children with relapsing steroid-sensitive nephrotic syndrome: The PREDNOS 2 randomized clinical trial. JAMA Pediatr. 2021: e215189.
19. Sinha A, Bagga A, Iyengar A, Mathew JL. Is two-month initial prednisolone treatment for nephrotic syndrome inferior to longer duration therapy? Indian Pediatr. 2014; 51:811-17.
20. Mayer G. Precision medicine in nephrology. Nephrol Dial Transplant. 2021;36(S 2):1-2.

Pediatrician's Perspective

The PREDNOS 2 study is a double-blind placebo control study to evaluate the usefulness of short course of steroids during upper respiratory infections to prevent relapse in children with SSNS. The study concluded that there was no difference in the relapse rates in both groups.

In my opinion, giving intermittent short course of steroids during episodes of upper respiratory infections will lead to overuse of steroids as these infections are common and are bound to occur frequently in children attending daycare and schools. There should also be clear criteria to define upper respiratory infection as allergic rhinitis can be confused as upper respiratory infection and will again lead to overuse of steroids.

Relapses during upper respiratory infections does not usually occur and aiming at reducing the risk of relapse by giving short course of steroids for 5-6 days is not really necessary nor is it helpful. When we weigh the risk vs benefits, the risks of overuse of steroids and the danger of self-medication by parents are more than the benefits.

Funding: None; *Competing interests*: None stated

JANANI SANKAR
Department of Pediatric Medicine and Infectious Disease, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India.
janani.sankar@yahoo.com

Web Table I Summary of the Studies

Study, year, sample size[a]	*Type of study*	*Study population*	*Intervention arm*	*Control arm*	*Outcome*
Pre PREDNOS 2					
Mattoo et al., 2000, *n*=36 (not reported)	Single center study with a follow up of 2 years wherein study population was divided in two arms alternately	Those on low dose (0.5 mg/kg) a/d maintenance prednisolone. 14 had received cyclophosphamide. Included cohorts were not on any other immunosuppressant.	Group 1: At onset of viral URTI a/d prednisolone dose was switched to daily dose for 5 d.	Group2: Advised to continue on a/d steroid as before despite viral URTI	Total number of relapses over the 2-year period in group 1 was 40 with a mean of 2.2 (0.87) per patient, and in group 2 it was 99 with mean of 5.5 (1.33) per patient (*P*=0.04)
Abeyagunawardena, et al., 2008, *n*=48 (40)	Single center randomized double-blind placebo controlled cross over trial. At onset of URTI patientwas randomly allocated to either place-bo arm or pred arm for the first viral URTI and the other arm for the second viral URTI.	Those on low dose (0.1-0.6mg/kg) a/d maintenance pred. Included cohorts were not on any other immunosuppressant.	The first viral infection was treated with placebo in 22 children and with pred in 18, and a relapse of NS was seen in 10 and four children, respectively. As this was a crossover trial, the second viral infection was treated with placebo in 18 children and with prednisolone in 22. A relapse was noted in nine and three children respectively.		48% relapses were noted when URTI was treated with placebo and 18% relapses were noted when episodes treated with extra dose of steroid (*P*=0.014).
Gulati, et al., 2011, *n*=100 (89)	Single center open label parallel group randomized control trial.	Those on low dose (0.5 to 0.75 mg/kg) a/d maintenance prednisolone with vermisole (*n*=32) or without levamisole (*n*=68). Those with steroid threshold >1mg/kg were excluded. Included cohorts were not on any other immunosuppressant.	At onset of viral URTI a/d pred dose was switched to daily for 7 d.	Advised to continue on a/d steroid as before despite viral URTI	Lower IAR in the intervention arm (rate difference, 0.7 episodes / patient per year; 95% CI 0.3, 1.1). 59% reduction in frequency of relapses seen in intervention arm (rate ratio, 0.41; 95% CI 0.3, 0.6). Reduction in IAR was not significant among those on levamisole along with low dose a/d steroid.
Abeyagunawardena, et al., 2017, *n*=48 (33)	Single center randomized double blind placebo controlled cross over trial. If the criteria for viral URTI were met, the patient was randomly allocated to either placebo arm or pred arm for the first year. The allocation was switched for the next year.	Previous SDNS but currently off any immunosuppressant for ≥3 mo.	In group 1, the 19 patients who completed the study received pred for the first year of observation and placebo for the secondyear. In group 2, the 14 patients who completed the study received placebo for the first year and pred for the second year. The study was completed in 2 years.		Within the intervention group, 65.6% did not relapse in contrast, to 40.6% in the control group (*P*=0.014).

[a]*Final number assessed given in parentheses.*

Systematic Reviews and Meta-Analysis: A Guide for Beginners

JOSEPH L MATHEW
From Department of Pediatrics, Advanced Pediatrics Centre, PGIMER, Chandigarh.
Correspondence to: Prof Joseph L Mathew, Department of Pediatrics, Advanced Pediatrics Centre, PGIMER Chandigarh.
joseph.l.mathew@gmail.com

Systematic reviews involve the application of scientific methods to reduce bias in review of literature. The key components of a systematic review are a well-defined research question, comprehensive literature search to identify all studies that potentially address the question, systematic assembly of the studies that answer the question, critical appraisal of the methodological quality of the included studies, data extraction and analysis (with and without statistics), and considerations towards applicability of the evidence generated in a systematic review. These key features can be remembered as six 'A'; Ask, Access, Assimilate, Appraise, Analyze and Apply. Meta-analysis is a statistical tool that provides pooled estimates of effect from the data extracted from individual studies in the systematic review. The graphical output of meta-analysis is a forest plot which provides information on individual studies and the pooled effect. Systematic reviews of literature can be undertaken for all types of questions, and all types of study designs. This article highlights the key features of systematic reviews, and is designed to help readers understand and interpret them. It can also help to serve as a beginner's guide for both users and producers of systematic reviews and to appreciate some of the methodological issues.

Keywords: *Forest plot, Pooled estimates, Risk of bias, Secondary research.*

Published online: June 28, 2021; ***PII:*** S097475591600350

Evidence-based (or evidence-informed) health-care requires the integration of high-quality research evidence, clinical expertise and patient (con- sumer) values [1]. However, the immense volume of primary research and its diversity in terms of methodology, necessitate that it be reviewed and synthesized to make rational interpretations and decisions. This necessity has led to an entire field of secondary research to synthesize data from primary research. Systematic reviews are the key pillar of such secondary research. The broad principle of systematic reviews is to apply "scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant research studies on a specific topic" [2]. Thus, in contrast to traditional narrative reviews, there is a rigorous attempt to limit bias in the process of selecting, reviewing and synthesizing primary research studies in systematic reviews. These efforts at minimizing bias have led systematic reviews to be regarded superior to primary research study designs, thereby finding a place at the top of the hierarchy of research evidence. In terms of research methodology, bias can be described as systematic error that leads away from the truth [3]. This is largely avoidable, in contrast to random error which occurs by chance [3], and hence, is unpredictable. The ultimate goal of systematic reviews is to facilitate healthcare decisions that are objective, reproducible and transparent.

Meta-analysis is a statistical tool that is used to mathematically pool data derived from a systematic review, and generate a summary conclusion [4]. Meta-analysis of data is inappro-priate if not derived from a systematic review. It would be akin to applying statistical tests on data which are not derived from primary research studies.

This article highlights the key features and methodological issues of systematic reviews and is designed to help readers understand and interpret them. This article is not intended to be a comprehensive handbook to inter-pret or conduct systematic reviews but can serve as a beginner's guide for both users and producers of systematic reviews.

Systematic reviews are initiated after preparing, registering, and publishing a review protocol. The process is similar to preparing protocols for primary research studies. Registration of systematic review protocols is broadly similar to registration of clinical trial protocols; however, different platforms are used. One such platform is PROSPERO, which serves as a database for registering protocols of systematic reviews [5]. This promotes transparency in the review process.

High quality reviews such as Cochrane reviews, publish systematic review protocols after stringent peer review. Some journals also publish systematic review protocols, whereas others expect them to be available online for access by anyone. Currently, it is difficult to publish a good quality systematic review without prior registration and publication (or disclosure) of the protocol. This is to ensure that appropriate methodology is used, detailed methods are

disclosed beforehand (a priori), and no modifications are made after data become available (post hoc). This makes the review process and the product, systematic, objective, reproducible, and trans-parent (summarized by the acronym SORT).

MAKING SENSE OF A SYSTEMATIC REVIEW

Healthcare professionals reading, appraising or conduc-ting a systematic review should focus on six key aspects (**Table I**).

Ask (Research Question)

The science of evidence-based medicine hinges on the art of framing and addressing research questions [6]. This is the most important step in any research study, including systematic review. The 'PICO format' [7] of research questions is better expanded to 'PICOTS' as follows.

- *P* (*Population and/or Patient and/or Problem*): It refers to the people in/for whom the systematic review is expected to be applied.
- *I* (*Intervention*): In the context of systematic reviews examining effects of treatment, 'I' encompasses medicines, procedures, health education, public health measures, or bundles/combinations of these. 'I' also includes preventive measures such as vaccination, prophylaxis, health education tools, and packages of such interventions. In some contexts, the intervention is not administered by the study investigators, but by nature, and the investigators are merely observing the effects. Therefore, 'I' can be better expressed as 'Exposure' abbreviated as 'E'. This is also true for systematic review of diagnostic test studies (wherein participants are 'exposed to' diagnostic tests), prognostic markers (wherein participants are exposed to one or more factors), and prevalence of certain conditions (wherein participants are naturally exposed to the condition).
- *C* (*Comparison*): People not receiving the intervention could receive an alternate intervention, or placebo, or nothing (depending on the research question). However, for some study designs and/or research questions, it may not be feasible to include a Comparison.
- *O* (*Outcome*): This refers to the broad parameters by which the effect of 'I' on 'P' in comparison to 'C' can be measured. In general, systematic reviews of interventions focus on efficacy, safety, and sometimes cost. Systematic reviews of diagnostic tests focus on measures of accuracy, reliability, and cost. Multiple specific outcome measures can be analyzed for each outcome being evaluated.
- *T* (*Time-frame*): Outcomes are meaningful only when the time-frame in which they are recorded are specified. For example, 'mortality' as an outcome can be recorded in various time-frames. Different outcomes in a systematic review may have different time-frames which should be

Table I Key Aspects of Systematic Reviews

Key principle	*Interpretation*	*Remarks*
Ask	What is the specific research question 'asked' or addressed in the systematic review?	The entire methodology of a systematic review interpretation of findings, and conclusions, depend on this.
Access	What literature sources were accessed (or searched) to identify the primary search studies to be included in the systematic review? What was the 'search strategy'?	The focus is to ensure that no study that can potentially answer the research question, gets missed.
Assimilate	What strategies were used to assimilate or synthesize or 'put together' the primary research studies?	In order to minimize bias, most systematic review prudently limit the included studies to those conforming to the best, or sometimes most appropriate study designs that can answer the research question.
Appraise	How were the included studies critically appraised for methodological quality?	This is to estimate the risk of bias in the primary studies, and the potential impact on the systematic review results and conclusions.
Analyze	What data was extracted from each primary study for synthesis? How were the data analyzed? What are the main findings? What is the level of confidence in these findings, based on the methodological aspects of the included studies?	The data extracted from the primary studies could be examined with a combination of qualitative and quantitative methods. Meta-analysis helps to obtain a pooled estimate of the included data.
Apply	Can the findings of the systematic review be applied in the patient or population of your interest?	Conclusions of a systematic review have to be integrated with clinical expertise and patient preferences/values for a truly evidence-informed healthcare decision.

specified clearly.

- *S* (*Study design*): Multiple study designs may be used in primary studies to address the same research question. However, study designs have inherent risks of bias (by virtue of the design itself) which results in a hierarchy of pri mary research study designs. Rando-mized controlled trials (RCT) are associated with the least risk of bias for evaluating interventions. Bias increases in non-randomized trials, other clinical trials, cohort studies (with and without comparison groups), case-control studies, case series, and case reports (in that order). Since the focus of systematic reviews is to review literature minimizing bias as far as possible, some systematic reviews include only methodologi-cally high-quality study designs (such as RCT), whereas others may include various study designs and examine the impact of lower-quality designs separately.

There are other formats (besides PICOTS) for framing and/or presenting research questions. The SPICE acronym covers issues such as setting, population, intervention, comparison and evaluation [8]. It is generally considered helpful to develop questions relating to qualitative research, and for evaluating project proposals and quality improvement. Another tool is SPIDER, which helps to structure qualitative research questions. It summarizes sample, phenomenon of interest, design, evaluation and research type [9]. Yet another format is ECLIPSE [10], that is reportedly helpful for questions addressing healthcare policies or services. The acronym covers expectation, client, location, impact, professionals, and service.

However, the PICO format remains the most popular version perhaps because it is the oldest, covers a variety of research questions, is 'portable' across study designs, and can be extended to secondary research, health tech-nology assessment, guidelines, and policy issues.

The research question in a systematic review is usually clearly specified in the introduction section. Often, no research question may be found but enough information may be provided for readers to frame one in the PICOTS format. However, systematic reviews that do not specify a research question, or facilitate the construction of one by readers, are likely to result in biased interpretations and should be read with caution. Research questions that have very narrow or highly focused 'P' run the risk of producing systematic reviews with limited generalizability. On the other hand, very broad questions can generate more noise than signal. The key is to have a research question where-in the elements are balanced to include the population of interest in a non-restrictive manner, yet have a high signal to noise ratio. The PICOTS template is applicable for systematic reviews addressing all types of research questions (**Table II**).

Access (Literature Search)

This step is designed to identify all literature that can potentially answer the research question. It includes several components to facilitate systematic, objective, reproducible, and transparent (SORT) search and inclusion of studies.

Types of studies: Systematic review authors may include only studies conforming to the most appropriate study design, or choose to include various types of study designs. The advantage of the first approach is that studies with higher risk of bias are eliminated upfront; however, the disadvantage is that there may be insufficient studies of high methodological quality, and these may not truly represent the real-world scenario. The second approach may yield more studies (hence larger sample size) but reduce the confidence in the overall result due to inclusion of lower quality primary studies. The way out is for systematic review authors to either include only the highest quality study design, or include multiple designs but perform separate analyses of high quality versus lower quality designs, and explore the difference.

Types of participants: This refers to the participant characteristics in the primary studies, such as age group, socio-demographic characteristics, duration of disease, and severity. Here also, choosing a very narrow set of criteria limits the generalizability of the systematic review; whereas, very broad criteria may end up combining apples and oranges to obtain a pooled result. A useful method is to ensure that the inclusion criteria are broad, but include objective methods of diagnosis and measurement of disease severity. For example, in diagnostic test studies, the participants should include people 'suspected to have the disease' or those 'with potential to have the disease', and not only those confirmed to have the disease.

Types of intervention/exposure: The PICOTS question in the Introduction section identifies the broad contours of the intervention/exposure, whereas the methods section provides greater detail of the intervention such as, dosage, frequency of administration, mode of adminis-tration, dura-tion of administration, and similar issues. When the interven-tion is a procedure, the skill/training of the operator and the healthcare setting may be additional factors. For studies measuring behavior change (in res-ponse to health education, legislation etc.), the 'inter-vention' may consist of a 'bundle' involving many different components, with or without reinforcement.

The intervention is actually an 'exposure' in diagnostic test studies, prognosis studies, and prevalence/incidence studies.

Types of comparison: All the details specified for the intervention should be specified for the comparison also. In

Table II Applicability of PICOTS to Systematic Reviews Addressing Various Types of Research Questions

Research question	*Intervention*	*Diagnosis*	*Prognosis*	*Prevalence/ Incidence*	*Association*
Example	Is plasma exchange therapy beneficial in COVID-19?	Can 'loss of smell' be used to diagnose COVID-19?	Do people with COVID-19 having co-existing diabetes or hypertension, fare worse?	What proportion of patients with COVID-19, have or develop acute respiratory distress syndrome?	Does international travel result in COVID-19?
P = Patient/ Population	People with severe COVID-19	People with suspected COVID-19	People with confirmed COVID-19	People with COVID-19	Indian citizens, residing in the country.
I = Intervention or Exposure	Plasma exchange therapy	Confirmation of 'loss of smell'	(Controlled and uncontrolled) Diabetes, or Hypertension		International travel (within the preceding 21 days)
C = Comparison	No plasma exchange	Reverse transcriptase PCR for novel Coronavirus	None of the above		No international travel (within the preceding 21 days)
O = Outcomes	Mortality, Need for invasive ventilation, Side effects, Cost	Diagnostic accuracy, Cost	Disease severity, Need for intensive care, Mortality	Acute respiratory distress syndrome (ARDS)	Development of COVID-19
T = Time-frame	Within 30 days of treatment (for all outcomes)	Not applicable*	From diagnosis to recovery or discharge or death.	From diagnosis to recovery or discharge or death.	Within 28 days of the date of conclusion of the travel.
S = Study design	RCT	Diagnostic test study	Cohort study with comparison group	Cross-sectional study (for prevalence) Cohort study (for incidence)	Case-control study.

**Diagnostic test studies are cross-sectional in the sense that the index test (confirmation of loss of smell) and reference test (RT-PCR) should ideally be performed at the same time, or if that is not feasible, within a narrow interval, during which there is no probability of a change in the diagnostic status of a given patient (from negative to positive, or vice versa). Similarly, the gap between the index test and diagnostic test should not be such that people who receive one test may get cured, or drop-out, or die before the other test is administered.*

intervention studies, the comparator may be another intervention (such as the current standard of care), placebo (if that is deemed safe and appropriate on ethical grounds), or no intervention (if safe/appropriate). In diagnostic test studies, there is no separate group of individuals for comparison, but the same group of participants receives the index test (exposure) and the reference test (comparison). Some primary research studies may not have comparison group (examples are clinical trials without a comparison group, cohort studies without comparison, and prevalence/ incidence studies). The information derived from such studies is inferior to those with comparison groups.

