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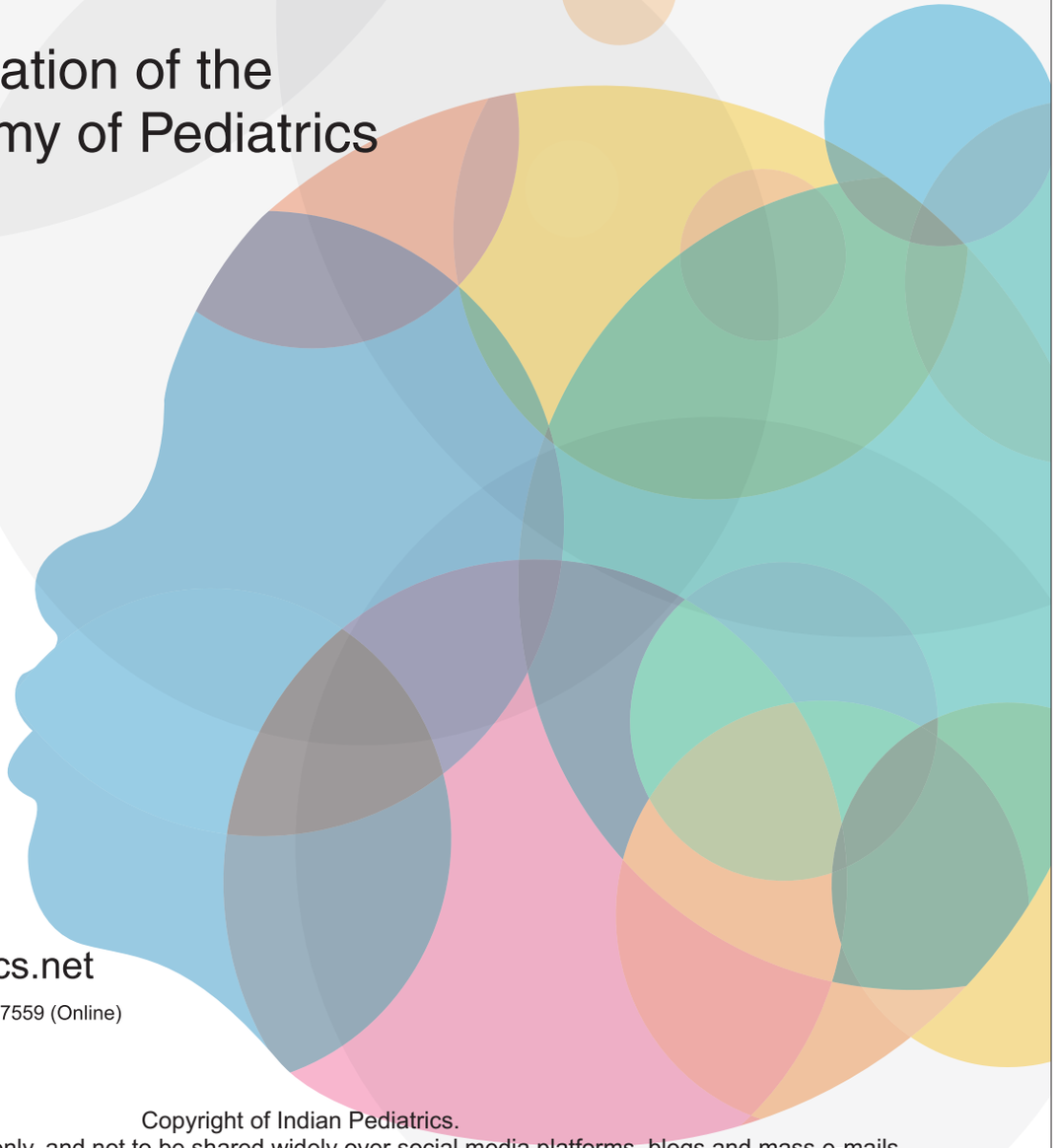

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# IAP Guidelines for pediatric skincare

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

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

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

Johnson's® CHOOSE gentle™

CLINICALLY mildness PROVEN®

## Evidence-based skincare regimen

### Cleansing regimen

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

Helps maintain the skin barrier function[5]

### Moisturizing regimen

Improves the skin barrier integrity[6,7]

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


*From birth to the first five years of life

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# Bidding Adieu to IAP Year 2022

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The year 2022 was quite exciting and invigorating, by the simple fact that the coronavirus disease (COVID) blues were quickly over, with people joyously moving out of the covid shell. And at the Indian Academy of Pediatrics (IAP) too, members regrouped with the motto "Academics with Camaraderie", and the vibe was so infectious that we had an unbelievable number of physical activities across the country this year. Our membership too has been increasing at a quick pace of around 1500 new members per year, to take us to an amazing figure of 39,000 members as on October 31, 2022.

PEDICON 2022, the National Conference of the Academy at Noida, gave IAP the much-needed confidence and belief that the epidemic has not shaken the spirit of the IAPians. Along with the flagship activities of the yester-years like NRP, NC-ECD and NTEP, the 13 new academic modules in various pediatric domains floated in the year kept the branches on their toes.

Central IAP could successfully enlist around 240 branches in this year's activities, and much more heartening was the fact that as many as 40 of them were undertaking CIAP activities for the first time. Initiating academic and community activities under the banner of Kashmir branch of IAP has been a long-awaited dream, which got materialized in November, 2022. We could successfully launch the UK branch of the Academy in July this year, and the inauguration of the Bahrain and Oman branches are round the corner.