Types of outcome measures: Just as in primary research studies, systematic reviews generally have one primary outcome and multiple secondary outcomes. Each outcome may have several methods of measurement/recording. Thus the broad term 'efficacy' may include outcomes like clinical cure, resolution, survival/mortality, need for escalation of therapy, duration of hospitalization, or quality of life measurements. Other surrogate outcomes of efficacy could be laboratory parameters, biomarker levels, radiological findings, or results of combinations of investigations. Each of these outcomes could be measured in multiple ways, and may be recorded at multiple time points, and/or using multiple instruments/tools, all of which are generally reported in the systematic review. Similarly, safety outcomes could include development of adverse events, count of serious adverse events, number of patients developing such events, number of events per patient, need for enhanced monitoring, etc. It is impossible to include every possible outcome measure in a systematic review. However, no important outcomes should be missed; patient-centric outcomes should be included; outcomes measured objectively are preferred; hard outcomes are considered superior to soft outcomes, and purely indirect/surrogate outcomes are less preferred. The methods section should include the time-frame of recording each of the included outcomes. Where the outcomes are recorded multiple times, separate analyses would be necessary for each.

Search methods for identification of studies

Where? This section defines the literature databases accessed to identify all the relevant evidence. High quality

systematic reviews search multiple electronic databases such as Medline, Embase, Cochrane Register of Trials, and other repositories. At the very least, two databases should be searched. Depending on the review question, additional literature databases may also be searched. In addition, most reviewers search other sources of literature including reference lists of included studies (this is referred to as hand-searching), clinical trials registries (for registered trials), conference abstract books/proceedings, and databases of non-indexed journals. In the Indian context, many journals are indexed in IndMED [11], although not in Medline. Similarly, Wangfang Data is a source of Chinese literature [12], and LILACS database includes Latin American and Caribbean literature [13]. There are also specific databases for different types of clinical problems and/or healthcare specialists. All these additional searches are focused on published sources of evidence. Some authors go further and search sources of unpublished literature (sometimes referred to as grey literature). These may be available through repositories of such studies (for example OpenGrey database includes over 7 lakh references of grey literature in Europe) [14].

How? Databases of published and unpublished literature have specific approaches to ensure comprehensive searches for all eligible primary studies. Systematic reviews thus undertake multiple searches of each database, with various combinations of keywords, exploiting the inbuilt filters in some of the databases. Although it may be convenient to search only English language publications, high-quality reviews do not restrict by language or any other criteria. This is so that no bias creeps in through selective inclusion (or exclusion) of primary studies. Such rigour increases the cost, duration, and workload of syste-matic review authors, but minimizes a major source of bias.

When? Systematic review authors are expected to declare the date of literature search, period over which each database was searched, and also provide updated searches just before the systematic review is published. All these efforts ensure that the evidence is current and the searches are reproducible.

Who? Literature searching is a key step of systematics reviews, and is generally conducted independently by more than one author. The outputs, eligibility, and selection are compared and is resolved by another independent author where there is mismatch. Although not essential, reference managers such as Endnote, Zotero, or Mendeley can be used to compile the search output, remove duplicate publications and obtain the final list of the preliminary search.

Assimilate (Inclusion and Exclusion of Studies)

Generally, a three-step approach is used to confirm the eligibility of primary studies for inclusion in the SR. This includes a preliminary screening of each study title, followed by screening the abstract of short-listed titles. The third step is to read the full-text of the short-listed abstracts to match against the set of eligibility criteria described above, for deciding on inclusion into the systematic review (or otherwise). Here too, the PICOTS framework is very helpful. Each step is carefully recorded and reasons for exclusion are documented for the studies excluded in the third step. This is done to ensure transparency and objectivity in study selection. It is good practice to ensure that screening of titles, abstracts, and full text for potential inclusion, is done by more than one reviewer, working independently.

It is also helpful to prepare a flow diagram showing the results of the literature searches, exclusion of publications with reasons, and the pathway to final inclusion of eligible studies. This is similar to the flow-diagram of participant recruitment in trials.

Appraise (Critical Appraisal of Included Studies)

All systematic reviews undertake critical appraisal of included studies for methodological quality. This refers to assessment of efforts made by investigators of primary studies to minimize bias during the conduct of their study. Bias or systematic error can creep into primary research studies with inappropriate study designs, and inappropriate study methods. The former includes choosing study designs that inherently have high(er) risk of bias, and insufficient precautions to address the common sources of bias within each study design. For example, in studies examining interventions, RCT is the ideal study design, and within RCT, sources of bias include selection bias, allocation bias, performance bias, and out-come reporting bias. Inappropriate study methods include using inappropriate tools for measuring outcomes, lack of calibration of instruments used to record outcomes, inappropriate recording methods, inappropriate/insufficient follow-up, etc.

Appraisal in systematic reviews is generally restricted to examination of study design issues and efforts to minimize bias due to this. There are standard online tools available for each type of study design. The Cochrane Risk of Bias tool [15] is considered a standard tool for RCT and includes appraising the methods used (and adequacy thereof) for key design elements in intervention trials viz., random sequence generation, concealment of allocation, blinding of study participants, blinding of outcome assessors, incomplete outcome reporting, and selective outcome reporting. There is an additional element for appraising any other bias. Software tools for systematic reviews, such as the Cochrane Review Manager or RevMan [16] have options for the pictorial representation of quality appraisal of included studies.

The Newcastle Ottawa Scale (NOS) is often used to assess the quality of non-randomized studies including case-control, cohort studies, and even qualitative studies [17]. The

NOS contains eight items, categorized into three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest (for case-control or cohort studies, respectively). For each item, a star system is used to allow a semi-quantitative assessment of study quality. High-quality studies are defined by a score 6 or more of 9 total points [18].

Another popular tool for non-RCT studies is the Risk of Bias in Non-Randomized Studies of Interventions tool, abbreviated as ROBINS-I [19]. It includes assessments of bias in pre-intervention (biases due to confounding as well as participant selection), at intervention (bias in classification of interventions), and post-intervention (biases due to deviations from the intended inter-ventions, missing data, measure ment of outcomes, and selective reporting).

The QUADAS-2 tool [20] can be used to evaluate the risk of bias of diagnostic test accuracy studies. It examines the risk of bias in four broad domains viz. patient selection, index test, reference standard, and flow and timing. Among these, the first three are also evaluated in terms of applicability.

There are specific tools for assessing quality of environmental health studies. These include tools developed by the Office of Health Assessment and Translation (OHAT) and Integrated Risk Information System (IRIS) [21]. There are also additional tools specific for animal studies. For example, SYCRLE's tool is an adaptation of the Cochrane Risk of Bias tool, and is used to assess internal validity, addressing selection, perfor-mance, detection, attrition and reporting biases [22].

Analyze (Data Extraction and Analysis)

Systematic reviewers prepare data extraction forms (that are not published, although Cochrane reviews present these details) which include the following information from each included study: *i*) Identification characteristics (authors, source, year); *ii*) Study characteristics (enrol-ment criteria, sample size, PICOTS information), *iii*) Appraisal for bias (using standard tools/checklists), *iv*) Data reflecting the outcomes specified in PICOTS, and *v*) Additional notes, if any.

Data to be analyzed could include descriptive data and quantitative data. Narrative synthesis of the extracted data is helpful to understand the perspectives of the primary studies in terms of the PICO elements. A table highlighting the descriptive characteristics of the included studies is very helpful for readers. Quantitative data are extracted for each outcome measure (specified in the review protocol). Data extraction is also generally done independently by more than one reviewer, with provision to resolve discrepancies. Sometimes, published versions of indivi-dual studies lack pieces of data that are important for the review. In such situations, the systematic review authors correspond with study authors to obtain missing data (and record the process).

In intervention reviews, numerical data of outcome measures (from included studies) usually conform to either dichotomous data (expressed as proportions) or continuous data (expressed as mean with standard deviations, or variations of this). Other forms of presentation include median (with interquartile ranges). In diagnostic test reviews, each included study provides information on the number of true positive, false positive, true negative, and false negative test results.

The extracted data may be considered for pooled analysis if there is sufficient data (although there is no strict definition for this), and the data are in a format conducive for pooling. For example, data from a study presenting an outcome as mean (standard deviation) is not amenable for pooling with data from another study presenting the same outcome as median (IQR), unless mathematical conversion techniques are applied to con-vert medians to means. Likewise, in studies reporting diagnostic tests, if only data on sensitivity and specificity are reported without the numbers from which they are derived, it is difficult to pool them. Such problems can be resolved if systematic review authors have access to the raw data from primary studies, and/or are able to undertake individual patient meta-analysis [23].

Meta-Analysis

The statistical procedure for pooling data from individual studies is called meta-analysis. Meta-analysis presents the estimate of effect from each included study, relative weight of each study in the pool, and the pooled estimate of effect. The relative weight depends on the variance in the result, which is impacted by the sample size and width of the confidence interval of the effect. In general, studies with less variance (i.e., narrower confidence interval of the effect) have greater relative weight, and studies with large sample sizes and narrow interval have the greatest weight. Understanding the concept of study weights is important because the pooled estimate of effect is not a mathematical average of the data from individual studies, but a weighted average.

The graphical output of meta-analysis is referred to as a forest plot. Although they may seem intimidating, a step-wise approach (**Fig. 1**) makes it easier to understand and interpret forest plots. **Fig. 1** presents a meta-analysis (from a fictitious systematic review) of six hypothetical RCTs comparing Option A vs Option B for a clinical condition.

Step 1: *What is the comparison?* This is presented at the top of the forest plot and shows the interventions being compared as well as the outcome.

Step 2: *What outcome measure is being compared?* Each outcome can be represented by several measures. Each outcome measure is analyzed in a separate forest plot.

Step 3: *How is the data presented?* Dichotomous data are compared using odds ratio (OR), risk ratio or relative risk (RR), or risk difference (RD). All are valid measures. OR are mathematically purer, but RR are easier to understand. RD can be used to calculate the number needed to treat (NNT). Continuous data are presented as mean difference (MD), or weighted mean difference (WMD), or standardized mean difference (SMD). All measures are presented with confidence intervals (usually 95%, but modifiable).

Step 4: *Which statistical model is used?* There are two statistical models viz. fixed effect (FE) and random effects (RE). The FE model assumes that there is a single common estimate of effect, and all studies aim to estimate that common effect. In contrast, the RE model assumes that there is no single common effect, but a distribution of true effects, which varies from study to study [24]. This model considers heterogeneity among studies in terms of participants, biological characteristics, disease characteristics, measurement tools, etc. Thus, in the FE model, it is assumed that studies do not estimate the true effect because of random error, whereas in the RE model, both random error and heterogeneity affect the pooled estimate of effect. **Web Fig. 1** presents the differences between FE and RE models of analysis, using the forest plot presented in **Fig. 1**.

Step 5: *Examine individual studies.* The forest plot shows the outcome data for each study, its effect (with confi-dence interval), relative weight in the pooled analysis, and a pictorial presentation of this data (which is usually a square whose position represents the effect, size represents the weight, and a horizontal line through the square represents the confidence interval).

Step 6: *Examine pooled effect*. The pooled effect is presented numerically as well as graphically. It represents a weighted average estimate of effect. The pictorial representation is with a diamond whose center corresponds to the pooled effect, and width represents the confidence interval.

A vertical line in the center of the forest plot represents the line of no effect. In the case of RR and OR, this corresponds to 1.0 and implies that the risk ratio (or odds ratio) is 1.0, confirming the absence of a difference between the groups. For mean differences, the line of no effect corresponds to zero, confirming that there is no difference between the groups. Therefore, it is obvious that confidence intervals whose bounds (limits) are on the same side of the line of no effect, suggest a statistically significant result, whereas confidence intervals crossing the line of no effect represent estimates that could lie on either side. No further tests of statistical significance are required; however, some forest plots present additional tests for this. Similarly, narrower confidence intervals suggest more precise estimates, and vice versa.

Step 7: *Examine and explore heterogeneity*. Hetero-geneity among studies refers to variation in the effect, which could be due to random chance or other factors. Random chance would be the only explanation for differences in estimates of effects if all studies were conducted in exactly the same way. In reality, studies are conducted somewhat differently, hence differences in effect result from random chance plus additional factors. This heterogeneity can be apparent by visual inspection of the pooled data wherein confidence intervals that fail to overlap suggest (but not confirm) the presence (but not the degree) of heterogeneity.

Currently, the Cochran statistic or more recently, the *I* square test (I^2) is used to mathematically calculate the degree of heterogeneity [25]. Currently, I^2 <50% is accepted as low degree of heterogeneity, I^2 between 50-75% as moderate degree, and I^2 >75% as high degree of heterogeneity. A *P* value of <0.10 suggests a statistically significant degree of heterogeneity, which should be explored to identify possible reasons. The RE model is generally preferred when there is significant heterogeneity among studies, for the reasons cited previously.

It may also be worth considering sub-group analysis when significant heterogeneity is evident. Here, studies sharing common characteristics are grouped together and pooled estimates of each sub-group are presented along with the overall estimate. **Web Fig. 2** presents an example wherein the studies presented in **Web Fig. 1** have been split into two sub-groups based on underlying disease severity. It is to be noted that the outcome presented in **Web Fig. 2** is different from that in **Web Fig. 1**.

It should be remembered that studies could have significant heterogeneity if they were so different so as to be non-amenable to pooling in a meta-analysis in the first place.

Authors have the option of undertaking sensitivity analysis of the results of meta-analysis. Here, studies with low(er) methodological quality are excluded from the analysis, and the pooled estimates of effect of only the high-quality studies are examined. This helps to determine how 'sensitive' the pooled estimates are to the exclusion of methodologically lower quality studies. Lower quality studies are prone to higher risk of bias and tend to over-estimate the effect of interventions. Results that are not sensitive to the exclusion of lower quality studies (meaning that the overall effect remains unchanged, even if the magnitude changes) are expressed as robust results.

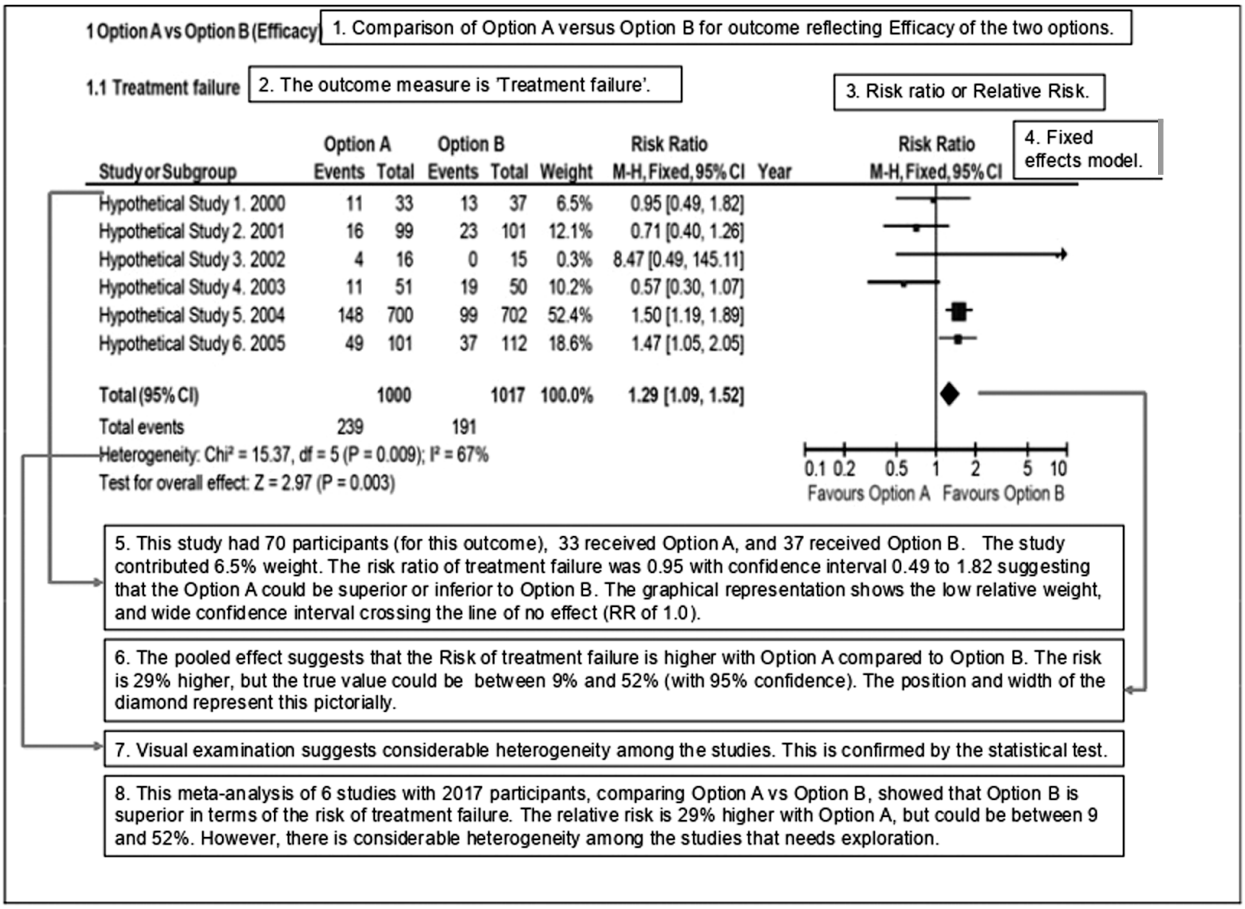


Fig. 1 Step-wise interpretation of a forest plot.

Step 8: *Interpret the forest plot*. The above steps facilitate interpretation of the pooled estimate of effect of the interventions being compared for one specific outcome, in terms of the parameter used to present the pooled esti-mate and the statistical model used to combine the data. Additionally, this is done considering the number of studies contributing to the pooled estimate, total number of participants, their individual characteristics and effects, methodological quality, and degree of heterogeneity.

Publication bias: Despite best efforts of systematic review authors to include all relevant studies addressing the research question, a review may be hampered by the non-availability of primary studies. Generally, primary studies with positive results (i.e. showing evidence of efficacy of interventions) are more likely to be published than those showing negative results. This can result in publication bias, wherein the publication (or non-publication of some studies) determines the direction or strength of the overall evidence [26]. This is why high quality systematic reviews make tremendous efforts to search for unpublished literature.

There are several methods to assess the probability of publication bias in systematic reviews. Begg and Mazumdar rank correlation test [27] for publication bias correlates the ranks of effect sizes (of various studies in the meta-analysis) against the ranks of the variance in the treatment effect.

One of the popular methods to assess publication bias, is using funnel plots. This refers to a scatter plot of all the studies in a meta-analysis with effect size on the x-axis and standard error on the *y*-axis. Ideally the plot also shows the estimated effect size (with confidence intervals) and the predicted effect size (with confidence intervals). The plot also shows a vertical line that runs through the (adjusted) combined effect and the corresponding lower and upper bounds of the confidence interval. Such a plot visually highlights whether there is asymmetry in the distribution of the included studies, which hints at publication bias. This approach works only where there are more than ten studies in the meta-analysis. Egger regression method shows "the degree of funnel plot asymmetry as measured by the intercept from regression of standard normal deviates against precision" [28].

When publication bias is suspected, systematic review authors should measure the impact of this on the estimated effect. This can be done using Duval and Tweedle trim and fill technique [29], which mathematically adjusts the pooled effect, accounting for funnel plot asymmetry.

In reviews showing efficacy of interventions with publication bias, Rosenthal analysis or the 'fail-safe N method' was used to try and identify the number of additional studies (with negative results) that would be needed to make the pooled estimate statistically insignificant [30]. Of course, this depends on making assumptions of data in unobserved/unpublished studies, hence is itself fraught with bias(es).

Apply (Considerations About Application of the Results of Systematic Reviews)

Both users and producers of systematic reviews have to make value-based judgements on three important issues viz., *i*) What does the evidence (accessed, assimilated, appraised and analyzed to answer the research question) show; *ii*) What is the quality of the overall evidence and the level of confidence that can be placed in it; and *iii*) Can the evidence be considered for use in clinical situations? Careful analysis of these three issues leads to the next and final step in evidence-informed healthcare practice viz., discussion of the evidence with individual patients by healthcare personnel with clinical expertise, to arrive at a shared decision.

Several new initiatives have been introduced to help systematic review users make better sense of the data presented. One of these is the Summary of Findings Table (SoFT) [31], that shows the absolute as well as relative effect of the intervention (including parameters like number needed to treat), the quantity of evidence, and the certainty of available evidence (which is an indirect measure of quality). SoFT are prepared for each of the key outcomes.

Another approach is to grade the evidence quality using an approach popularized by the acronym GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [31]. This approach allows systematic review producers and users to apply semi-objective judg-ments on factors that may limit the quality of evidence in the review. The key factors used are study limitations (viz., risk of bias), inconsistency (due to heterogeneity), indirectness, imprecision, and publication bias. A detailed explanation of the GRADE approach is outside the scope of this article.

Often the various analyses in systematic reviews do not point in the same direction. A common situation is one wherein some measures of efficacy favor one treatment, whereas other measures do not. Further, sometimes efficacious interventions may be less safe, or there is insuffi-cient data to confirm safety. Therefore, the overall decision on whether to use the intervention may need more information than that reported in a systematic review.

It should be emphasized that evidence-based practice is not the mere application of systematic review findings to patients (healthcare consumers). The best research evidence that needs to be integrated with clinical expertise and patient values and preferences, to arrive at a shared decision (between the healthcare recipient and provider). Thus paradoxically, a shared decision to not apply the findings of a systematic review, on account of issues related to clinical expertise and/or patient values, is also well-aligned with the principles of evidence-based healthcare.

Strengths, limitations and challenges of systematic reviews: Systematic reviews of well-designed and well-conducted studies are the keystone of high-quality research evidence. The information from systematic reviews can be included in development of evidence-based guidelines and recommendations, health technology assessment, healthcare policy decisions, or health payment/reimbursement decisions. However, systematic reviews only provide research evidence on what works in research settings (referred to as efficacy), but not necessarily on what will work in real-world settings (referred to as effectiveness). The gap between efficacy versus effectiveness, and methods to plug it, are beyond the scope of this article. Second, users of systematic reviews look for answers to decision questions (exemplified by: Shall I use this intervention?) whereas producers of systematic reviews generate answers to research questions (exemplified by: Does this intervention work?). The difference between answers to research questions and decision questions needs to be clearly understood for appropriate use of systematic reviews in clinical practice.

Although systematic reviews include many methodological refinements to reduce bias, they are completely dependent on the quantity and quality of the primary studies available to answer the research question. This can lead to the piquant situation where an excellent systematic review finds limited (or no) evidence, and concludes the need of more research. Although this does not diminish the value of the systematic reviews, it may sometimes be unhelpful for decision-makers.

Despite attempts to minimize bias, certain forms of bias can creep into systematic reviews. These include publication bias, sponsorship bias (sponsored studies are published more often, especially when they show signi-ficant results), and intentional or unintentional emphasis of systematic review authors to highlight only some aspects of the systematic review [32]. Some of these anticipated biases can be addressed by ensuring that the conduct and reporting of systematic review conform to guidelines established for the

Key Messages

- Systematic reviews involve the application of scientific methods to reduce bias in review of literature.
- The key components of systematic reviews can be summarized as: Ask, Access, Assimilate, Appraise, Analyze and Apply.
- Meta-analysis is a statistical tool that provides pooled estimates of effect from the data extracted from individual studies included in the review.

purpose. These are exemplified by the PRISMA tool [33,34]. PRISMA is an acronym for 'Preferred Reporting Items for Systematic reviews and Meta-Analyses'. The checklist comprises 27 individual items that systematic review authors are expec-ted to report. It also includes a flow chart summarizing the output of literature search in terms of studies identified, screened (after removal of duplicate publications), eligible for inclusion, those excluded, and those actually included. Extensions of the original PRISMA tool include PRISMA-P for systematic review protocols, PRISMA-IPD for reviews with individual patient data, and PRISMA-NMA for network meta-analyses.

Finally, users of systematic reviews should not blindly believe everything presented in the review, but learn to critically appraise systematic reviews for validity, significance and applicability. Standard tools and checklists available for the purpose can be very helpful [35]. Last but not the least, readers of *Indian Pediatrics* may benefit from the Journal Club section wherein systematic reviews have been critically appraised from time to time.

Note: Additional material related to this paper is available with the online version at *www.indianpediatrics.net*

REFERENCES

1. Sackett D, Strauss S, Richardson W, et al. Evidence-Based Medicine: How to practice and teach EBM. 2nd ed. Churchill Livingstone: 2000.
2. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Synthesis of best evidence for clinical decisions. Ann Intern Med. 1997;126:376-80.
3. PennState Eberley College of Science. Lesson 4: Bias and Random Error. Accessed October 01, 2020. Available from: *https://online.stat.psu.edu/stat 509/node/26/*
4. Comprehensive Meta-analysis. Accessed October 01, 2020. Available from: *https://www.meta-analysis.com/pages/why_do.php?cart=*
5. National Institute for Health Research. PROSPERO International prospective register of systematic reviews. Accessed October 01, 2020. Available from: *https://utas.libguides.com/SystematicReviews/Protocol*
6. Mathew JL, Singh M. Evidence based child health: Fly but with feet on the ground! Indian Pediatr. 2008;45:95-8.
7. Virginia Commonwealth University. How to conduct a literature review (Health Sciences). Accessed October 01, 2020. Available from: *https://guides.library. vcu.edu/health-sciences-lit-review/question*
8. http://www.knowledge.scot.nhs.uk/k2atoolkit/source/identify-what-you-need-to-know/spice.aspx
9. Cooke A., Smith D, Booth A. Beyond PICO: The SPIDER tool for qualitative evidence synthesis. Qualitative Health Research. 2012;22:1435-43.
10. Booth A, Noyes J, Flemming K, et al. Formulating questions to explore complex interventions within quali-tative evidence synthesis. Accessed October 01, 2020. Available from: *https://library.nd.edu.au/evidencebased practice/ask/question*
11. Infolibrarian. Bibliographic databases. Accessed October 01, 2020. Available from: *http://infolibrarian.com/edb.html*
12. E-Resources for China Studies. Accessed October 01, 2020. Available from: *http://www.wanfangdata.com*
13. LILACS, health information from Latin America and the Caribbean countries. Accessed October 01, 2020. Available from: *https://lilacs.bvsalud.org/en/*
14. OpenGrey. System for information on grey literature in Europe. Accessed October 01, 2020. Available from: *http://www.opengrey.eu*
15. Sterne JAC, Savoviæ J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
16. Cochrane Training. RevMan 5. Accessed October 01, 2020. Available from: *https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download*.
17. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Accessed October 02, 2020. Available from: *http://www.ohri.ca/programs/clinical-epidemiology/oxford.asp*
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.
19. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions BMJ. 2016;355:i4919.
20. University of Bristol. QUADAS-2. Accessed October 01, 2020. Available from: *https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/*
21. OHAT Risk of Bias Rating Tool for Human and Animal Studies. Accessed February 27, 2021. Available from: *https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool _508.pdf*
22. Hooijmans CR, Rovers MM, De Vries RB, et al. SYRCLE's risk of bias tool for animal studies. BMC Med Res Meth. 2014;14:1-9.
23. Cochrane Methods. About IPD meta-analyses. Accessed October 01, 2020. Available from: *https://methods.*

cochrane.org/ipdma/about-ipd-meta-analyses
24. Borenstein M, Hedges L, Rothstein H. Meta-analysis. Fixed effect vs. random effects. Accessed October 01, 2020. Available from: *https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf*
25. Heterogeneity in Meta-analysis. Accessed October 01, 2020. Available from: *https://www.statsdirect.com/help/meta_analysis/heterogeneity.htm*
26. Dalton JE, Bolen SD, Mascha EJ. Publication bias: The elephant in the review. Anesth Analg. 2016;123:812-3.
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1088-101.
28. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
29. Duval S, Tweedie R. Trim and fill: A simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56:455-63.
30. Rosenthal R. The file drawer problem and tolerance for null results. Psycholog Bulletin. 1979;86:638-41.
31. Schünemann HJ, Higgins JPT, Vist GE, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. Accessed October 01, 2020. Available from: *www.training.coachrane.org/handbook/current/chapter-14*
32. Drucker AM, Fleming P, Chan AW. Research techniques made simple: Assessing risk of bias in systematic reviews. J Invest Dermatol. 2016;136:e109-e14.
33. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Accessed October 01, 2020. Available from: *http://www.prisma-statement.org*
34. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.
35. Critical Appraisal Skills Programme. 10 questions to help you make sense of a Systematic review. Accessed October 01, 2020. Available from: *https://casp-uk.net/wp-content/uploads/2018/01/CASP-Systematic-Review-Checklist_2018.pdf*

The Concept of Self-Directed Learning: Implications for Practice in the Undergraduate Curriculum

ANSHU,[1] PIYUSH GUPTA,[2] TEJINDER SINGH[3]

From [1]Department of Pathology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra; [2]Department of Pediatrics, University College of Medical Sciences, New Delhi; [3] Departments of Pediatrics and Medical Education, SGRD Institute of Medical Sciences and Research, Amritsar, Punjab.

Correspondence to: Dr Tejinder Singh, Professor of Pediatrics and Medical Education, SGRD Institute of Medical Sciences and Research, Amritsar 143 501, Punjab. drtejinder22@gmail.com

Self-directed learning (SDL) is a modality where learners are expected to take responsibility for their own learning, diagnose gaps in their learning, frame their own goals and resources for learning, implement appropriate learning strategies and evaluate learning outcomes. Flexibility and creativity in designing assignments for students to work individually or collaboratively are the keys to promoting SDL. The recent competency-based curriculum document from the National Medical Commission does not elaborate the concept or implementation of SDL, leaving it open to individual interpretation. We, herein, discuss the concept of SDL, address common misconceptions surrounding SDL, and elucidate strategies by which SDL skills can be inculcated in medical students using pre-existing opportunities in the curriculum. Flipped classrooms, reciprocal teaching, technology-enhanced methods, problem-based learning, and group projects are excellent ways of promoting SDL. SDL requires efforts and policies both at the teachers' level and at the institutional level; and is an important input to achieve the goal of being a lifelong learner by the Indian medical graduate.

Keywords: *Competency-based curriculum, Indian medical graduate, Lifelong learner, Medical education*, *Self-directed learning.*

The concept of self-directed learning (SDL) is probably as old as mankind. One of the best-known examples of SDL is the story of Ekalavya from the Indian epic, the Mahabharata [1]. Each one of us has had our own *Ekalavya* experiences, where we have learnt a skill or an art by ourselves, without a teacher or the pressure of examinations. We charted out our targets all by ourselves in both formal and informal situations, created our own learning goals, made decisions about what and where to learn from, developed our own time frames for learning, and eventually, decided the levels of proficiency or expertise which satisfied us. Institutionalization of SDL, on the other hand, is a relatively recent phenomenon.

While the term has existed in general education, and the 1997 Medical Council of India regulations [2] did mention self-learning, its importance in medical education in India was emphasized in 2019, when the Medical Council of India mooted a new curricular model. Since the term 'self-directed learning' first appeared in the amended Regulations on Graduate Medical Education (GMER) [3] and dedicated time was allocated, it has become the new buzz word. However, in the absence of any guidelines, many teachers and students find it difficult to apply the concepts of SDL in routine undergraduate teaching.

WHAT IS SELF-DIRECTED LEARNING?

The most popular and accepted definition of SDL is that given by Malcolm Knowles in 1975 [4]: *"Self-directed learning is a process in which individuals take initiative, with or without the help of others, in diagnosing their own learning needs, formulating goals, identifying human and material resources for learning, choosing and implementing appropriate learning strategies, and evaluating learning outcomes"*. While Knowles [4] identified the five cognitive activities that need to be undertaken when following an SDL process, Sargeant, et al. [5] added another element, which is the willingness of the learners to drive their own learning (**Box I**).

Educational psychologists view SDL as a complex process that comprises psychological characteristics,

Box I Activities to be Undertaken During a Self-Directed Learning Process

- Diagnose one's own learning needs
- Formulate goals
- Identify resources for learning
- Choose and implement appropriate learning strategies
- Evaluate learning outcomes
- Willingness to drive one's own learning

personal characteristics, and personal actions. These include components such as self-efficacy, intrinsic motivation, self-assessment, beliefs, learning styles and ability to set goals.

SDL is rooted in the application of critical thinking, self-management skills, social skills, communication skills, analytical skills, and research skills. So, learners with good SDL skills will be able to independently find resources egged on by their curiosity to learn, connect newer concepts with their previous knowledge, monitor their comprehension, inquire about things they do not understand, synthesize what they have learnt, and apply that learning in a practical context. As can be seen, these are skills which transcend specific disciplines, but are necessary for the overall personal and professional development of a learner.

Some Myths About SDL

SDL means self-learning under the directions of a teacher: In essence, all learning is self-learning. Even when a teacher gives a lecture, it is the student who is learning. However, SDL is not synonymous with self-learning. Telling students to sit in the classroom or library and read a chapter is not SDL. What makes self-directed learning different is the '*locus of control.*' In SDL, it is the learner who takes the initiative and controls the direction of learning. 'Locus of control' refers to learners' belief in their abilities to control life events [6]. Individuals who have a predominantly internal locus of control believe they have the power to direct and control the events which affect their lives [7]. On the other hand, individuals who have an external locus of control believe that events in their life are controlled by factors such as fate, chance or fortune, which are beyond their control.

To help learners become self-directed, responsibility for learning must be gradually shifted from the teacher to the student. Teachers must purposefully move the onus of learning from teacher-as-model, to joint responsibility of teacher and learner, to independent practice, and application of knowledge by learner [8-10]. It is quite like teaching a child to ride a bicycle, where you gradually run alongside, steady her when the bike wobbles, and eventually allow her to ride independently minus any scaffolds. Our task as teachers will be to gradually nudge students to shift their locus of control internally, so that they enjoy the learning process and move towards deep learning, rather than become exam-oriented rote learners who are satisfied by superficial learning.

The teacher has no role to play in SDL: The term 'self-directed learning' does not imply that there is no need for a teacher. Let us recall Knowles' [4] definition here, where he talks about learning 'with or without help' from others. One of the key skills of self-directed learners is to know when to seek help or support [4]. A learner may choose to learn on his own, or with the help of others, or to learn with others. It is the student's prerogative to ask for help if required. When a learner seeks help, a teacher must be accessible or available to help. The teacher's role is that of a facilitator of learning, rather than a dispenser of content. They ensure that the learner does not deviate from the intended learning objectives.

SDL is a teaching strategy: Self-directed learning is an underlying principle of adult learning. It is not a teaching strategy or a special session. The idea of providing protected time for SDL perhaps was to provide time in the schedule for informal learning. Using this time to ask students to 'sit quietly and do SDL' is inappropriate. In a lighter vein, this misconception can be compared to the erroneous belief that medical education is only for medical education departments, or preventive advice is to be given only by preventive medicine departments. Nothing could be more damaging to the cause of SDL. SDL should be conceptualized as a set of skills which need to be inculcated by students and requires special training like other skills [11]. SDL as an approach needs to percolate into the way the students learn, and learner autonomy must be promoted irrespective of what teaching strategies we use. Restricting it to a few sessions would be extremely counterproductive.