The Standard Treatment Guidelines in Pediatric Office Practice have been reaching our members thrice every week, throughout this year. It is quite heartening to note that more than 75% of the authors for STG are young pediatricians, and we wish to see them contribute to the academic corpus of IAP in a big way in the years to come.

The year also saw IAP taking up community and charity activities at a big scale. The U5MR 25 by 2025 project, which focused on 57 high-burden aspirational districts with a under-five mortality rate of more than 50, has taken off with much zeal and enthusiasm, with the IAP District Champions passionately behind it and UNICEF and District Health administration proactively facilitating the initiative. The distribution of "Superhero Kits", with selected items conveying messages on undernutrition and anemia, was launched on Children's Day at Barabanki District in Uttar Pradesh. These kits are to be distributed to under-privileged children in 100 families each in the chosen 50 districts this year, and will be continued as a Charity Project from Central IAP, with deserving children as direct beneficiaries.

Central IAP has also been able to provide a single point access to all IAP portals through the revamped IAP website and the introduction of the PEDCARD. Self-updating of member data and profile is an important feature in the new website. The Pedcard mobile app, once installed on your home screen, can take you to any IAP site or activity with a single click. Apart from this, the Pedcard will be offering loyalty services in the near future on purchase of subscriptions to academic publications, and other products.

The regular flagship academic journals of Central IAP, *Indian Pediatrics* and *Indian Journal of Practical Pediatrics*, and the Drug Formulary continued their academic work in the year with documented increase in their reputation. My sincere gratitude to all the Office bearers and Executive Board members of 2022, and all the academy members for their unstinted support and for keeping the team inspired all through the year.

Jai IAP, Jai Hind!

INVITED COMMENTARY

# Albendazole for Neurocysticercosis in Children: How Long is Long Enough?

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The World Health Organization (WHO) recently provided guidelines for the diagnosis and treatment of viable parenchymal neuro-cysticercosis (VPN) [1]. A strong recommendation has been provided for anti-helminthic therapy for VPN, if lesions are not numerous or associated with raised intracranial pressure/hydrocephalus. This recommendation is associated with 'moderate'evidence for both cyst resolution and seizure control. For single enhancing lesions, the recommendation for anti-helminthic therapy has low evidence, and has been given a conditional recommendation by WHO. Guidelines for VPN have also been provided by the Infectious Diseases Society of America(IDSA)/ American Society of Tropical Medicine and Hygiene (ASTMH) [2]. Albendazole therapy alone for 10-14 days is recom-mended for 1-2 cysts, and combinational albendazole and praziquantel for 10-14 days for more than two cysts [2].

Recently, the Association of Child Neurology (AOCN) has also issued consensus guidelines for treatment of neurocysticercosis (NCC) in India [3]. As per these guidelines, albendazole therapy should be administered for 10-14 days for single viable lesion, and a combination of albendazole and praziquantel for 10-14 days for more than one ring-enhancing lesion.

In all these guidelines, the treatment recommen-dations for children are the same as for adults. However, extremely limited number of children have been enrolled in the randomized trials that form the evidence base for these recommendations. Moreover, the optimum duration of treatment with anti-helminthic drugs is stated as a 'research gap' in the WHO guidelines.

In face of the above information, the study by Singla, et al. [4] attempts to cover an important gap in the literature. In this open-label trial, the authors examined the efficacy of albendazole given for 14 days vs 28 days in children with newly diagnosed active NCC. The 14-days therapy was comparable to the 28-days therapy in achieving complete radiological resolution of the lesions at six months [6 (18.8%) vs 9 (27.3%); OR (95%CI) 0.61 (0.19 to 1.98); *P*=0.56]. Similar efficacy was also observed for proportion of children with seizure recurrence [5 (15.6%) vs 2 (6.1%); OR (95%CI): 2.87 (0.51-16.0); *P*=0.26] and calcification on follow-upimaging [26 (81.2%) vs 23(69.7%); OR (95%CI): 1.88 (0.59-5.99); *P*=0.39]. Several studies from India have previously attempted to assess optimal duration of anti-helminthic therapy. For 1-3 lesions, even shorter regimens of 7 days have been tried against 28 days, with comparable efficacy [5]. In a recent study by Johnson, et al. [6], 7-days regimen of albendazole vs 28-days regimen was compared for single-lesion NCC in children. Outcome measures including lesion resolution, seizure control and cognitive outcomes were found to be comparable between the two regimens.

In terms of combination therapy for NCC, for more than two cysts, combination of albendazole with prazi-quantel is given a strong recommendation by IDSA/ASTMH.The AOCN recommends combination therapy for more than one lesion. In the study by Singla, et al. [4], a small proportion of patients had more than one (2 to 3) lesions, and all were given albendazole monotherapy [4]. The role of combination therapy has been assessed in a recent study by Singh, et al. [7]. In this randomized, double blind, placebo-controlled trial, children with persistent NCC were assigned to receive either alben-dazole monotherapy, albendazole and praziquantel combination therapy, or placebo for 30 days. A higher proportion of children (62%) showed complete radio-logical lesion resolution at six months, compared to albendazole alone (26.3%) (*P*=0.02).

In the study by Singla, et al. [4], the overall rates of complete lesion resolution were very low (27.3%) compared to previous studies [5,8], with high rates of calcification (81.2%). This is an important consideration, as calcification of NCC predisposes to the recurrence of seizures. The limited recruitment sample in the study, attributable to convenience sampling, may have contri-buted to these

findings. Although seizure recurrence was comparable in the study by Singla, et al. [4], it would be interesting to observe this proportion in a longer follow-up as well as assess predisposing factors for calcification. Some of the predisposing factors that have been reported as determinants of calcification include larger size of lesions (>10 mm), presence of calcification on SWAN-MRI image [9], presence of edema, higher dose of albendazole, more than 24 months with seizures, lower dexamethasone dose, late anti-parasitic treatment, and milder antibody response [10].

Despite a lack of robust high-quality evidence, there seems to be a shift in the guidelines towards recommendation of relatively shorter duration (10-14 days) of anti-helminthic therapy for VPN. This regimen offers several advantages. Albendazole therapy for more than 14 days requires monitoring of liver function, which may be avoided with shorter regimens. Moreover, adherence is likely to be better. The study by Singla, et al. [4] adds strength to these recommendations. Several gap areas are also identified, including long-term outcomes following albendazole therapy, as well as need for retreatment, if any, of persistent active lesions. Certainly, there is urgent need for further robust, randomized trials for anti-helminthic therapy in children, addressing duration and, whether it may be further shortened, as well as for long-term outcomes including eventual seizure recurrence, cognition and quality of life-based outcomes that follow anti-helminthic therapy.

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INVITED COMMENTARY

# Complications in Transfusion-Dependent Thalassemia

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Thalassemia syndromes are one of the most common monogenetic diseases distributed worldwide. They are a group of hereditary blood disorders which result from a defect in the synthesis of either alpha or beta globin chains. Due to this defect, there is an imbalance in the ratio of alpha and beta chains resulting in ineffective erythropoiesis and a chronic hemolytic anemia. Based on the severity of the phenotype, beta-thalassemia is divided into two groups: transfusion-dependent thalassemia (TDT) and non-trans-fusion dependent thalassemia (NTDT) [1]. Although, the triad of chronic anemia, ineffective erythropoiesis and iron overload is seen in both the conditions, their clinical course and complications differ. Leg ulcers, gall stones, thrombosis and pulmonary hypertension are more common with NTDT [2]. With the advances in the understanding of pathophysiology and therapeutic modalities of beta-thalassemia, there has been a signi-ficant improvement in the management and the life expectancy of the patients with TDT. This has translated into new complications being identified that are associated with increasing age [3].

Endocrine complications are amongst the most common complications attributed to iron overload and inadequate chelation. These include hypogonadism, delayed puberty, growth retardation, hypothyroidism, hypoparathyroidism and adrenal dysfunction. In a study of 82 Malaysian patients with TDT, 65% had at least one endocrine dysfunction; short stature was the commonest problem (40.2%), followed by pubertal disorders (14.6%), hypoparathyroidism (12.3%), diabetes mellitus (5.2%) and overt hypothyroidism (4.9%) [4]. Subclinical hypothyroidism was seen in 13.4% patients. The authors suggested that early referral to endocrinologist aids timely recognition of endocrine complications which is important for optimal growth and chances of successful reproduction. Another study carried out among adole-scents with TDT revealed that normal or delayed onset of puberty with spontaneous progression was seen in 72.4% patients, while 27.6% patients had pubertal arrest or failure and were receiving hormonal replace-ment therapy (HRT) [5]. All patients on HRT had short stature. High serum ferritin was found to be significant deter-minant of delayed puberty. Low vitamin D levels and altered bone metabolism have also been observed in several studies. In a study of 32 patients on regular blood transfusion, 25(OH)D3 levels were significantly lower in older children compared to younger children. These patients also had higher ferritin levels. Authors suggested that hepatic iron overload may be associated with low 25(OH)D3 levels which may be an indicator of vitamin D deficiency and altered bone metabolism [6]. Another study on bone mineral density (BMD) in regularly transfused patients found that prevalence of suboptimal BMD was 86% at lumbar spine and 74% at femoral neck [7]. Regular monitoring of BMD and other biochemical parameters was advised in patients on regular transfusion [7]. Decreased BMD is major risk factor for the development of fractures and the prevalence increases with increasing age. Use of HRT and hypogonadism are additional risk factors [8].

This issue of the journal has two studies on the complications of TDT [9,10]. In the study by Handattu, et al. [9], children with TDT above the age of 5 years underwent comprehensive endocrine and metabolic bone disease evaluation – children older than 10 years also underwent *X*-rays of the thoracolumbar spine and dual energy *X*-ray absorptiometry (DEXA) scanning. Of the 37 patients studied, hypogonadism was found to be the commonest endocrine deficiency followed by short stature, abnormal glucose metabolism, subclinical adrenal insufficiency, hypothyroidism and hypopara-thyroidism [9]. Vitamin D insufficiency/deficiency was seen in 12 (60%) patients followed by hypocalcemia in two patients. Low bone mass and osteoporosis evidenced by vertebral fractures was also observed in four patients, all of whom had multiple endocrine deficiencies. The authors concluded that vertebral fractures can occur in the second decade of life in patients with TDT and are associated with endocrine abnormalities [9]. However, the correla-tion with any risk factors such as age, number of trans-fusions, and serum ferritin level was not assessed in the study [9].

In the second study, Kumaravel, et al. [10] have evaluated the risk of premature atherosclerosis in children with TDT. The carotid intima-media thickness (CIMT) was measured and correlated with clinical and biochemical parameters in children aged 2-15 years receiving regular blood transfusions. Significantly higher CIMT values were observed across all age groups compared to controls. Older age and higher serum ferritin values were significant risk factors for increased CIMT; dyslipidemia did not have a significant correlation with CIMT. The authors concluded that children with TDT are at increased risk of premature atherosclerosis [10]. In another study [11], 115 Egyptian children aged 5-18 years with TDT had significantly higher CIMT compared to controls. CIMT had a positive correlation with serum triglycerides. The study concluded that subclinical atherosclerosis started prematurely in children with beta thalassemia and CIMT can be used as a simple, accurate and non-invasive modality for early detection of athero-sclerosis.