SDL means learning alone: Learning can happen in different settings. The social interaction between peers in an educational environment is key to constructing one's own learning. This is the concept of 'community of inquiry' [12], where collaboration and sharing enable cross-pollination of ideas, shapes understanding and helps learners to construct their own meaning out of content. Teachers need to find opportunities to allow students to explore different contexts in groups where they see the functioning of health professionals or understand processes and systems.

TEACHING AND ASSESSMENT STRATEGIES

Assessing readiness for self-directed learning

Readiness is a combination of ability and intrinsic motivation. Signs of readiness for SDL include self-discipline, being organized, ability to work autonomously, ability to communicate well, openness to accept feedback, and ability to self-reflect. Readiness is situational – a student maybe self-directed in one subject, and maybe a dependent learner in another. It may even be task specific. A student may "not be able" or "not willing" or "not motivated" to do a certain task at hand. Learners are at different stages of readiness for self-directed learning (**Fig 1**) [13].

Gerald Grow [10] proposed the Staged self-directed learning (SSDL) model, which suggests that teachers can help or hinder students advance through the stages of

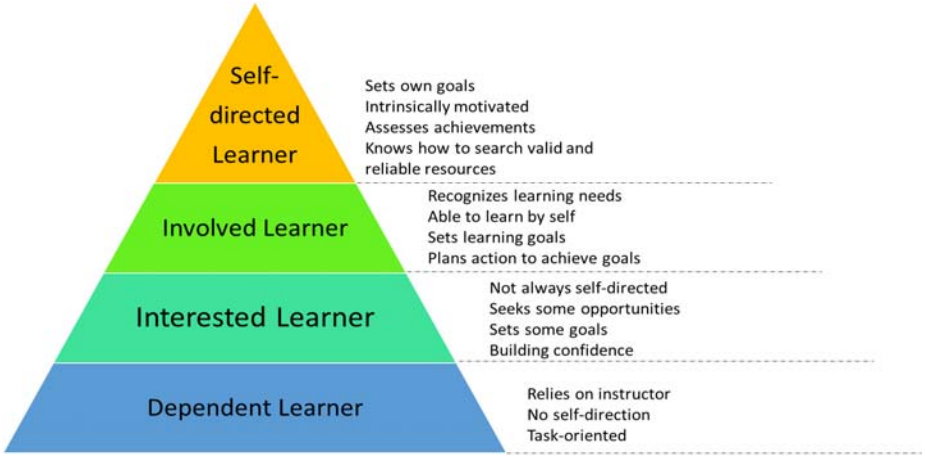


Fig. 1 Levels of self-directed learners.

increasing self-direction by providing them feedback after assessment. This is done by giving them greater autonomy and training them to shift to an internal locus of control. In **Table I**, we have summarized the various teaching and assessment strategies that can be utilized for different stages of self-directed learners according to the SSDL model [10].

Mismatch between learner SDL level and teaching style

Problems arise when the teaching style does not match with the learner's stage of self-directedness. Say for example, if stage 4 learners are taught by an authoritarian teacher, some learners might still function and retain their autonomy; but lack of challenge might cause others to retreat into boredom or resent such teaching.

Teachers require to balance their teaching styles with the students' level of self-direction, and to gradually empower them to reach higher levels. A 'good teacher' is not one who delivers exhorbitant content, but one who can be flexible and alter teaching styles according to the learner needs. Specific teaching strategies work for teaching students at each stage, and several different strategies can work. Unless flexibility in methodology is allowed, SDL cannot be achieved to its fullest potential.

PUTTING SDL INTO PRACTICE

Several instructional strategies have been shown to be useful in promoting SDL. Many concepts included in the new curriculum, such as the student-doctor concept [14,15], early clinical exposure [16], problem-based learning [17,18], case-based learning [19], reflective practice [20], or the flipped classroom concept [21,22], have self-directedness of varying degrees.

Fig. 2 summarizes different strategies by which SDL can be promoted in the undergraduate curriculum. Additional ways to incorporate self-directedness into educational practice are suggested below.

Identify pre-existing opportunities in the curriculum: Students who are exposed to problem-based or case-based learning, group projects, community visits, flipped classroom models etc. already have some experience of self-directed learning. These tasks can be honed further to promote higher levels of self-directedness. For example, some institutes have a village adoption scheme where students are allotted families in the community to follow-up throughout their course. Here students are asked to explore and perform different tasks (e.g., conducting a dietary survey, collecting data about immunization, gather-ing information about ventilation or sanitation in the house-holds etc.) within their adopted families. Such tasks allow students to learn on their own in the community context.

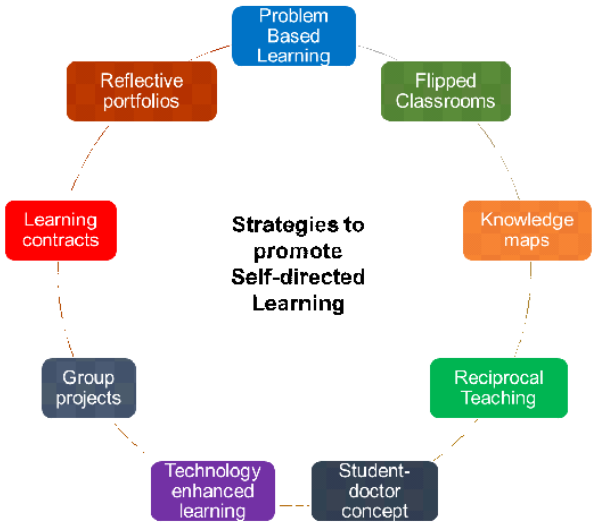


Fig. 2 Some strategies to promote self-directed learning.

Table I Teaching and Assessment Strategies to Use with Different Levels of Learners

Stages of SDL in learner	*Teaching approaches to use*	*Assessment strategies*
Stage 1: Dependent learner		
The student is a dependent learner. They need explicit instructions on what to do, how to do and when to do something. They prefer teachers who are credible authorities or coaches who will "make them learn".	- Establish purpose and relevance of the session - Share learning objectives with learners - Organize content clearly - Formal lectures, structured tutorials work; some may require one-to-one coaching - Think aloud. Allow students to see your cognitive and metacognitive processes. - Talk about common mistakes - Modelling and demonstration: when teaching structured content or skills, e.g.: steps of resuscitation. - Notice whether learners are understanding. Pay attention to the individual learner - Gradually move learners away from dependency by involving them in design and content of learning	- Formative assessments can include summarizing and questioning to check for understanding - Ask students to reflect on learning - Give well-designed assignments with defined assessment criteria - Be strict about deadlines - Give frequent, timely, constructive feedback, correct errors immediately - Reward success and uplift self-esteem
Stage 2: Interested learner		
The student is an interested learner like moldable clay. Approachable teachers with a charismatic personality work well with these learners. Learners will respond well to personal interaction. The first part of the interaction involves explaining concepts and the next part involves getting the learner to express their own understanding and exhibit their learning.	- Bring motivation and enthusiasm into the classroom - Teaching here is directive, but also supportive: pay attention to both content and process of learning - Listen carefully to what students are saying; keep a two-way dialogue happening with learners - Strategies such as lecture followed by demonstration or discussion, or assignments given after an introduction to the topic work here. - Anticipate misconceptions and correct them - Use scaffolding: use questions to check for understanding; use prompts to build bridges with background knowledge; provide cues to allow students find their own answers - Teacher-led discussions work; teach the group process - Set high standards	- Introduce the topic followed by an assignment where students have something hands-on to do - When providing feedback, gradually phase out praise (extrinsic motivation) and phase in encouragement (which builds intrinsic motivation) - Maintain records of students' progress
Stage 3: Involved learner		
The student is an involved learner with her own experiences. Teachers and students share decision-making, with students increasingly taking over this role. They see themselves as participants in their own learning.The teacher's role here is that of a facilitator of learning. Gradually students must be helped to transition towards independence through use of collaborative learning and teamwork.	- Make learners conscious of learning strategies, tools and techniques which work best for them. - Use student-led discussions. Listen to them, draw them to share their ideas and experiences - The teacher works with the learners as an equal, stepping in and out of the group when required - Give open-ended scenarios which encour-	- Individual or group projects with faculty facilitator - Give students open-ended assignments which require them to apply their knowledge and create something new. E.g.: designing a management plan in a certain patient context - Provide them written assessment criteria and checklists to monitor their own performance

contd...

contd. from pre-page

Stages of SDL in learner	*Teaching approaches to use*	*Assessment strategies*
	age problem solving; Increase task complexity - Encourage activities which require critical thinking such as seminars and group discussions - Introduce collaborative activities which encourage students to relate their own experiences to the course content - Let students make mistakes; teach learners to be accountable for individual work as well as to the group - Form learning contracts with them	- Ask questions which require students to find evidence to support their claims or justify their answers - Provide records of learner progress
Stage 4: Self-directed learner		
Students take responsibility for the direction of their learning. They set their own goals and are able to monitor and assess their own performance with or without the presence of teachers. They have meta-cognitive and self-regulative ability, as well as, time management and project management skills. They are able to gather required information and critique the quality of the resources. A teacher's role for these autonomous learners is that of a consultant. Note here that self-directed learners need not be loners. They have to acquire collaborative and social skills to work in teams.	- Delegate independent work to students; supervise them - Allow students to monitor their own - Individual assignment or self-directed learning - Set a structured challenge and leave the learner to carry it out on their own - Emphasize tasks which are important in the long-term outside the class - Encourage collaborative work between learners - The relationship between the students and the task takes precedence, rather than the teacher-student relationship. - Focus on the product rather than the process - Teachers need to be available to suggest changes, supervise or monitor progress, but essentially, they empower the learner to be independent.	- Provide broad templates of what is expected as the final assessment product group project - Dissertation and internships are other examples of independent work - Supervise students by holding meetings to check progress, discuss problems, monitor group work and give timelines

Clarify the learning goals: One of the challenges which students face in SDL is not knowing "what to learn" and the other is not knowing "when to stop". Once teachers explain the relevance of the topic in the beginning, it motivates students to pursue learning. Students must be introduced to the learning goals of the task or assignment, made aware of what is expected of them, how they will be assessed, and given deadlines of submission. These individual or team assignments must give learners the flexibility to choose their own learning methods and give them the freedom to be creative and express themselves.

Help students identify gaps in their learning: Use of knowledge maps (in the form of mind maps and concept maps) not only help in creation of additional knowledge, but also identify gaps in learning [23]. This is an important step in developing metacognitive skills. The construction of knowledge maps demands a lot of content knowledge, and deep understanding of concepts. When working in a team to develop these maps, students learn analytical skills, communication skills and collaborative skills, thus fostering SDL.

Gradually shift the onus of learning to the student: The clerkship or student-doctor phase allows student to learn about the continuity of health care [15]. This concept allows the student to first observe, then work under supervision, and then gain skills to function independently. The flipped classroom, which is increasingly finding favour in health sciences education, shifts from passive learning to accelerated learning. It fosters skills at cognitively demanding levels such as analysis, synthesis, and evaluation [24,25].

Design challenging tasks appropriate to the learner level: The Daloz model [26] talks about the need to have the right mix of support and challenge to enable the growth of

students. For example, instead of simply listing out principles of correct prescription writing, they could be asked to critically appraise actual prescriptions and learn about the common errors. One could move to more complex group tasks where an audit of appropriate antibiotic usage could be done.

Gradually allow the learner to become autonomous: The difficulty level of the tasks can gradually be increased as the learners progress over various stages of the under-graduate course. At the early stages, more didactic teaching might help to scaffold learning, and students might be given a list of recommended reading. As they progress to higher classes, they might be expected to search for their own resources and demonstrate their understanding through assignments (using the concept of "assessment as learning"). A problem that teachers could face is dealing with different levels of learners in the same class. One way of managing this is to give students some options or variety in assignments. Not all tasks will be equally complex, but they will all be designed to fulfil the same learning objectives.

Design collaborative tasks: As explained earlier, learning cannot occur in isolation. So, the design of the course must incorporate collaborative activities which allow student-student interaction. When collaborative tasks are given, it is preferable to have a mix of learners at different levels in the groups. Peer teaching helps. Also, seeing some students achieve a task improves learners' beliefs in their self-efficacy. Group research projects with a teacher as a facilitator, where students themselves decide which sub-ject they wish to explore, is an excellent way to propagate deep learning at higher levels. By providing a tangible output, projects make assessment of SDL easy.

Another way to encourage SDL through collaboration for lower levels of self-directed learners is to practice reciprocal teaching [27]. Reciprocal teaching involves a two-way dialogue where reading sessions are carried out in small collaborative groups. Reciprocal teaching promotes enquiry, metacognitive skills, self-monitoring, immediate feedback, and critiquing skills. Small group teaching, group discussions, tutorials and integrated sessions are the best place to introduce reciprocal teaching.

Give students freedom to learn at their own time and pace: Teachers need to learn to give up control and allow students autonomy. Getting students to develop their own learning goals, question what they have learnt, find their own learning resources, developing learning contracts, writing reflections, giving them tasks to work on autonomously – all have elements of SDL.

Give opportunities to practice SDL: SDL is a set of skills which require practice to make it a habit [11]. Teachers need to design tasks which allow students to gain profi-ciency by providing opportunities for deliberate practice.

Problem-based learning (PBL): PBL is one of the best examples of using SDL skills. Here the tutor tries to push students to the brink of their knowledge, from where they construct new knowledge. It must not be confused with problem-solving, which is perhaps why many presume that SDL can be restricted to a session. Many excellent reviews describe how the PBL process fosters SDL skills [28-30]. The learning strategies used in these methods emphasize active learning, self-assessment, metacognition, and reflection. It can be pointed out here that it is not necessary to implement the 'classical' models; and even partial implementation (with partial benefits) may be useful.

Flipped classrooms: Flipped classrooms involve a kind of reversal in the sequence of teachers' and students' roles, thereby promoting SDL. Here students are given some pre-reading material or asked to search their own material prior to class. Pre-reading might be given in the form of handouts, slide presentations or case-based triggers. Whenever available, technology can be invoked, and online quizzes or videos can be provided [22]. This preparation helps students self-regulate their learning, select appropriate study material, develop their own study strategies, and learn to pace their learning. The classroom time is used to elaborate difficult concepts, have collaborative discussions, or clarify doubts. After the classroom time, students could be asked to apply their knowledge to some tasks. Best practices and tips for using flipped class to promote SDL have already been described [22,25].

Use technology to promote SDL: Technology can strengthen SDL skills in several ways [31]. It can provide interesting, interactive, and pedagogically useful platforms, which can amplify the benefits of learning. Record keeping and retrieval can be made easier with optimal use of technology. Assessments with defined criteria help in ensuring that the learner's progress is documented over time. It is important to celebrate progress and achieve-ment, rather than being focused only on the final exami-nation marks.

Encourage reflective practice: Allowing students to reflect about the process of learning is an essential compo-nent of SDL. Reflective practice helps learners link new knowledge with the old, promote higher order thinking and take on further responsibility for their learning. Reflections can be either used as standalone interventions, or over time, these can become part of student learning portfolios. Portfolios are systematic collections of work done by the student with evidence of their learning [32]. A major feature which distinguishes portfolios from logbooks is the element of reflection, which promotes metacognitive skills. Use of portfolios as learning and assessment tools has been

described earlier [33]. Since the new CBME curriculum mandates the use of logbooks, adding an element of reflection to promote SDL should be easy [32].

Provide honest and specific feedback: Students often over-estimate or under-estimate their potential. Students with higher self-efficacy beliefs tends to have higher goals than those who have low belief in their worth [34]. It is here that honest and explicit feedback helps them understand the reasons for their success or failures better, and this enhances their self-efficacy belief [35,36]. Furthermore, a safe non-threatening learning environment, where it is acceptable to falter and fail, is essential to bolster self-efficacy.

Develop learning contracts: Another technique which can be used to enhance SDL skills is a learning contract. A learning contract is a form of an agreement that a student makes with herself, to learn [37]. The student writes a document, which specifically states what and how she will learn in a defined time in the presence of a teacher. Both the student and the instructor agree to this plan of action. This is not a commitment to work for an instructor; the instructor is only a witness to the contract. Writing and adhering to learning contracts is an easily adaptable intervention. We feel that this should be increasingly used in our system after training of teachers and students in framing a learning contract. The Foundation course can be a useful opportunity to achieve this. We have provided some examples of learning contracts in **Web Table I-IV**. These contracts include not only knowledge, but also skills, attitudes, and communication competencies.

Challenges in Implementation

Whenever a change is introduced, resistance is expected. Regulatory norms might not be sufficient to implement change. Faculty training is mandatory to erase any mis-givings that they might have about losing control or adopting an unfamiliar approach. Secondly, one might encounter dependent students who are so used to directed teaching that they might be reluctant to move towards self-directedness. This might be a flaw in our education system, which needs to be corrected [38]. One way to do this will be to structure the course in such a way that learners are gradually empowered over time to take up responsibility towards their own learning.

One must be conscious that learners might be at different levels of readiness towards SDL. Pushing only one educational strategy in the form of SDL might not work in a context where learners are not used to working autonomously. Hence teachers will have to use a mix of teaching-learning styles until all students are comfortable with working on their own.

When designing courses which use the principles of SDL, it is important to plan for flexibility. When learners are given an opportunity to learn autonomously, each learner will experience it differently. As long as they adhere to the learning objectives defined in the course, learners are free to use different formats to demonstrate that they have actually learnt something. Self-directed learners need time, opportunities, and freedom to explore. These must be built into the educational environment.