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PERSPECTIVE

# Conception of National Biologics Registry for Pediatric Rheumatology: Need of the Hour and the Way Forward

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The outcome for children with rheumatic diseases has been dramatically altered by the use of biological therapies. Increasing use of these agents will need careful monitoring for long term safety, particularly in children. Current data on safety of these drugs stem exclusively from Western literature. There is clear need for a registry of all children with rheumatic diseases who are commenced on biological agents to ensure appropriate pharmacovigilance. In this perspective, we discuss the need for and the role of a biologics registry for children with rheumatic diseases in India.

**Key words:** *Biosimilar, Rheumatic diseases, Safety*.

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## Scope of Biologics in Clinical Practice

The advent of biological agents has resulted in significant improvement in management and outcomes for patient with rheumatic diseases. Biologicals are biotechnology-derived products of biological origin which can modulate our immune system. Biosimilar or similar biotherapeutic products are the products approved by regulatory agencies based on their demonstration of similarity with the original biological molecule in terms of quality, safety and efficacy [1,2]. Children with rheumatic conditions, which require long-term steroids, experience its side-effects like growth retardation. With the advent of biologicals targeting specific cytokines, steroid-free remission is increasingly becoming a reality for majority of subjects with underlying rheumatic conditions [1-3]. For instance, 60-90 % of children with JIA who failed disease control with first line conventional disease modifying anti-rheumatic drugs (*cDMARDs*) showed significant clinical response with use of biologics [4].

Ever since the approval of first biological agent infliximab, an anti-TNF agent, for rheumatoid arthritis, there has been an exponential growth of biologicals and biosimilar agents for management of many rheumatic disorders [3,5], as well as other conditions such as inflammatory bowel disease, psoriasis etc. [6,7]. More recently, biologics (IL-1, IL-6 antagonists) are being used for curtailing the hyper-inflammatory state due to COVID-19 infection both in adults and children [8].

## Challenges in the Use of Biologics and A Ray of Hope

The original biological molecules are cost prohibitive, particularly in low- and middle-income countries (LMICs). Subsequent to expiry of patents for original biological molecules, various economical biosimilar agents have emerged. In India, guidelines on biosimilar is in existence since 2012, and many of the biologicals and biosimilar agents are gradually coming under the ambit of reimbursement schemes funded by central and state governments [2]. Another potential development in this regard is the discovery of small molecules such as Janus kinase (JAK) inhibitors. The annual cost of generic tofacitinib for a 40 kg child in India currently is approximately INR 1300-1500/month, compared with INR 250000 for adalimumab [9]. JAK inhibitors have the advantage of oral administration, which is particularly important for children.

## Advantages of Registries: Slating the Ground Realities

Even though the efficacy of biological agents has been proven in well-designed randomized controlled trials (RCTs), the results of these trials reflect outcome in controlled study settings, within a limited time frame, thereby restricting their generalizability and their ability to detect rare adverse events. Unlike RCTs, registries have the potential to record the long-term outcomes of these drugs as well as data regarding drug survival, cost

**Box I Key Observations From Pediatric Biologic Registries**

*German Registry for Biologics in Pediatric Rheumatology (BiKeR registry)* [18,22-24]

- Use of TNF, IL-1 or IL-6 inhibitors is associated with increased risk of infections.
- Cytopenias and hepatic events were associated with tocilizumab and canakinumab.
- No increased risk for malignancies, uveitis or other autoimmune disorders except inflammatory bowel disease.

*Childhood Arthritis and Rheumatology Research Alliance (CARRA registry)* [19]

- Use of TNFi was associated with increased risk of psoriasis.

*Pharmachild registry* [25]

- Observed significant number of opportunistic infections in JIA patients on immunosuppressive therapy.

*British Society for Pediatric and adolescent Rheumatologists (BSPAR), BiKeR and Pharmachild registry* [26]

- Comorbidities like varicella, tuberculosis and uveitis were reported.

*TNF; tumor necrosis factor, IL; interleukin, TNFi; tumor necrosis factor inhibitor.*

implications, immunogenic events and barriers to the use of these agents in real-life settings over many decades [6,10]. For monitoring the pattern of adverse effects of biologics, various biological registries are operational in UK, Europe and America e.g., German registry for biologics in pediatric rheumatology (BiKeR), Italian Lombardy rheumatology network (LORHEN) registry, Danish DANBIO registry, Spanish BIOBADASER registry and British Society of Rheumatology Biologics Register (BSRBR) [6,11-13]. The key observations from some of the major pediatric registries, which bear a clinical implication on day-to-day practice, are summarized in **Box I**.

## Indian Scenario

It is unfortunate that such biologic registries are not in existence in LMIC settings like ours, despite widespread availability and use of these agents. Isha, et al. [14], in a case series of 11 subjects, demonstrated the efficacy of biologics in JIA; however, the study was not designed to capture long term safety signals with use of biologics. The increased risk of infection, particularly reactivation of latent tuberculosis, is a major concern with use of TNF inhibitors in endemic regions like India, with data from adult population having demonstrated an approximately four-fold increase in tuberculosis in those exposed to anti-TNF compared with TNF naïve subjects with rheumatoid arthritis [15]. In the authors' own experience, the reactivation of latent tuberculosis with anti-TNF may have fatal complications [16]. The high background rate of tropical infections and latent tuberculosis [17], coupled with other challenges like unregulated prescription practices and variable follow up, demands for a biological registry in our country. Setting up a biological registry would not only help in capturing the outcome and safety of biological agents in the long-term, but also can be used for cost analysis, evaluating the barrier to compliance and thus would prove pivotal in framing guidelines for judicious use of these agents in resource limited settings.

Though setting up a pediatric biologic registry in LMIC settings would offer numerous advantages as highlighted above, its inception and maintenance foresees challenges such as funds, manpower and inter-institutional coordination. Registries such as BiKeR [18], Pharmachild [19], CARRA [20] are funded by industry and supported by non-governmental organizations and the government. In our setting, reciprocating the model of industry-academia collaboration seems a viable option, wherein the registries would be funded by industry, while the data acquisition, interpretation and reporting would be led by academic institutions. The Government can help by ensuring industry is required to do this as part of their pharmacovigilance.

Despite the challenges, it seems appropriate to consider a biologic registry in our settings. In an ideal world there should be a national registry for all patients on biologicals across all specialties. We believe that pediatric rheumatology specific registry could be the start, which in time might expand to include children across all specialties that are commenced on novel therapies such as biologics or small molecules. However, to be pragmatic, we propose to conceive a biologic registry for pediatric rheumatology, and the experience from this would gradually take it further to broader spectrum as above.

*Contributors*: NKB, AVR: concept and design; NKB: literature review and compiled the initial draft; SK,AVR: reviewed the draft for intellectual inputs. All authors contributed and approved the final version of the manuscript.
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RESEARCH PAPER

# Fourteen Days vs 28 Days of Albendazole Therapy for Neurocysticercosis in Children: *An Open Label Randomized Controlled Trial*

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**Background**: There is a paucity of literature to support 14-days albendazole therapy for neurocysticercosis (NCC).

**Objective**: To compare the efficacy of 14-day and 28-day albendazole therapy in the management of children with newly diagnosed active NCC.

**Study design**: Open-labelled randomized controlled trial

**Participants***:* Children aged 1-14 years with newly diagnosed active neurocysticercosis.

**Intervention**: Albendazole (15 mg/kg/day) for either 14 days or 28 days.

**Outcome**: The primary outcome measure was proportion of children with radiological resolution of active lesion at 6-month follow up. Secondary outcome measures were proportion of children with seizure recurrence, duration to seizure recurrence and calcification on follow up imaging.

**Results:** 65 children with newly diagnosed NCC were randomized to receive albendazole therapy for 14 days (*n*=32) or 28 days (*n*=33). The proportion of children with complete resolution was comparable between the two groups [6 (18.8%) vs. 9 (27.3%); OR (95%CI):0.61 (0.19 to 1.98); *P*=0.56]. Similarly, proportion of children with seizure recurrence [5(15.6%) vs 2(6.1%); OR (95%CI): 2.87(0.51-16.0); *P*=0.26] and proportion of children with calcification on follow-up imaging [26(81.2%) vs 23(69.7%); OR (95%CI): 1.88 (0.59-5.99); *P*=0.39] were also comparable. There were no major side-effects noted during the study.

**Conclusion:** 14-day treatment with albendazole therapy is as effective as 28-day treatment in achieving radiological resolution at six-month follow up. However, high rate of calcification in both the groups indicates need for further evaluation with an adequately powered study and longer follow up

**Keywords**: Duration, Seizure recurrence, Calcification.

***Trial registration*:** CTRI/2020/03/023792

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Neurocysticercosis (NCC) is a common parasitic infestation of the central nervous system and is possibly the most common risk factor for acquired epilepsy worldwide [1]. Antiparasitic treatment with albendazole increases the radiological clearance and is known to reduce the recurrence of seizures [2,3]. There is wide heterogeneity in clinical practice regarding the duration of albendazole treatment ranging from 7 days, 14 days to 28 days for single and/or multiple NCC. In a study by Johnson, et al. [4], it was observed that long term clinical, radiological, and cognitive outcome in children with single neurocysti-cercosis was comparable among those who received 7-days and 28-days of albendazole therapy. The limited number of adult and pediatric studies on 14-days duration of albendazole therapy have revealed 69-95% resolution of radiological lesion at 6-month follow up [5-7].

In a recent consensus statement of Association of Child Neurology (AOCN) [8], 10-14 days of albendazole therapy is recommended for management of single viable NCC and combination of albendazole with praziquantel for more than one lesion. Further, the AOCN guideline clearly mentions that the quality of evidence is strong for use of albendazole therapy for management of NCC, but not for the duration of therapy. Considering the paucity of data on short-term efficacy of 14-days albendazole therapy, the present study was conducted to compare the efficacy of 14-days vs 28-days course of albendazole therapy in children with newly diagnosed active neurocysticercosis.

*Invited Commentary: Pages 908-9.*

## METHODS

This open-labeled, randomized controlled trial was conducted from February 2020 to March 2021, in the Department of Pediatrics, Neurology and Biochemistry of a tertiary care, referral center of India. Ethics approval was obtained from the Institutional Ethics Committee. The trial was registered in the Clinical Trial Registry of India (CTRI). After taking written informed consent from the parents,

consecutive children aged 1-14 years, newly diagnosed with active neurocysticercosis were enrolled. Neurocysticercosis was diagnosed based on Revised Del Brutto criteria for Neurocysticercosis [9]. The lesion was considered to be NCC when either scolex was demonstrable, or the lesion was thin walled, cystic, less than 2 cm, in typical location of grey matter and white matter junction or basal ganglia [8]. The lesion was considered active when MRI demonstrated T2 hyperintensity in the core of the lesion. Children who had received albendazole or diagnosed with neurocysti-cercosis in the preceding three months, those with intellectual disability, recognized progressive neurological illness, renal, pulmonary, cardiac, or hepatic dysfunction, were excluded from the study.