Promotion of SDL is not a task which can be success-ful if only one or few teachers veer students towards self-directedness. It requires a collective effort of the entire institution as a policy. This holds true in our circum-stances where students might not have been exposed to SDL in their school years. The transition to self-directed-ness in these learners must be done in a phased manner, gradually nudging them towards SDL. These expectations need to be communicated and clarified right in the beginn-ing of professional courses. In fact, right in the Foundation course, learners can be oriented towards the concept of metacognition (awareness and understanding of one's own learning), self-regulated learning (ability to under-stand and control one's learning environment), and SDL (taking charge of their own learning process), and pro-vided with guidance on how they might learn skills of time management, and project management. In all, the educatio-nal environment determines whether students will embrace SDL.

CONCLUSION

SDL is a set of skills that can be taught, learned, and acquired. It is not a teaching strategy, but a philosophy to be imbibed. The SDL process needs personal and environ-mental characteristics for identification and correction of gaps in understanding [11]. SDL is a habit of practice. Teachers need to provide opportunities for students to inculcate this habit. Restricting SDL to only a few sessions or only for knowledge-based tasks is an error, which needs to be avoided. The educational environment should be tailored to allow flexibility in methodology to achieve SDL goals.

Contributors: Anshu: conceptualized the model, developed its detailed outline and prepared the initial draft of the manuscript; TS,PG: provided critical comments on the manuscript and developed learning contracts. All authors approved the final version of manuscript.

Funding: None; *Competing interest*: None stated.

Note: Additional material related to the paper is available at *www.indianpediatrics.net*

REFERENCES

1. Pattanaik D. Ekalavya. *In*: Jaya: An Illustrated Retelling of the Mahabharata. 2010; Penguin Books.p.64-65.
2. National Medical Commission. Regulations on Graduate Medical Regulations (Amendment), 2019 (online). Accessed Dec 12, 2021. Available from: *https://www.nmc.org.in/ActivitiWeb Client/open/getDocument?path=/Documents/Public/Portal/Gazette/*

GME-06.11.2019.pdf
3. Medical Council of India. Competency based undergraduate curriculum for the Indian Medical Graduate. Vol 1-3 (2019). Accessed Dec 12, 2021. Available from: *https://www.nmc.org.in/information-desk/for-colleges/ug-curriculum/*
4. Knowles MS. Self-Directed Learning: A Guide for Learners and Teachers. Cambridge Adult Education, Prentice Hall Regents; 1975.
5. Sargeant J, Bruce D, Campbell CM. Practicing physicians' needs for assessment and feedback as part of professional development. J Contin Educ Health Prof. 2013;33: S54-S62.
6. Strauser DR, Ketz K, Keim J. The relationship between self-efficacy, locus of control and work personality. Journal of Rehabilitation. 2002;68:20-26.
7. El-Hosany WAE, Sleem WF. Nursing student's experience on locus of control and its relationship with learning perfor-mance and academic support: A comparative study. Am J Nursing Science. 2017;6:315-23.
8. Duke NK, Pearson PD. Effective practices for developing reading comprehension. *In*: Farstup AE, Samuels SJ (Eds.). What Research Has to Say About Reading Instruction. 3rd edition. Intern Read Association.2002:205-42.
9. Fisher D, Frey N. Better Learning Through Structured Teaching: A Framework for Gradual Release of Responsibility. Second edition. ASCD; 2014.
10. Grow, GO. Teaching learners to be self-directed. Adult Educ Qrt. 1991;41:125-49.
11. Ginzburg SB, Santen SA, Schwartzstein RM. Self-directed learning: A new look at an old concept. Med Sci Educ. 2020;31:229-30.
12. Garrison DR, Anderson T, Archer W. Critical inquiry in a text-based environment: Computer conferencing in higher education model. Internet and Higher Education. 2000;2:87-105.
13. Pearson PD, Gallagher G. The gradual release of responsibility model of instruction. Contemporary Educational Psychology. 1983;8:112-23.
14. Checkley EW, Prosser CJ, Sandler RD. Student doctors: Learning from the front line. Med Sci Educ. 2021;31:1549-50.
15. Poncelet AN, Hudson JN. Student continuity with patients: A system delivery innovation to benefit patient care and learning (continuity patient benefit). Healthcare (Basel). 2015;3: 607-18.
16. Satishkumar S, Thomas N, Tharion E, et al. Attitude of medical students towards early clinical exposure in learning endocrine physiology. BMC Med Educ. 2007;7:30.
17. Nerali JT, Telang LA, Telang A, et al. The role of self-directed learning in problem-based learning. Health Professions Education. 2016;4:125-6.
18. Choi E, Lindquist R, Song Y. Effects of problem-based learning vs. traditional lecture on Korean nursing students' critical thinking, problem-solving, and self-directed learning. Nurse Educ Today. 2014;34:52-6.
19. McLean SF. Case-based learning and its application in medical and health-care fields: A review of worldwide literature. J Med Educ Curric Dev. 2016;3:S20377.
20. Al-Shehri A. Learning by reflection in general practice: A study report. Educ Gen Pract. 1995;7:237-48.
21. Zainuddin Z, Perera CJ. Supporting students' self-directed learning in the flipped classroom through the LMS TES BlendSpace. On the Horizon. 2018;26:281-90.
22. Singh K, Mahajan R, Gupta P, Singh T. Flipped classroom: A concept for engaging medical students in learning. Indian Pediatr. 2018;55:507-12.
23. Hanewald R. Cultivating lifelong learning skills in undergraduate students through the collaborative creation of digital knowledge maps. *Procedia*- Social and Behavioral Sciences. 2012;69:847-53.
24. Moravec M, Williams A, Aguilar-Roca N, O'Dowd DK. Learn before lecture: A strategy that improves learning outcomes in a large introductory biology class. CBE Life Sci Educ. 2010;9:473-81.
25. Schwartzstein RM, Roberts DH. Saying goodbye to lectures in medical school - paradigm shift or passing fad? N Engl J Med. 2017;377:605-7.
26. Daloz L. Effective Teaching and Mentoring: Realizing the Trans-formational Power of Adult Learning Experiences. Jossey-Bass;1986.
27. Palincsar AS, Klenk L. Dialogues promoting reading comprehension. *In*: Means B, Chelemer C, Knapp MS, editors. Teaching Advanced Skills to At-risk Students. Jossey-Bass;1991.p. 112-40.
28. Virk A, Mahajan R, Singh T. Conceptualizing problem-based learning: an overview. International J App Basic Med Res. 2022; 12: 1-3
29. Dolmans DHJM, Snellen-Balendong H, Wolfhagen IHAP, van der Vleuten CPM. Seven principles of effective design for a problem-based curriculum. Med Teach. 1997;19:185-9.
30. Albanese MA, Mitchell S. Problem-based learning: a review of literature on its outcomes and implementation issues. Acad Med. 1993;68:52-81.
31. Saxena S. How technology supports SDL. Accessed Jan 6, 2022. Available from: *https://edtechreview.in/news/824-how-technology-supports-self-directed-learning*
32. Shah N, Singh T. The promising role of the logbook and portfolio in the new competency-driven medical curriculum in India. South-East Asian J Med Educ. 2021; 15:18-21.
33. Joshi M, Gupta P, Singh T. Portfolio based learning and assessment. Indian Pediatr. 2015;52:231-34.
34. Locke EA, Latham GP. Building a practically useful theory of goal setting and task motivation: A 35-year odyssey. Am Psychol. 2002;57:705-17.
35. Hattie J, Timperley H. The power of feedback. Rev Educ Res. 2007;77:81-112.
36. van de Ridder JMM, Stokking KM, McGaghie WC, et al. What is feedback in clinical education? Med Educ. 2008;42:189-97.
37. Boone WR, Dickey JF, Keller DF. Contract learning: A tool for motivating dairy students. J Dairy Science. 1979;62:1848-51.
38. Premkumar K, Vinod E, Sathishkumar S, et al. Self-directed learning readiness of Indian medical students: A mixed method study. BMC Med Educ. 2018;18:134.

Web Table I: Competency Addressed: Abdominal Examination

PE 26.7 Perform examination of abdomen, demonstration of organomegaly, ascites etc.
PE 29.12 Perform examination of the abdomen, demonstrate organomegaly
Timeline: One week

Learning Objectives	*Learning resources*	*Evidence*	*Criteria for assessment*	*Action plan for future*
1. To gain appropriate knowledge about the contents of abdomen, and placement of various organs in it. 2. To be able to examine the abdomen of children of various ages in a compassionate and systematic manner, and describe the findings correctly 3. To be able to detect any organomegaly ascites, or palpable masses with appropriate examination technique and describe the findings	1. Read the clinical methods book and view authenticated videos available offline/online related to correct procedure of examination of abdomen 2. Observe examination of abdomen by faculty/ residents in pediatric OPD/wards 3. Ask my seniors/peers to help me in identifying abnormal abdominal examination findings in hospitalized patients 4. Practice abdominal examination on bedside as desired and record video (with patient permission)	1. Demonstrate my examination technique to peers/tutors, at bedside 2. Get my recordings reviewed by peers/tutors and obtain their feedback 3. Write my reflections on the process (in the logbook)	1. Tutor/resident will validate my examination techniques directly (at bedside) or review my video recording and give feedback 2. Compare how I perform in an OSCE station on examination of abdomen and demonstration of organomegaly/ ascites (compared to a standardized itemized checklist or assessed on global rating scale by a skilled examiner)	1. Practice in more complex patients

Web Table II: Competency addressed: Intravenous Cannulation

24.16 Perform IV cannulation in a model
Timeline: Two weeks

Learning objectives	*Learning resources*	*Evidence*	*Criteria for assessment*	*Action plan for future*
1. To gain appropriate knowledge of surface marking of common veins used for IV cannulation, and demonstrate them 2. To be able to identify and select the age-appropriate device for cannulation, and 3. To demonstrate preparation of cannulation site, with all aseptic precautions 4. To correctly insert IV cannula in a model, fix it, and dispose waste as per standard guidelines	1. Revise surface anatomy of superficial veins by visiting the Anatomy Museum and learning resources (textbook). Practice on peers 2. Observe all devices being used for IV cannulation in the Pediatric Emergency/wards 3. View videos on preparation of site, and aseptic precautions which are available online or offline 4. Retrieve/prepare a checklist for correct procedure on insertion and waste disposal 5. Visit the skills lab and practice insertion and fixing IV cannula on model	1. Record my practice sessions 2. My reflections on the exercise 3. Observing free flow of blood after insertion, on a model 4. Obtain Feedback from peers/tutors on my recordings	1. Validation by tutor of my recording and filled up checklists on at least 3 occasions 2. OSCE station used by the department during next round of OSCE	1. Practice IV cannulation in real patients under supervision 2. When confident perform IV cannulation independently in real patients

Web Table III: Competency Addressed: Communication with Patients

AETCOM 23: Demonstrate ability to communicate with patients in a patient, respectful, non-threatening, non-judgmental and empathetic manner
Timeline: One week

Learning Objectives	*Learning resources*	*Evidence*	*Criteria for assessment*	*Action plan for future*
1. To gain appropriate knowledge and skills to communicate with a patient. 2. To use appropriate communication skills.	1. Observation of my communication by residents/ senior residents of the department. 2. Role plays with peers 3. Facility for recording (my mobile!) 4. Kalamazoo consensus statement regarding communication	1. Review of recording of my communication with peers during role plays using checklist given on page 85 of AETCOM booklet. 2. Feedback from peers/tutors/ patients 3. My reflections on the exercise	1. Tutor/ senior resident will review the recording and provide feedback using checklist 2. OSCE station used by the department during next round of OSCE 3. Comparison with Kalamazoo criteria	1. Compare progress in my OSCE scores over time 2. Practice communication in more settings

Web Table IV: Competency Addressed: The Role of the Physician in the Community

PE 35.1 Identify, discuss, and defend medicolegal, socio-cultural and ethical issues as they pertain to health care in children (including parental rights and right to refuse treatment)
Timeline: 2 weeks

Learning Objectives	*Learning resources*	*Evidence*	*Criteria for assessment*	*Action plan for future*
1. To gain appropriate knowledge about children's rights, parents' rights and responsibilities 2. Learn laws related to care of children 3. Ethical issues in healthcare of children 4. Common social and cultural issues related to children in Indian context	1. Books on ethical issues 2. Journals 3. Internet resources 4. From legal experts related to child laws 5. From social activists dealing with issues related to children	1. Identify issues in children in care homes 2. Write a case study raising the problems and solutions 3. Feedback from peers/tutors/'patient' 4. My reflections on the exercise	1. Tutor/Sr. Resident will review case study and reflections and provide feedback	1. Discuss some of the issues with health activists and see how they approach and deal with simple and complex cases

Cardiac Evaluation in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With COVID-19

Multisystem inflammatory syndrome in children (MIS-C) is notorious for its cardiac involvement. We present a single center data of 71 children, of which 57.7% had myocarditis and 26.8% had coronary artery aneurysms. 45.1% required intensive care support and 29.6% needed inotropes - 91.5% received IVIG. All patients responded to therapy with no mortality.

Keywords: *Coronary artery aneurysm, Myocarditis.*

Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a stormy multisystem disease with the brunt of the disease on the heart, causing sudden severe myocarditis, shock and coronary artery aneurysms (CAA) [1].

Patients satisfying the WHO MIS-C criteria admitted at the Institute of Child Health, Kolkata, a tertiary care hospital, between July and December, 2020 were evaluated for cardiac affection clinically, through laboratory investigations and echo-cardiography at admission and post- treatment. Ethical clearance was taken from the Institutional Ethics Committee and written informed consent was taken from the parents/ guardians. Treat-ment protocols and outcomes were noted down. Follow up echo-cardiography was done at 2,6 weeks, 3 and 6 months. The initial and follow up echocardiographies were performed by a trained pediatric cardiologist.

Seventy-one MIS-C patients with a median age of 6 years were admitted. (Quartile 1 being 3 and quartile 3 being 8, IQR 5). Of these, 41 (57.7%) had myocarditis (disproportionate tachycardia, electrocardiogram changes and echocardiographic changes), and 22 (30.9%) had low ejection fraction (EF) (35-47%). Cardiac symptoms manifested unpredictably around 3 to 7 days of fever and the usual clinical presentation was disproportionate tachycardia and sudden onset hypotension. Intensive care admission was needed by 45.1% and 29.6% required inotropic support. Cardiac affection accounted for the most important cause of intensive care admission. None had any evidence of valvular involvement or heart block.

CAA (>2 z-score) and Kawasaki disease (KD) like manifestations were seen in 26.8%. Four had left anterior descending (LAD) artery dilatation (mean +3.18 z-score), three had left main coronary artery (LMCA) dilatation (mean +2.51 z-score) and four had both (mean LMCA +3.57 *z*-score and LAD +3.31 z-score). Two had multiple CAAs involving LAD, right coronary artery (RCA), and LMCA. One child had only RCA dilatation (+2.87 z-score), and five had z-score <+2.5 z-score. None had z- scores >5.

Sixty five (91.5%) children received intravenous immunoglobulin (IVIG), mostly at 2g/kg. However, 7 adolescents, because of the need for large dose and consequent financial burden, were administered 1 g/kg along with methylprednisolone (MP). Of these 65 children, 43 also received MP. The remaining 8.5% received MP only. EF improved after 48 to 72 hours of initiation of therapy. Patients presenting with shock and requiring inotropes, were initiated on MP together with IVIG. Fourteen patients required respiratory support (supplemental oxygen, non-invasive ventilation) and four had to be intubated. All patients additionally received 5 mg/kg of aspirin for 6 weeks (**Table I**).

Following initiation of immunotherapy, inotropes could be tapered off over 48 to 72 hours and all children had normalization of EF within 5 to 7 days. Three patients with CAAs had persistent dilatations at discharge and two had transient increase in size following initial IVIg therapy. 89.5% patients with CAAs had regression by 6 weeks and the remaining dilatations normalized over 6 months.

Since the very first reports and case series on MIS-C, cardiac involvement is reported as the major cause of morbidity [1,2]. Affecting almost half the patients, the lesions range from ventricular dysfunctions, coronary dilatations, arrhythmias to heart blocks and they usually require ICU support [3,4]. The pathogenesis of cardiac dysfunction remains unclear. Post-infectious hyperinflammation is commonly postulated though direct viral injury has also been thought of. MIS-C has some similarities to KD but these are usually older children with higher frequency of ventricular dysfunction, higher NT-pro-BNP and thrombocytopenia. Coronary artery dilatation in MISC is mostly mild to moderate but few giant aneurysms have been reported [5,8].

Management of MIS-C has been extrapolated from KD and adult studies and is being regularly updated [7,8]. Initially, starting therapy with IVIG with or without steroids was pro-

Table I Clinical Characteristic and Management in Children With MIS-C (*N*=71)

Characteristics	*No (%)*
Myocarditis	41 (57.7)
Low ejection fraction	22 (30.9)
Coronary artery dilatation	19 (26.8)
Management	
Intravenous immunoglobulin ± methylprednisolone	65 (91.5)
Methylprednisolone	6 (8.5)
Intensive care admission	32 (45.1)
Inotrope requirement	21 (29.6)
Respiratory support[a]	14 (19.7)
Mechanical ventilation	4 (5.6)

MISC: multisystem inflammatory syndrome in children associated with COVID-19. [a]Moist oxygen, non-invasive ventilation.

posed. However, with time, the threshold for instituting steroids has decreased. In unresponsive cases, pulse methylprednisolone is advocated with tapering on follow-up. Aspirin is added in anti-platelet doses. In cases with giant aneurysm or thrombosis enoxaparin is given. Successful usage of interleukin 1 blocker anakinra has been demonstrated. Due to lack of knowledge regarding the long-term complications, moderate to longterm follow-up is required both clinically and echocardiographically.

Acute myocarditis with or without CAA is the predominant cardiac affection seen in MIS-C. Echocardiography is an essential tool in early diagnosis as well as in deciding optimum treatment. Early identification, supportive care by a multidisciplinary team preferably in an intensive care unit, and aggressive immuno-therapy reverts the inflammation rapidly without significant residual lesions.

Ethics clearance: IEC, Institute of Child Health; No. EC/250/2021 dated August 25, 2021.
Contributors: PL: Case diagnosis, management, preparation of final manuscript; JNB: Case management, preparation and editing the manuscript; MG, PG, HD: Case management, preparation of manuscript; AKS: Case diagnosis, echocardiographic evaluation.
Funding: None; *Competing interest*: None stated.

PRIYANKAR PAL,[1] JIGNA N BATHIA,[*] MIMI GANGULY,[2] PURBASHA GUPTA,[2] HRIDAY DE,[2] ANIL KUMAR SINGHI[3]
Departments of [1]Pediatric Rheumatology, and [2]Pediatric Medicine, Institute of Child Health; [3]Pediatric Cardiology, Medica Superspeciality Hospital; Kolkata, West Bengal.
**jigna.bathia@hotmail.com*

REFERENCES

1. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395: 1771-78.
2. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334-46.
3. Pignatelli R, Antona CV, Rivera IR, et al. Pediatric multisystem SARS-CoV-2 with versus without cardiac involvement: a multicenter study from Latin America. Eur J Pediatr. 2021;180: 2879-88.
4. Clark BC, Sanchez-de-Toledo J, Bautista-Rodriguez C, et al. Cardiac abnormalities seen in pediatric patients during the SARS-CoV-2 pandemic: An international experience. J Am Heart Assoc. 2020;9:e018007.
5. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429-36.
6. Matsubara D, Kauffman HL, Wang Y, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol. 2020;76:1947-61.
7. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143:21-32.
8. Sperotto F, Friedman KG, Son MBF, et al. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: A comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.

NEWS IN BRIEF

The MELODY trial for RSV

Nirsevimab is a long acting monoclonal antibody against the fusion protein of the respiratory syncytial virus. In the phase III MELODY trial recently published – a single dose of Nirsevimab reduced the incidence of medically attended RSV infections by 74.5%. The other option so far had been Palivizumab, another monoclonal antibody, which could protect infants for only 1 month and needed 5 doses to cover the entire RSV season. The secondary end point of the trial was hospitalizations. This occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (P=0.07). Nirsevimab has also been used in high risk infants with congenital heart disease and chronic lung disease and shown adequate safety and tolerability.

Since the lifting of curbs after the COVID pandemic, there was a spike in RSV infections in 2021. Nirsevimab may offer a ray of hope, especially to high risk premies.
(*NEJM 3 March 2022*)

Upper age limit for NEET-UG entrance removed

Since 2017, there had been an upper age limit for appearing in the national eligibility-cum-entrance test for undergraduate training (NEET-UG) in India. It was 25 years for unreserved candidates and 30 years for reserved candidates. This has now been scrapped by the National Medical Commission.

Prior to the NEET, the age cut-off in the AIPMT exam applied to only 15% of the seats. When the NEET phased out the AIPMT, this age limit became applicable to all seats. This was challenged in May, 2018 in the Supreme Court. The petitioners felt the rule was unfair to women and candidates from underprivileged backgrounds, who may not be able to follow the same timeline as others. The removal of the age limit will allow more candidates to apply including those who missed the age cutoff due to delay or postponement of examinations, which occurred in 2021 and 2022.
(*The Indian Express 10th March 2022*)

Gouri Rao Passi
gouripassi@hotmail.com

Hypersenstivity Signs of Tuberculosis – Is It Synonymous of Latent Tubercular Infection?

Diagnosing and treating latent tubercular infection (LTBI) is an important strategy to accelerate the decline in global tuberculosis and to achieve elimination. Presence of clinical signs of hypersensitivity reaction to tubercular protein is an important manifestation of tubercular infection in children. Some of the manifestations seen in children are erythema nodosum (EN), phlyctenular keratoconjunctivitis (PKC) and tuberculous rheumatism. Tuberculous rheumatism is a form of reactive arthritis characterized by non-erosive symmetric polyarthritis that occurs in the presence of tubercular infection where no other known cause of polyarthritis can be detected. PKC is a non-infectious inflammatory process, with morphologic expression of a delayed-type hypersensitivity reaction to diverse antigens [1].

An 11-year-old boy with normal development and anthropometry presented with redness and itching in the right eye since 1 week, painful skin rashes on the shin, and with pain in both the knee joints associated with difficulty in walking. The pain significantly limited his routine activities and worsened with activity. There was no associated morning stiffness. The patient did not report any other symptoms like fever, loss of appetite, weight loss, chest pain and cough. There was no significant past medical history. He was not taking any medications. His childhood immunizations were complete and included BCG vaccine at birth. There was a history of contact with a person in the household who had pulmonary tuberculosis and was on treatment. There was no family history of rheumatologic disease or autoimmune disease.

On ocular examination, lids and adnexa were normal. An elevated pinkish white nodule of approximately 1×1 mm in size with surrounding engorged hyperemic vessels was present at one O'clock position at limbus (**Web Fig. 1a**). Multiple erythematous and tender nodules were present over the shin of tibia, which were 2-4 cm in diameter and poorly demarcated (**Web Fig. 1b**). Bilateral knee joint tenderness was present with limitation in range of movements and with no other signs of inflammation. There was no generalized lymphadenopathy. Cardiovascular and respiratory examination was normal. Laboratory tests revealed a normal blood count; erythrocyte sedimentation rate was 30 mm at the first hour. C-reactive protein, rheumatoid factor and anti-streptolysin titer were normal. Chest radiograph was not suggestive of active tuberculosis infection. HIV status was non reactive. Induced sputum was negative for acid fast bacilli and CBNAAT was also negative. *X*-ray of both the knee joints was reported as normal. Tuberculin skin test was done using 2 TU of PPD RT 23 and reaction read at 48 hour was 24 mm with blistering. Thus, the patient was diagnosed to have LTBI presenting as hypersensitivity reactions. The child was started on Isoniazid prophylaxis, and was asked to continue it for 6 months.

The current diagnostic tools in LTBI are TST (tuberculin skin test) and IGRA (interferon gamma release assay), but the definitive diagnosis of LTBI is still complicated. Currently there is no gold standard diagnostic tool for LTBI [2]. LTBI screening is indicated in populations with high risk of progression to tuberculosis disease. The high risk population include household contacts of confirmed pulmonary tuberculosis cases (particularly children <5 years of age), people living with HIV, patients initiating anti–TNF treatment and on dialysis. As the risk of progression from LTBI to active tuberculosis is maximum in under-five children, WHO recommends treatment of LTBI in this age group. However, in high burden countries like ours, WHO also recommends treatment of LTBI in children older than 5 year and adults, though the evidence for the same is not very conclusive [3]. Treatment regimens available are – isoniazid monotherapy, rifampicin mono-therapy, isoniazid plus rifampicin combination and isoniazid and rifapentine combination. Isoniazid monotherapy for 6-12 months has efficacy in preventing progression to tuberculosis disease in 90% [4]. There is a need to identify other risk groups where LTBI treatment may be warranted.

In our case, though the child was older than 5 year, we started him on isoniazid prophylaxis, as there was a history of household contact (open case) with tuberculosis and presence of clinical features of hypersensitivity. Upon subsequent follow-up, the child's rash and phlycten had disappeared, and he was comfortable with no pain in the knees. An adult patient presenting with tuberculous rheumatism and erythema nodusum with positive tuberculin test has previously been reported [5], but all the hypersensitivity signs seen in a single patient have not been previously reported. We suggest that presence clinical hypersensitivity signs in a patient could be included as one of the diagnostic criteria to diagnose LTBI.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Madhu S Pujar,* Vineela Mikkilineni, Megha P
Department of Pediatrics, JJM Medical College, Davanagere, Karnataka.
**mspujar@hotmail.com*

REFERENCES

1. Wiriyachai T, Boonsathorn S, Apiwattanakul N, et al. A rare case of primary sinonasal tuberculosis presented with phlyctenular-kerato conjunctivitis in a pediatric patient. Medicine (Baltimore). 2021; 100: e24787.
2. Chapman HJ, Lauzard M. Advances in diagnosis and treatment of latent tuberculosis infection. J Am Board Fam Med. 2014;27:704-12.
3. Jain A, Lodha R. Management of latent tuberculosis infection in children from developing countries. Indian J Pediatr. 2019;86: 740-45.
4. Saha S, Kumar A, Saurabh K, et al. Current status of treatment of latent tuberculosis infection in India. Indian J Med Sci. 2019;71: 54-59.
5. Rizvi Z, Iqbal T, Javed A, et al. Erythema nodosum: A conse-quence of tuberculosis. Cureus. 2019;11:e4724.

Two Faces of Brugada Syndrome

Brugada syndrome is a genetically determined channelopathy, with an incidence of 1/1,000-10,000 people. It is responsible for 4-12% of sudden cardiac deaths (SCD) with the ventricular fibrillation (VF) mechanism. Brugada syndrome type 1 is characterized by a convex elevation of the ST segment ≥2 mm and negative T wave. The only effective treatment reducing risk of SCD for a patient with Brugada syndrome is the implantation [1,2].

Case 1: A 16-year-old boy was referred due to significant family history (SCD with VF in father at the age of 42 year, with history of repeated episodes of syncope and wheezing at night for several months, and SCD of several cousins aged 24-50 in the father's family). The patient was asymptomatic, and denied symptoms such as syncope or palpitations. The boy's 19-year-old brother was diagnosed with type 1 Brugada syndrome (**Fig. 1**), and was managed by the implantation of a subcutaneous cardioverter-defibrillator (s-ICD). Our patient's resting ECG (along with elevated intercoastal space ECG), 72-hour Holter ECG, exercise test and echocardiographic examination showed no significant deviations. Ajmaline provocation test was performed. Genetic testing including analysis of 11 genes and 168 exons associated with Brugada syndrome showed the presence of a likely pathogenic variant in the *SCN5A c.2947_2951dupGGTCT* gene, p. (Leu985Valfs *162). The same mutation was also confirmed in the boy's brother. Due to the positive genetic test result, deterioration of the patient's quality of life, another death in the family (uncle age 58) despite the lack of clinical symptoms, the patient was implanted a s-ICD.

Case 2: An 11-year-old boy was referred with suspicion of Pediatric inflammatory multisystem syndrome temporally-associated with SARS-CoV-2 infection (PIMS-TS). The patient had temperatures up to of 39.5 °C along with nausea for 4 days, but no respiratory or cardiovascular complaints. Due to multi-ple desaturations to SpO2 92%, he required oxygen therapy. Laboratory tests revealed leukocytosis with lymphopenia and thrombocytopenia. There was an increased concentration of inflammatory markers (CRP 393. 8mg/L) and borderline concentration of troponin I (0.037ng/mL). Serum IgG antibodies against SARS-CoV-2 were positive. Echocardio-graphic examination revealed an uneven outline of the left coronary artery. In addition, moderate mitral, pulmonary, and tricuspid valves regurgitation were observed. An ECG recorded during an episode of fever revealed a 2-3 mm ST-T segment elevation, such as in Brugada syndrome type 1 (**Fig. 2**). Treatment was done as per protocol including intravenous immunoglobulin, and later the child also received intravenous steroids. In control ECG exami-nations, including the examination with the V1 and V2 electro-des placed 1 and 2 intercostal spaces above the conventional site, no characteristic features of Brugada syndrome were found. A gradual improvement in the clinical condition and normalization of laboratory parameters were observed. Resting ECGs of the patient's immediate family were normal. Patient was instructed with preventive recommen-dations as in Brugada syndrome. The boy was directed for genetic testing and he remains under cardiology follow-up.

The diagnosis of Brugada syndrome can be set after recording the characteristic morphology in lead V1 and/or V2 (or after switching these electrodes to the 2nd, 3rd intercostal space - nominal or high leads) during resting ECG spontaneously or after a drug provocation test (intravenous administration of a sodium channel blocking drug) [3]. Cardiac arrest is most often preceded by symptoms, such as: heart palpitations, syncope, and breathlessness at night. The disease is 8-times more common in males. Several genes are responsible for the disease, the most common mutations are associated with *SCN5A* gene, and several pathogenic variants are described. However, experts disagree on the usefulness of genetic testing. In AHA/ACC/HRS 2017 guide-lines, it is mentioned that "genetic testing may be useful in the diagnosis and care of relatives of people with Brugada syndrome."

In asymptomatic patients diagnosed with Brugada syndrome, it is recommended to avoid drugs contraindicated in Brugada syndrome, strictly prohibit the consumption of alcohol and psychoactive substances, avoid fever, avoid heavy meals, monitor vital parameter (mainly at night) [2]. Several adult patients have been described in whom the resting ECG during the acute phase of SARS-CoV-2 disease revealed abnormalities of repolarization suggestive of Brugada syndrome, though all had fever and ionic disturbances [3-5]. In most patients, ECG changes normalized spontaneously after resolution of fever and did not cause serious ventricular arrhythmias. Our second patient had several risk factors that could have led to Brugada-like changes in ECG,

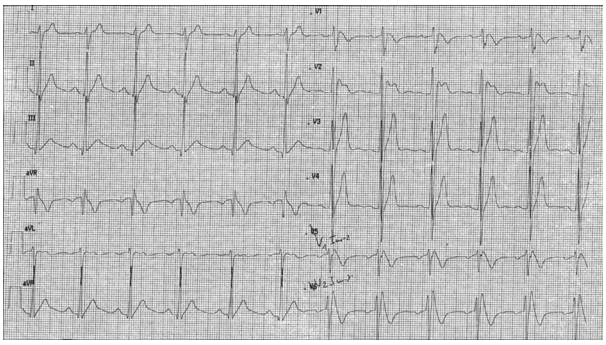


Fig. 1 ECG record of patient 1 with type 1 Brugada syndrome.

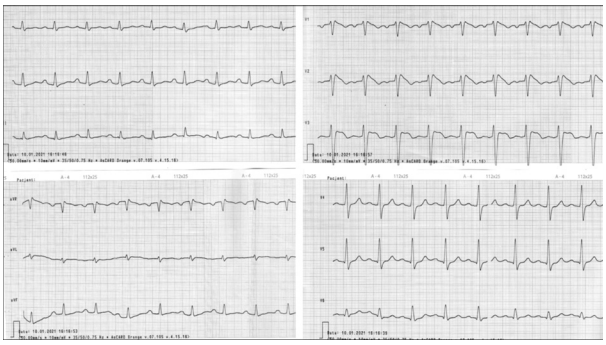


Fig. 2 Brugada-like changes in the ECG of patient 2 with pediatric inflammatory multisystem syndrome (PIMS-TS).

including fever, ionic disturbances (hyponatremia, hypophosphatemia), as well as damage to the myocardium itself in the course of PIMS-TS syndrome (i.e., changes in the coronary arteries) with negative family history [5-7].

In conclusion, Brugada syndrome is a disease, which, when detected too late, can result in SCD. However, as our two cases show, its diagnosis as well as the implementation of appropriate preventive therapy is not always easy.

Note: Both authors contributed equally to this work.

PIOTR KĘDZIORA,* ALEKSANDRA STASIAK
Department of Pediatric Cardiology and Rheumatology, Medical University of Lodz, Poland.
**piotr.kedziora.dr@gmail.com*

REFERENCES

1. Gonzalez Corcia MC, Sieira J, Pappaert G, et al. implantable cardioverter-defibrillators in children and adolescents with Brugada syndrome. Am Coll Cardiol. 2018;71:148-57.
2. Siera J, Brugada P. The definition of Brugada syndrome. Eur Heart J. 2017;38:3029-34.
3. Papadakis M, Papatheodorou E, Mellor G, et al. The diagnostic yield of Brugada syndrome after sudden death with normal autopsy. J Am Coll Cardiol. 2018;71:1204-14.
4. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: ExecutiveSummary. Circulation. 2018;138:210-71.
5. Long B, Brady WJ, Bridwell RE, et al. Electrocardiographic manifestations of COVID-19. Am J Emerg. 2021;41: 96-103.
6. Vidovich MI. Transient Brugada-like electrocardiographic pattern in a patient with COVID-19. JACC: Case Reports. 2020; 2:1241-49.
7. van de Poll SWE, van der Werf C. Two patients with COVID-19 and a fever-induced Brugada-like electrocardiographic pattern. Neth Heart J. 2020;28**:**431-36.
Chang D, Saleh M, Garcia-Bengo Y, et al. COVID-19 infection unmasking Brugada syndrome. Heart Rhythm Case Rep. 2020; 6:237-40.

Infantile Anti-N-Methyl-D-Aspartate Receptor Encephalitis Post-SARS-CoV-2 Infection

The spectrum of neurological conditions associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is evolving. Here, we describe a case of N-methyl-D-aspartate receptor encephalitis (NMDAR-E) with possible temporal association with SARS-CoV-2.

A 10-month-old typically developing boy presented with poor feeding and irritability for 5 days. On day 3 of illness, he developed fever and loose stools with 2 episodes of convulsions on day 5 of illness, when he was brought to our hospital. It was associated with loss of pre-morbidly normal eye contact. He had an upper respiratory tract infection (URTI) 40 days prior to illness onset. At presentation, his axillary temperature was 98.2^0 F, pulse rate was 92/minute, respiratory rate was 24/minute and blood pressure was 84/54 mmHg. General physical and systemic examinations were unremarkable. On neurological examination, baby was not interested in surroundings and had poor interaction with caregivers. Cranial nerve examination was unremarkable. Motor system examination revealed normal power and tone, with brisk deep tendon reflexes. Peri-oral dyskinesias and bilateral striatal toe were present. Cerebellar and meningeal signs were absent. In view of fever, diarrhea, seizures, acute onset encephalopathy with extrapyramidal movements, possibilities considered at admission were post-infectious immune-mediated conditions (central nervous system demyelination, autoimmune encephalitis, post-COVID multisystem inflammatory syndrome (MIS-C)) and inherited metabolic disorder. Prior to referral, baby had a normal cerebrospinal fluid (CSF) study and C-reactive protein (CRP) with elevated white cell count (WBC, 26×10^9/L). Initial investigations at our center revealed elevated WBC (24 $\times10^9$/L, N61L30), normal CRP (1 mg/L) and procalcitonin (0.25 ng/mL). SARS-CoV-2 IgG antibodies were strongly positive (index-20.7, >1.0 positive). Erythrocyte sedimentation rate (22 mm/first hour), lactate dehydrogenase (515 U/L), ferritin (19.5 ng/mL) and echocardiography (normal) were not consistent with MIS-C.