A detailed history, including demographic details, type and duration of seizure, dietary pattern, perinatal details, family history, developmental status and treatment particulars, was taken. Examination was done according to a pre-designed proforma. Imaging details including number and location of NCC with or without presence of perilesional edema were also recorded.

Block randomization was done using variable block size of 2, 4 and 6 using computer-generated random number tables in two groups: Albendazole (15 mg/kg/day in two divided doses; maximum daily dose being 800 mg) for 14 days and 28 days. Sequentially numbered, opaque, sealed envelopes containing group codes were prepared. Envelop was opened at the time of randomization, and the patient was allocated to their respective group. Children of both groups received short course of oral dexamethasone (0.6 mg/kg/day) for 5-7 days, which was commenced two days prior to albendazole therapy and continued for 3-5 days after starting albendazole. Any of the antiepileptic drugs - phenytoin, carbamazepine or valproate was continued for seizure prophylaxis, as per the treating unit protocol.

All children were followed up for a minimum duration of 6 months. At the end of six-month study period, a repeat MRI Brain/CECT head was performed. Lesion on follow up MRI was classified as complete resolution (no residual lesion), calcified lesion (presence of blooming on GRE images) and resolution of active lesion (when T2 hyperintense core in the lesion has become isointense or hypointense). The primary outcome of the study was proportion of children with resolution of active lesion and secondary outcome was proportion of children with seizure recurrence and duration to seizure recurrence. Parent reported adverse effects were recorded.

Assuming that proportion of children with resolution of NCC lesions at 6 months with 14 days therapy would be 68% and 79% with 28 days therapy of albendazole [5,10], taking a power of 80%, alpha error of 5% and 0.3 as the margin on risk difference under two tailed test, sample size of 73 in each group was computed, However, owing to logistic constraints, a convenience sample size was adopted.

*Statistical analysis:* All data collected were entered in Microsoft Excel (MS Excel). Data were analyzed using SPSS 21.0 version. Intention-to-treat analysis was done. Proportion of children with resolution of active lesion and those with seizure recurrence were compared using Chi-square test or the Fischer exact test. Time to seizure recurrence were compared using the student '*t*' test or Wilcoxon rank sum test. A *P* value of <0.05 was considered significant.

## RESULTS

A total of 65 children were enrolled (**Fig. 1**). The baseline demographic, clinical and radiological characteristics of enrolled children in both the groups were comparable. (**Table I**) The proportion of children with complete resolution, seizure recurrence and calcification on follow-up neuroimaging, were comparable between the groups. However, the mean (SD) duration to seizure recurrence was significantly longer with 14-day treatment [46.4 (7.9) days] as compared to 28 days treatment [22.5 (14.9) days]; (*P*=0.03) (**Table II**). There were no reported clinical adverse events in both the groups. Predictors for calcification of lesion like age, duration of albendazole therapy and number

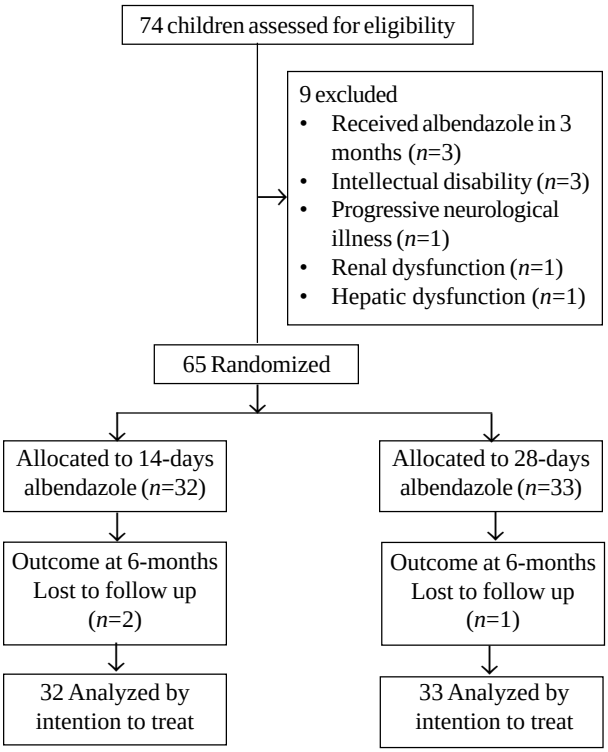


**Fig. 1** Study flow chart.

**Table I Characteristics of Children With Neurocysticercosis Treated With Two Albendazole Regimens (*N*= 65)**

| *Characteristics* | *14-days group (n=32)* | *28-days group (n=33)* |
|---|---|---|
| Age[a] | 8 (6.5, 11) | 7 (4, 10) |
| Male gender | 21 (65.6) | 19 (57.6) |
| *Type of seizure* | | |
| Primary generalized | 10 (31.2) | 7 (21.2) |
| Focal with awareness | 16 (50) | 22 (66.7) |
| Secondary generalized | 5 (15.6) | 2 (6.1) |
| Focal without awareness | 1 (3.1) | 2 (6.1) |
| Seizure duration (min)[a] | 8 (4.7, 18.5) | 10 (5, 20) |
| Seizure frequency[a,b] | 1 (1, 1) | 2 (1, 3) |
| Seizure-therapy interval (d)[a,c] | 7.5 (3, 26) | 13 (2, 144) |
| *Predominant lobe involved* | | |
| Frontal | 10 (31.3) | 6 (18.2) |
| Parietal | 17 (53.1) | 23 (69.7) |
| Occipital | 2 (6.3) | 1 (3) |
| Temporal | 3 (9) | 3 (9.1) |
| *Number of lesion*[d] | | |
| One | 26 (81.2) | 28 (84.8) |
| Two | 5 (15.6) | 4 (15.1) |
| *Anti-seizure medication* | | |
| Phenytoin | 16 (50) | 19 (57.6) |
| Valproate | 13 (39.6) | 10 (30.2) |
| Carbamazepine | 3 (9.4) | 2 (6.1) |
| Levetriacetam | 0 | 2 (6.1) |