Over the next 24 hours, extrapyramidal movements worsened with appearance of generalized and oro-linguo-buccal dystonia with athetosis. Hence, possibility of anti-NMDA encephalitis was considered. MRI brain was normal. CSF showed 20 cells (95%L), sugar 65 mg/ dL (blood sugar: 102 mg/dL), protein 27 mg/ dL. CSF-polymerase chain reaction (PCR) was negative (*Eschershia coli K1, Hemophlilus influenzae, Listeria monocytogenes, Streptococcus agalactiae, Streptococcus pneumonia*, Cytomegalovirus, enterovirus, HSV1, HSV2, HHV6, Human parechovirus, Varicella zoster virus and *Crypto-coccus neoformans/gatii)*. CSF sample for NMDA antibodies was sent to the laboratory.

Child was started on intravenous immunoglobulin (2 g/kg) and pulse methylprednisolone (30 mg/kg/day for 5 days) on day 8 of illness. CSF sample was reported strongly positive for anti-NMDA antibodies (indirect immunofluorescence assay). Computed tomography (CT) of abdomen and pelvis for tumor screening was negative. By day 5 of pulse steroids, there was no improvement in extrapyramidal movements or encephalopathy. Considering severe infantile form of anti-NMDAR encephalitis poorly responsive to first line therapy, weekly rituximab infusion (375 mg/m^2/dose/week for 4 doses) was initiated in the second week of illness, along with addition of azathioprine for long-term immunosuppression (2 mg/kg/day). Two weeks after last rituximab dose, baby remained encephalopathic. Extrapyramidal movements were partially controlled with clonidine, baclofen and clonazepam. In view of refractory disease, monthly cyclophos-

phamide (750 mg/m^2/dose) was administered for 3 doses. Following the first dose, baby achieved sustained eye contact and neck-control within a week. By one month, he could recognize parents, sit with support, creep and vocalize; mild oro-motor dyskinesia and bilateral hand athetosis persisted. Symp-toms completely resolved after the second cyclophosphamide dose. Steroids were tapered off over 3 months after initial pulse dose. At the time of last follow-up, extrapyramidal movements were well controlled and baby was regaining age-appropriate milestones.

To the best of our knowledge, this is the first case of anti-NMDAR-E associated with SARS-CoV-2 in an infant aged <12 months. Anti-NMDAR-E, characterized by severe movement with encephalopathy, can be triggered by viral infections or tumors. Herpes simplex virus (HSV) encephalitis is the most commonly associated viral trigger, and can result in anti-NMDAR-E 4-6 weeks, or longer after an acute encephalitis episode [1].

SARS-CoV-2 is known to result in strong immune activation, which is broadly termed as MIS-C [2]. Post-SARS-CoV-2 immune-mediated manifestations can present within two weeks to a median of 25-45 days after an acute infection [3]. Anti-NMDAR-E associated with SARS-CoV-2 has been reported in only three children aged 23 months [4], 7 years [5] and 14 years [6]. All three children had a positive SARS-CoV-2 RT-PCR with evolution to encephalitis from acute infection in two children, and no clinical infection in one child. In our case, only IgG antibodies were positive, indicating a prior infection, which on history may be correlated with the preceding URTI. Considering the high population seropositivity, a true cause-effect relation cannot be ascertained. A positive RT-PCR test during the acute URTI episode and a positive family history would have streng-thened the causal association. Molecular mimicry probably best explains the pathogenesis for SARS-CoV-2 associated anti-NMDAR-E. Whether it can result in late-onset CNS ence-phalitis, similar to HSV encephalitis, remains to be elucidated. The present report, in conjunction with previous reports, supports the association of SARS-CoV-2 with NMDARE. Future research focusing on association between SARS-CoV-2 and early autoimmunity can help understand the underlying pathogenesis.

PRABHJOT KAUR,[1] VINAY MV,[2] BABU S MADARKAR[3]*
Divisions of [1]Pediatric Neurology, [2]Pediatric Hematology-Oncology, and [3]Neonatology, Department of Pediatrics, Rainbow Children's Hospital, Bengaluru, Karnataka.
**babumadarkar@yahoo.co.in*

REFERENCES

1. Sahar N, Nurre M, Simon Q. Infectious trigger for autoimmune encephalitis: A case report and literature review. Case Rep Infect Dis. 2019;2019:0-4.
2. Desai I, Manchanda R, Kumar N, et al. Neurological manifestations of coronavirus disease 2019: Exploring past to understand present. Neurol Sci. 2021;11:1-13.
3. Ramos-Casals M, Brito-Zerón P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. Nat Rev Rheumatol. 2021;17:315-32.
4. Burr T, Barton C, Doll E, et al. N-Methyl-d-aspartate receptor encephalitis associated with COVID-19 infection in a toddler. Pediatr Neurol. 2021;114:75-6.
5. Sarigecili E, Arslan I, Ucar HK, et al. Pediatric anti-NMDA receptor encephalitis associated with COVID-19. Childs Nerv Syst. 2021;37:3919-22.
6. Sánchez-Morales AE, Urrutia-Osorio M, Camacho-Mendoza E, et al. Neurological manifestations temporally associated with SARS-CoV-2 infection in pediatric patients in Mexico. Childs Nerv Syst. 2021;1-8.

ERRATA

Please note following corrections in the article titled "Early goal-directed therapy with and without intermittent superior vena cava oxygen saturation monitoring in pediatric septic shock: A randomized controlled trial." published in Indian Pediatr. 2021;58:1124-30.

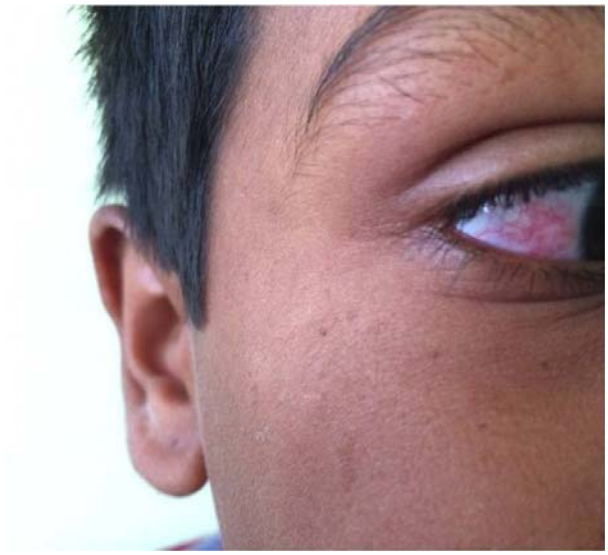
In Table I, which shows baseline characteristics of the study participants, mean (SD) lactate value in the control group should be '4.6 (2.9) mmol/L' in place of '66.3 (10.4) mmol/L.' in the same table, mean (SD) ScvO2 in the intervention group should be '66.3(10.4)%' in place of '4.6 (2.9)%.'

Appropriate corrections have been done in the web version at *https://www. indianpediatrics.net/dec2021/1124.pdf*

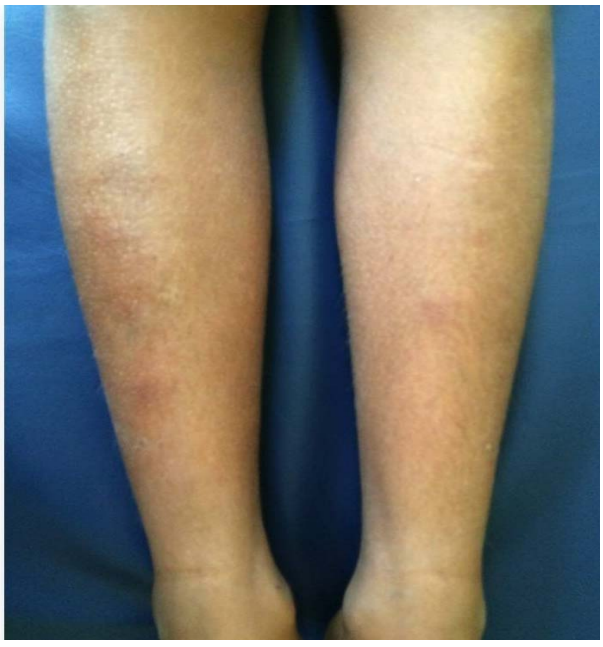
Please note following corrections in the article titled "Low-dose (0.05 unit/kg/hour) vs standard-dose (0.1 unit/kg/hour) insulin in the management of pediatric diabetic ketoacidosis: A randomized double-blind controlled trial" published in Indian Pediatr. 2021;58:617-23.

On page 620, column II, first para, second sentence should be "The hypokalemia was more in malnourished children in the standard-dose group (P=0.31), and more children in the standard-dose group required a higher concentration of dextrose and tapering of insulin infusion at least once to counter the falling blood glucose (Table II)." in place of "The hypokalemia was more in malnourished children in the standard-dose group (P=0.31), and more children in the standard-dose group required a higher concentration of dextrose and tapering of insulin infusion at least once to counter the falling blood glucose P>0.005)."

Appropriate corrections have been done in the web version at *https://www. indianpediatrics.net/july2021/617.pdf*



Web Fig. 1a Hypersensitivity reactions in LTBI. (a) Right eye showing elevated pinkish white nodule at 1 o'clock position at the limbus surrounding engorged hyperemic vessels.



Web Fig. 1b Lower limbs showing multiple erythematous, papulonodular skin lesions, 2-4 mm diameter over the shin of tibia.

Encephalitis-like Presentation in Infants of Bodo Tribe – Thiamine Deficiency or Leigh-like Disease?

We read with interest the recent study [1] on basal ganglia disease mimicking acute encephalitis syndrome (AES) among infants of Bodo tribe, Assam. Studies from India [2,3] have previously also described clinical improvement in AES following thiamine administration. We seek the authors' responses to the following observations:

i) According to World Health Organization clinical case definition of AES [4], acute onset of fever with change in mental status is required. Thus, how appropriate is the term AES in the absence of fever in about 30% of the study participants in their study [1].

ii) Injectable medication given to the patients contained thiamine along with other vitamins, deficiency of which may also cause encephalopathy with basal ganglia involvement. How was the clinical response ascribed only to thiamine and not to other vitamins?

iii) Of the 50 infants studied in the current study, lactate levels were done in only four infants; however, other investigations, if done, are not mentioned. The study included infants with basal ganglia changes with all the study participants having seizures, but there is no data related to involuntary movements such as dystonia. The lack of features like dystonia, in spite of radiologic evidence of basal ganglia involvement, is not explained. What were the other neuroimaging findings apart from those in the basal ganglia – were the brainstem and cerebellar structures involved?

iv) Sastry, et al. [5] reported life-threatening cardiac failure with pulmonary hypertension in infants who were exclusively breastfed by mothers that followed vegetarian diet, with a prompt response to thiamine. What was the incidence of pulmonary hypertension/cardiac failure in the current study? Rao, et al. [2] described overlapping features, between Leigh disease, an inherited metabolic disorder, and thiamine deficiency. Was there any associated significant family history present in these infants?

v) What were the dietary habits of mothers of these infants? Majority of the infants were malnourished, what were the other nutritional deficiencies noted, if any?

Vykuntaraju K Gowda,* Uddhava Kinhal
Department of Pediatric Neurology,
Indira Gandhi Institute of Child Health,
Bangalore, Karnataka.
**drknvraju08@gmail.com*

REFERENCES

1. Webster JJ, Beryl S, George K, et al. Basal ganglia disease mimicking acute encephalitis syndrome among infants of bodo tribe, Assam. Indian Pediatr. 2021;58:1183-4.
2. Rao SN, Mani S, Madap K, et al. High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. J Trop Pediatr. 2008;54:328-32.
3. Nazir M, Lone R, Charoo BA. Infantile thiamine deficiency: New insights into an old disease. Indian Pediatr. 2019;56:673-81.
4. Solomon T, Thao TT, Lewthwaite P, et al. A cohort study to assess the new WHO Japanese encephalitis surveillance standards. Bull World Health Organ. 2008;86:178-86.
5. Sastry UMK, Jayranganath M, Kumar RK, et al. Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: a prospective observational study. Arch Dis Child. 2021;106:241-46.

AUTHORS' REPLY

We thank the readers for their interest in our clinical observations [1].

i) According to the WHO, clinically a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year, with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) [2]. We agree that only 70 % of our patients had associated fever; though, all had new-onset seizure and altered sensorium.

Our study from North-eastern India sheds light on a treatable cause of possible thiamine deficiency, which presents clinically like an acute encephalitis syndrome. Rao, et al. [3] also reported a cohort of infants from southern India, responding to thiamine. Large community-based studies are needed to find the etiology as to whether it is thiamine deficiency or either of infantile Leigh-like *SLC19A3* gene defect, THTR2 deficiency, or biotin-thiamine responsive basal ganglia disease [1].

ii) We agree to this possibility; though, available literature does not support this contention. There are case reports of vitamin B12 deficiency causing bilateral globus pallidus abnormalities in adults. In the myriad of presentations of vitamin B12 deficiency, basal ganglia involvement is one of the rarest associations [4]. Among infants, infantile tremor syndrome is associated with vitamin B12 deficiency or mutations affecting the metabolic pathway. However, cortical atrophy, and prominence of ventricular system and subarachnoid space are the frequently reported radiological manifestations [5].

iii) **Table I** shows the laboratory parameters of the infants in both the groups. Cerebrospinal fluid analysis was done for 8 infants, which were unremarkable (6 in the non-exposure group and 2 in the exposure group).

Table I Laboratory Parameters of the Two Groups

Parameter	*Non-exposure group (n=23)*	*Exposure group (n=27)*
Hemoglobin (g/dL)	9.4 (0.9)	9.3 (1.0)
Platelets (10^9L)	481 (147)	535 (15)
Total counts (cell/mm^3)	12560 (6895)	14434 (7438)
Polymorph (%)	56 (17)	58 (18)
Lymphocytes (%)	35 (16)	32 (16)
Sodium (mmol/L)	131 (7.5)	134 (7)
Potassium (mmol/L)	5 (0.6)	5.1 (0.5)
Creatinine (mg/dL)	0.65 (0.15)	0.53 (0.27)
CSF	*n*=6	*n*=2
Total counts (cell/mm^3)	7 (1.5)	4 (2.8)
Neutrophils (%)	Nil	Nil
Total protein (mg/dL)	45.2 (21.3)	38.4 (10)
Glucose (mg/dL)	82 (40)	95 (30)

Values are presented as mean (SD). CSF-cerebrospinal fluid.

iv) No patient was in cardiac failure clinically. None of the infants underwent echocardiography. During the period covered in the report, we did not have the facility to do RBC transketolase activity, genetic analysis and vitamin B12 levels. No infant had dystonia. However, among the two patients with neurological sequelae followed-up as outpatients, one had raised tone in all limbs and the other had spastic diplegia.

v) The Bodo community daily diet consists of polished rice with lentil soup, tubers and meat. The rice is taken along with boiled vegetables and leaves. Raw dried freshwater fish are also part of their diet. They are known to consume a lot of tea. *Paan*, a preparation combining betel leaf with areca nut, sometimes with tobacco, is commonly consumed. Heat-stable thiamine antagonists are known to be present in several plants including tea and betel nut. They include polyphenols; these and related compounds are found in red beets, red cabbage, betel nuts, coffee and tea [6]. They react with thiamine to yield the non-absorbable thiamine disulfide. Thiamine deficiency in Thailand was reported to be linked with tea drinking and chewing of fermented tea leaves; tannins being the major component having anti-thiamine activity. Thiaminases are present in the raw tissues of many fishes, chiefly freshwater fishes. These are heat labile and can be effective antagonists of the vitamin when consumed without heat treatment [7].

Maternal subclinical thiamine deficiency could be a possible factor for thiamine deficiency in these exclusively breast-fed infants. Maternal thiamine deficiency during pregnancy often leads to infantile beriberi in such communities and is thought to account for a large proportion of the high infant mortality rates found in the Philippines, Burma, Cambodia, Laos, Vietnam, and probably also in other rice-eating countries [8]. Thankaraj, et al. [9] also reported infantile cardiac beriberi responding to thiamine in northeastern rural India, where 23 (92%) infants presenting with acute cardiac failure recovered with thiamine administration.

Response to thiamine was dramatic in our cohort of patients. Clinically they presented with an acute encephalitis syndrome-like picture. With many cases of AES having no definite etiology, our study suggests the addition of thiamine in the treatment protocol for AES, and also informs readers to consider the possibility of thiamine deficiency in a patient with encephalopathy without apparent etiology and in an appropriate setting.

JEMIN J WEBSTER
Baptist Christian Hospital,
Mission Chariali,
Tezpur, Assam.
jeminwebster@hotmail.com

REFERENCES

1. Webster JJ, Beryl S, George K, et al. Basal ganglia disease mimicking acute encephalitis syndrome among infants of Bodo tribe, Assam. Indian Pediatr. 2021;58:1183-84.
2. Solomon T. New WHO Japanese encephalitis surveillance standards. Bull World Health Organ. 2008;86.
3. Rao SN, Mani S, Madap K, et al. High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. J Trop Pediatr. 2008;54:328-32.
4. Sharrief AZ, Raffel J, Zee DS. Vitamin B(12) deficiency with bilateral globus pallidus abnormalities. Arch Neurol. 2012;69: 769-72.
5. Holla RG, Prasad AN. Infantile tremor syndrome. Med J Armed Forces India. 2010;66:186-7.
6. Hilker DM, Somogyi JC. Antithiamins of plant origin: Their chemical nature and mode of action. Ann NY Acad Sci. 1982; 378:137-45.
7. World Health Organization. Thiamine deficiency and its prevention and control in major emergencies. WHO;1999.
8. Austin B. Micronutrients I: Vitamins in Health and Disease. Mother Child Nutr. Trop. Subtrop., 2016. p. 317-21.
9. Thankaraj S, Koshy RM, Ismavel V. Infantile cardiac beriberi in rural north east India. Indian Pediatr. 2020;57:859-60.

Early Goal-Directed Therapy and Superior Vena Cava Oxygen Saturation Monitoring in Pediatric Septic Shock: Few Concerns

We read with interest the recent publication on early goal-directed therapy [1]. We have the following concerns:

Among the therapeutic end-points of shock, lactate <1.6 mmol/L was taken as one of the therapeutic end-points but Sepsis-3 guidelines [2] have defined lactate >2 mmol/L as one of the parameters for the definition of septic shock [2]. The reason for the same should be clarified for the benefit of the readers.

It would have added value to the study if therapeutic end-points of shock had also included cardiac index, as recommended by American College of Critical Care Medicine [3].

GOLLA RAMAKRISHNA, DAISY KHERA*
Department of Pediatrics,
AIIMS, Jodhpur,
Rajasthan.
**daisykhera78@gmail.com*

REFERENCES

1. Jain P, Rameshkumar R, Satheesh P, Mahadevan S. Early goal-directed therapy with and without intermittent superior vena cava oxygen saturation monitoring in pediatric septic shock: A randomized controlled trial. Indian Pediatr. 2021;58:1124-30.
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.
3. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017;45:1061-93.

AUTHORS' REPLY

We thank the readers for their interest in our study [1]. In our study, the therapeutic end-points of shock cut-off for lactate as <1.6 mmol/L or decreasing trend was taken from a similar study published by Sankar, et al. [2]. Our study started in 2015, while the Sepsis-3 guidelines were published in 2016 [3].

The target of therapeutic end-point of septic shock recommended by the American College of Critical Care Medicine (ACCM) includes cardiac index between 3.3 and 6.0 L/min/m2 [4]. The level of evidence was graded as grade 2C as per the GRADE system mentioned by surviving sepsis campaign [5]. Though echocardiography facility was available in our setting, based on the available evidence, concern about pediatric age group cardiac index data (validation and normality) at the time of protocol preparation and study from similar study setting [2], We decided to adopt the end-point of septic shock without cardiac index.

R RAMESHKUMAR,* PJAIN
Department of Pediatrics, JIPMER,
Puducherry 605 006.
**krramesh_iway@yahoo.co.in*

REFERENCES

1. Jain P, Rameshkumar R, Satheesh P, et al. Early goal-directed therapy with and without intermittent superior vena cava oxygen saturation monitoring in pediatric septic shock: A randomized controlled trial. Indian Pediatr. 2021;58:1124-30.
2. Sankar J, Sankar MJ, Suresh CP, et al. Early goal-directed therapy in pediatric septic shock: Comparison of outcomes 'with' and 'without' intermittent superior venacaval oxygen saturation monitoring: A prospective cohort study. Pediatr Crit Care Med. 2014;15:e157-67.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.
4. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017;45:1061-93.
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med. 2013;41:580-637.

Bai Jerbai Wadia Hospital for Children and Institute of Child Health and Research, Mumbai

NC JOSHI,[1] SHAKUNTALA S PRABHU[2]

[1]Department of Pediatrics; and [2]Medical Director; Bai Jerbai Wadia Hospital for Children and Institute of Child Health and Research, Parel, Mumbai 400012, Maharashtra. s.s.prabhu@wadiahospitals.org

THE BEGINNING

With a legacy of more than nine decades, Bai Jerbai Wadia Hospital for Children and Institute of Child Health and Research is the first and the largest hospital in the country devoted for child health and welfare. It is the first ever public hospital established in India exclusively for children by a joint agreement between the Municipal Corporation of Greater Mumbai and the Wadia Family in the year 1929. Late Sir Cusrow Wadia and Late Sir Ness Wadia, the two sons of Bai Jerbai Nowrosjee Wadia built this children hospital in her memory and declared it open on 12 December, 1929. Realization of the need for special care for children and establishing a hospital for them in the heart of the city, amidst the working classes of Mumbai, by itself displays the vision and philanthropic ideals and legacy of serving the poor on part of the founders.

Over the years, the foresight of the management and the faculty heads, who were committed to strike a balance amongst the four pillars of medical academia as in patient care, administrative, education and research, has modelled this institution to have a pride of place among the pediatric hospitals in India.

The Early Years

The hospital was started with a bed strength of 126 with medical and surgical indoor and a novel outpatient department in a separate building with 24 hour emergency which was the first in India for children. Basic pathology investigations and radiology services were also made available. Departments of physiotherapy and occupational therapy were started to complement Orthopedic department and for rehabilitation of handicapped children. Social Service Department with Child Guidance Clinic rendering services for the deserving, a special school for bedridden children and a recreation center were the other features in the initial period.

Dr. RN Cooper was the founder principal medical officer followed by Dr. Arthur De Sa who also established the pediatric surgery department. The recognition of this hospital in the early years was due to the dedicated and pioneering efforts of Dr. Cooper, Dr. De Sa, Dr. RV Sanzgiri and Dr. Katrak. They were pioneers in recognizing pediatric medicine and surgery as separate specialties. During this period training of residents was the only teaching activity.

The Middle Years – 1950 to 1990

During the next phase of expansion of the institute, one more floor was added to the hospital in 1964 and bed strength went up to 300 beds. There were parallel developments of both pediatric medicine and surgery when Dr. RA Irani, Dr. SM Merchant, Dr. SJ Dalal and later, Dr. Jer Master, Dr. MP Desai, Dr. KP Mehta and Dr. KN Shah joined the institute. The main focus during this time was to make the institute a high quality and cost-effective tertiary health care center by adding pediatric and neonatal intensive care units. Pediatric intensive care was established by Dr. Uma Ali and Neonatal intensive care unit was coordinated by Dr. Prem Sheth.

In 1975, the Burns unit and Skin Bank were established by Dr. SS Keswani and Dr. Arvind Vartak. The hospital was then recognized by University of Bombay for under-graduate and post graduate training in pediatrics through its affiliation to Seth G S Medical College. The College of Physicians and Surgeons also recognized this hospital for DCH and FCPS. The hospital was also recognized by Royal College of Physicians and Child Health and Royal College of Surgeons. A full-fledged post-graduate training program took shape consisting of daily ward rounds, post emergency teaching clinics, weekly inter hospital pediatric meetings, monthly grand rounds and postgraduate seminars which are still a routine now. The Dr. SM Merchant Auditorium is used for such teaching programs, workshops and small conferences.

The novel feature of this hospital was the establishment of specialty clinics in cardiology, endocrinology,

nephrology and epilepsy with EEG for the first time in India. The aim was to provide adequate and essential diagnostic services for this subset of commonly seen conditions along with clinical research for greater insight into their epidemiology, etiopathogenesis and clinical patterns in Indian settings, thereby offering greater opportunities for learning and training in these specialties.

The Hospital in the Later Years and Today (1990-till date)

After 2000, these specialty clinics were expanded further into divisions offering cutting-edge sub-specialty care, simultaneously maintaining basic general pediatrics.

Pediatric Cardiology division, which was the first subspecialty to be established in 1968 by Dr Jer Master and later assisted by Dr NC Joshi, has now become a state of art center for cardiac sciences with cardiac surgery and interventional cardiology.

The Thyroid clinic was started by Dr Meena Desai in 1969 and she did exemplary work in congenital hypothyroidism. It has now become one of the largest pediatric endocrinology divisions in the country.

Nephrotic syndrome clinic was started in 1975 by Dr. Kumud Mehta. First peritoneal dialysis was done in 1980 and Hemodialysis department was started in 2010, and now is a full-fleged pediatric nephrology department with a renal transplant center.

Epilepsy Clinic was started in 1989 by Dr KN Shah. Since 1994, it has become a full-fledged, busy neurosciences department. Pediatric neurosurgery department under Dr Chandrashekhar Deopujari was established in 1996.

Dr Zinet Currimbhoy started the hematology and immunology clinic in 1984, which has now evolved into a super specialty hemato-onco unit with Bone Marrow Transplant and Stem Cell Therapy.

Pediatric HIV was started by Dr Rashid Merchant in 1998 and TB clinic was started in 2007. Pediatric drug-resistant TB center, first one in India, was established in 2018.

Dr. Saroj Parekh started the Liver Clinic, which has now evolved into a full fledged Pediatric Gastroenterology division with endoscopy and motility lab under Dr Ira Shah. In 2015, pediatric pulmonology services were started by Dr. YK Amdekar.

Another major milestone during this stage was the establishment of a research laboratory which had modern, sophisticated, diagnostic equipment with Radioimmunoassay, Hematology and Immunology sections and recently the Molecular laboratory. This research laboratory is recognized by Department of Science and Technology, ICMR and WHO. ICMR has also established an independent Genetic Research Laboratory here.

Pediatric Surgery Department flourished under Dr S J Dalal's guidance with Dr Vinod Kapur starting laparoscopy in 1974, Dr Ashok Mathure taking care of respiratory anomalies and Dr Vishnu Waingankar and Dr Ila Meisheri having started the Urosurgery division. Currently Dr Pradnya Bendre has set up a 'state of art' endoscopy and minimal access surgery center. There is also a perinatal surgery division which holds credit for having operated on conjoined twins. We have a special center devoted to cleft lip and palate surgeries under Dr Mukund Thatte.

The Pediatric Orthopedic surgery department started surgery for complex deformities and spine problems under the luminaries Dr Yagnik, and Dr Ashok Johari. The Club foot clinic is one of the busiest in Western India.

The radiology services were started very early under the guidance of Dr Nadkarni and presently the hospital has round the clock dedicated pediatric ultrasound and CT/MRI services.

The Pediatric palliative care department is first of its kind in India and specialized anesthesia and rehabilitation services are there to compliment patient care.

COMMUNITY INITIATIVES

BJWHC has conducted numerous health camps for children across many states including several areas in Maharashtra like Palghar, wherein the impact can already be measured in the community with decrease in number of malnourished children. BJWHC is also providing support for capacity building, disaster management, screening and treatment of health conditions and knowledge management for Government and non-profit organizations.

State Center of Excellence in Pediatric Nutrition, supported by UNICEF, is a hub of State nutrition programs.

BJWHC has received Nursing Excellence Certificate from National Accreditation Board for Hospitals and Healthcare for 2 consecutive terms, which is rare for a public hospital. The hospital has NABH and NABL accreditation and moving towards complete digitization.

Every year the entire community comes together to participate in the Little Hearts Marathon (LHM), which is a social event to engage the community and help spread awareness for prevention of cardiac diseases in children. More than hundred thousand children have supported the cause of LHM over the last 6 years.

EDUCATION AND TRAINING

There are 35 pediatric super specialty programs along with undergraduate and postgraduate degree and diploma courses. Fifteen fellowship courses, under the aegis of Maharashtra University of Health Sciences and Indian Academy of Pediatrics as well as DNB super specialty courses in pediatric hematology, neonatology and pediatric cardiology, pediatric intensive care, pediatric gastroenterology are run by the hospital

Since 2004, a biannual week-long national post-graduate clinical teaching program is being held along with a month-long clinical DCH and DNB clinical observership. The faculty over the last many decades has been feted in numerous national and international platforms.

The hospital has won over 50 national and international health sector service awards and the motto of the hospital – *In deo fide et perseverantia*, meaning Trust in God and Perseverance, sums up its philosophy.

What keeps the hospital at the forefront of Pediatrics in India and beyond, is the professional competence, continuous innovation and dedication of all departments who manned the hospital during last nine decades.

THE ICONS OF THE INSTITUTION

The path-breaking personalities responsible for the initial growth and development of the hospital were Prof. SM Merchant.

Dr SM Merchant joined the hospital in 1949 and was primarily associated with its initial growth and also mentored future leaders. He promoted establishment of subspecialties and was also a research innovator and set up the research laboratory. He was a teacher par excellence and one of the towering figures of pediatric medicine in India. He used to consider the hospital as his family, and used to say that people working here are the foundations of the institute and they should be brought together, helped to flourish academically, and made to feel valued.

Recently, since 2012, the hospital has grown by leaps and bounds under the visionary leadership of Dr Minnie Bodhanwala. Due to her pioneering efforts, the hospital now has 525 beds, of which 225 are intensive care beds.

Acknowledgements: The authors would like to thank Dr M Bodhanwala, CEO Wadia Hospitals for permission to use photographs from the hospital collection and also providing valuable inputs. Dr Sanjay Prabhu and Dr Mihir Oswal coordinated the manuscript development.
Funding: None. *Competing interests*: Both authors are working as faculty members in the institute.

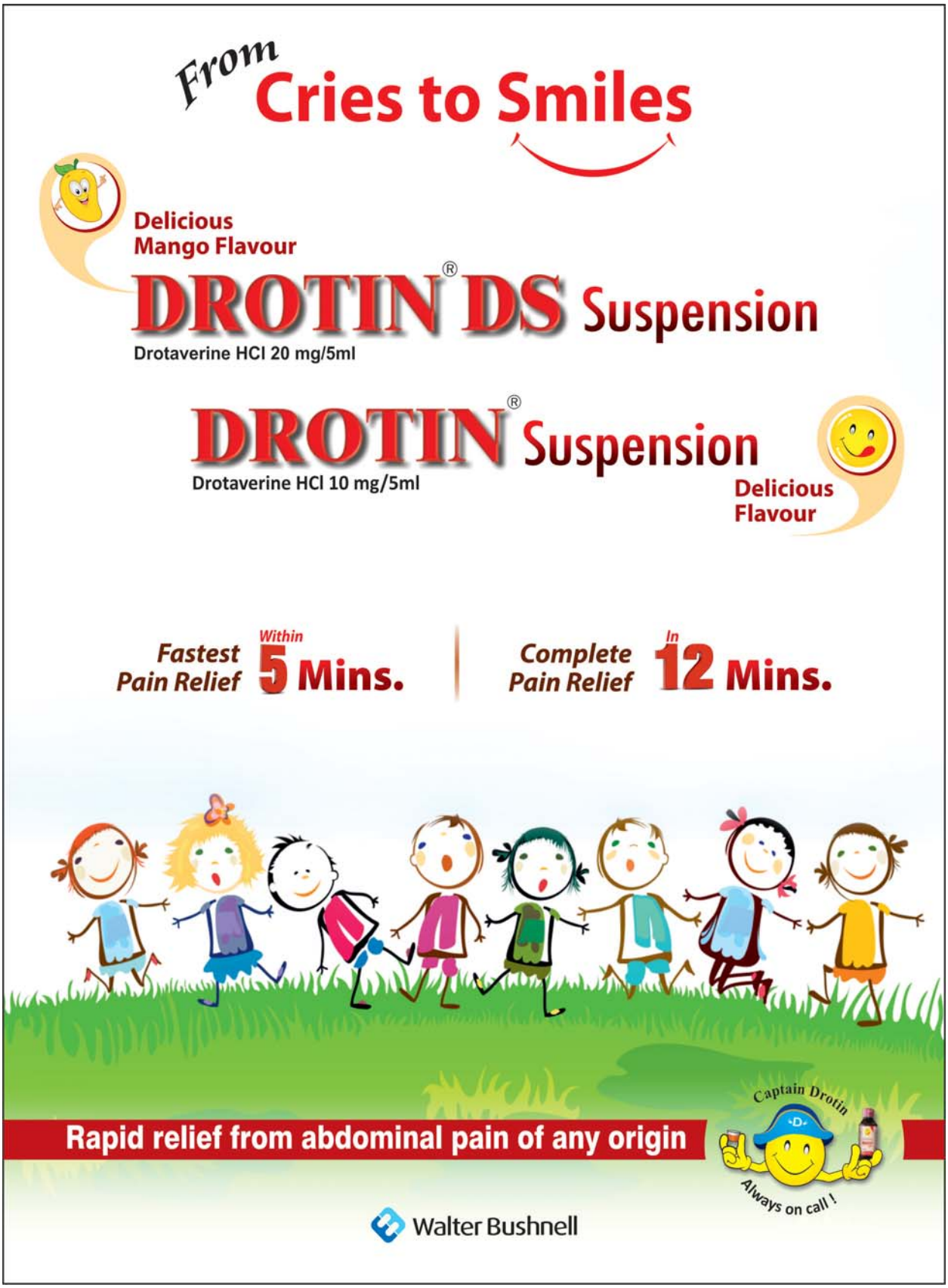
The hospital in1929.

The hospital in 2019.

Aerial View of BJWHC.

Dr. SM Merchant

Legends of Bai Jerbai Wadia Hospital for Children – 15 February, 2018.


From Cries to Smiles
Delicious Mango Flavour
DROTIN® DS Suspension
Drotaverine HCl 20 mg/5ml
DROTIN® Suspension
Drotaverine HCl 10 mg/5ml
Delicious Flavour
Fastest Pain Relief Within 5 Mins.
Complete Pain Relief In 12 Mins.
Rapid relief from abdominal pain of any origin
Captain Drotin
Always on call !
Walter Bushnell

Printed and published by Dr Devendra Mishra on behalf of Indian Academy of Pediatrics and printed at Cambridge Press, Kashmere Gate, Delhi-110006 and published at 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049. Editor: Dr Devendra Mishra