*Values are expressed as no. (%) or [a]median (IQR). All P>0.05. [b]before therapy; [c]Interval between seizure and initiation of therapy; [d]three lesions in 1 child in each group.*

of lesions, were assessed by logistic regression analysis for possible association. None of these variables could independently predict the development of calcification.

## DISCUSSION

This randomized controlled trial revealed comparable rates of complete resolution of lesion and proportion of children developing calcification between children receiving 14-days and those receiving 28-days of albendazole therapy. We found that that only 18.7% (*n*=6) children in 14-days treatment group and 27.3% (*n*=9) in 28-days treatment group had complete resolution of the lesion, while all the remaining children developed calcification of lesion at 6-month follow up.

Traditionally, neurocysticercosis has been treated with 28 days of albendazole therapy and many of the studies have demonstrated 31-91% resolution of lesion at 6 months [11-13]. The few studies that have looked for resolution of lesion at 3-4 months have demonstrated 75-91% of resolution [6,14]. Type of neuroimaging (MRI or CT), and timing of neuroimaging plays a crucial role in deciding the resolution of lesion. In a study by Singhi, et al. [15], 42% and 39% of patients had resolution at 1 month follow up and 77% and 79% at 3 months follow up, when treated with 1 week and 4 weeks of albendazole, respectively. Complete resolution of lesion with 28-day albendazole therapy was seen in 27.3% in our study as compared to 75-91% resolution seen in previous Indian studies, at 3-6 months follow up [11,12,15]. In contrast, majority of our patients had calcification of the lesion rather than complete reso-lution. Presence of one or more than one active NCC lesion, presence of perilesional edema, time lag between clinical presentation and treatment initiation could be some of possible factors for lower rates of resolution and higher rates of calcification in the present study. Variable period of follow-up and variation in the choice of neuroimaging in previous studies could possibly contribute to this wide discrepancy.

In a study by Kaur, et al. [16], incidence of seizure recurrence was 9.6% and 3.4% at 6-month follow up in 7-day and 28-day albendazole group, respectively. Though, seizure recurrence in our study was comparable to previous studies, long term follow up would have answered the risk of epilepsy, especially with three-fourth of the lesions calcifying.

Calcified neurocysticercosis has an important role in pathogenesis of seizure and resulting morbidity in neurocysticercosis. In a study from Peru, 220 patients with parenchymal neurocysticercosis from three randomized controlled trials were assessed and it was observed that 38% of these patients had calcification of lesion [17]. They observed that predictors of calcification included those where the cyst size is larger than 14mm, cysts with perilesional edema, patient with seizure recurrence beyond 24 months, and those who received higher dose of

**Table II Outcome Among Enrolled Patients in 14-Days and 28-Days Albendazole Treatment Arms (*N*=65)**

| *Outcome measure* | *14-days group (n=32)* | *28-days group (n=33)* | *OR (95% CI)* | *P value* |
|---|---|---|---|---|
| Complete resolution | 6 (18.8) | 9 (27.3) | 0.61 (0.19-1.98) | 0.56 |
| Seizure recurrence | 5 (15.6) | 2 (6.1) | 2.87 (0.51-16.0) | 0.18 |
| Time to seizure recurrence (d)[a] | 46.4 (7.9) | 22.5 (14.9) | – | 0.03 |
| Calcification | 26 (81.2) | 23 (69.7) | 1.88 (0.59-5.99) | 0.39 |

*Values are expressed as no. (%) or [a]mean (SD).*

**WHAT IS ALREADY KNOWN?**

- There is robust evidence for albendazole therapy in neurocysticercosis but not on the duration of therapy.

**WHAT THIS STUDY ADDS?**

- 14-day treatment with albendazole is as effective as 28-day treatment in achieving radiological resolution at six-month follow up.

albendazole regimen. In the present study, rates of calcification were comparable between the two groups and none of the variables predicted the rates of calcification.

Limitations of the study include small sample size, underpowered owing to convenience sampling. Other limitations include unmasked inter-ventions, lack of serial scans at one-to-three month interval, non-measurement of size of neurocysticercosis lesion, and recording only parent reported adverse effect profile with no laboratory monitoring. A longer follow-up, beyond 6 months could have predicted the risk of seizure recurrences.

Fourteen-day albendazole therapy was found to be safe and effective therapeutic option among children with three or less than three lesions with proportion of children achieving resolution of lesion, being comparable to those receiving 28 days therapy. These preliminary findings may support the existing revised guidelines advocating 14 days treatment for single active neurocysticercosis. However, high rate of calcification noted in the present study in both the groups indicates need for further evaluation with an adequately powered study and long-term follow-up, before 14-day albendazole treatment can replace 28-day albendazole treatment of neurocysticercosis in children.

*Ethics clearance*: An institutional ethical approval was obtained before the commencement of the study.
*Contributors*: JSK, NDV, SL, SD: concept and design of the study; AS, NDV, JSK: drafting the manuscript and review of literature; JSK, SD, SL: critical review of the manuscript for intellectual content and final approval of the version to be published. All authors approve of the final version.
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RESEARCH PAPER

# Metabolic Bone Disease in Children With Transfusion-Dependent Thalassemia

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**Objective:** This study aimed to detect metabolic bone disease and endocrinopathies in a cohort of patients with transfusion-dependent thalassemia (TDT). **Methods:** This prospective study was conducted between March 2020 - August 2021. Children with TDT older than 5 years, receiving regular blood transfusion, underwent comprehensive endocrine and metabolic bone disease evaluation, which included screening for short stature, delayed puberty, diabetes mellitus, hypothyroidism, adrenal insufficiency and hypoparathyroidism. Children older than 10 years also underwent. *X*-ray of thoracolumbar spine, and dual energy *X*-ray absorptiometry (DXA) scanning. **Results:** Out of 37 patients (19 males), with mean (SD) age 15 (6) years, hypogonadism was the commonest endocrine deficiency seen in 15 (62%), followed by short stature, abnormal glucose metabolism, subclinical adrenal insufficiency, hypothyroidism, and hypoparathyroidism. Vitamin D insufficiency/deficiency was seen in 12 (60%) and hypocalcemia in 2 patients. Low bone mass was seen in 8, and osteoporosis, as evidenced by vertebral fractures, in 4 patients. Of the four patients with vertebral fracture, three were aged ≤18 years, one was symptomatic, two each had grade 1 and grade 2 fractures, one had multiple vertebral fractures, and all four had hypogonadism and multiple endocrine deficiencies. **Conclusion:** Vertebral fractures occur even in the second decade among patients with TDT, and are often associated with endocrinopathies, most commonly hypogonadism. Early screening and prevention of vertebral fractures is necessary.

**Keywords:** *Bone density, Endocrinopathies, Fracture, Vertebra, Vitamin D deficiency.*

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Chronic endocrinopathies are one of the commonest comorbidities reported in patients with transfusion-dependent thalassemia (TDT), especially with increasing age. Metabolic bone disease (MBD) is also a major health concern in this group of patients [1,2], with a much higher rate of traumatic and non-traumatic fractures [3,4]. This is due to several factors, many of them preventable, including vitamin D deficiency, inadequate physical activity, and endocrinopathies [1]. While several studies from India have examined other endocrine deficiencies in thalassemia, less attention has been paid to bone health. Prevention is often neglected because of lack of awareness and lack of facilities to test. We undertook this study to examine the burden of poor bone health in our population, and whether the current guidelines for age at complication screening are sufficient.

## METHODS

This study was conducted in the Department of Paediatrics, Kasturba Medical College, Manipal, from March, 2020 to August, 2021. Thirty-seven patients, aged more than five years with TDT, who were on regular transfusion were included in the study. Clearance from institutional ethics committee and consent and/ or assent, as applicable, were obtained before recruitment. During admission for blood transfusion, these patients underwent evaluation for underlying endocrine and metabolic bone disease. This included detailed history, and physical examination, particularly looking into growth and puberty.

*Invited Commentary: Pages 910-11.*

The height, weight, and body mass index (BMI) of all participants were measured by standard techniques and were interpreted against Indian standards [5]. All patients underwent screening for underlying delayed puberty, diabetes mellitus, hypothyroidism, adrenal insufficiency, and hypoparathyroidism. Twenty patients, older than 10 years, also underwent screening for metabolic bone disease, which included serum 25(OH) vitamin D, *X*-ray thoraco-lumbar spine, dual energy *X*-ray absorptiometry (DXA) scan of lumbar spine.

Short stature was defined as height <-2SDS (standard deviation score) [1]. Girls with breast stage 1 after 13 years of age, or boys with testicular volume <4 mL after 14 years of age were diagnosed to have delayed puberty. Among children who are already into puberty, failure to progress to the next Tanner stage in 6 months was labelled as arrested puberty. Patients without any sign of puberty beyond 16 years were diagnosed to have hypogonadism [1]. For this report, we used hypogonadism as an umbrella term to represent delayed/arrested puberty and hypogonadism, as all these entities represent the same pathophysiological processes at various ages. Diagnoses of impaired glucose tolerance, impaired fasting glucose, diabetes mellitus, hypothyroidism, adrenal insufficiency, hypoparathyroidism, and vitamin D deficiency were made as per standard guidelines [6-8].

Lateral *X*-ray of the thoracolumbar spine was taken in patients older than 10 years. Anterior, middle and posterior heights of the vertebral bodies from T6-L4 were measured, and whenever the vertebral height ratio was <0.8, a diagnosis of vertebral fracture was entertained, as per Genant semi-quantitative method [9,10]. DXA scan of the lumbar spine was done in the same patients, using the Hologic Horizon W (S/N303088M) machine, and BMD was interpreted as per International Society for Clinical Densitometry (ISCD 2019) criteria, after adjusting for height [11].

Hormonal assays were performed using commercially available electrochemiluminescence immunoassay (ECLIA) kits, while calcium, phosphorous, alkaline phosphatase were tested by spectrophotometric methods and plasma glucose by hexokinase method.

*Statistical analysis*: EZR software version 3.2 *(http://cran.r-project.org/web/packages/Rcmdr/index.html)* was used for checking normality of data and data analysis.

**Table I Baseline Characteristics of Children With Transfusion-Dependent Thalassemia (*N*=37)**

| *Parameter* | *Value* |
|---|---|
| Age at enrollment (y) | 15 (6) |
| Male[a] | 19 (51) |
| Weight SDS | -1.66 (0.94) |
| Height SDS | -1.28 (1.35) |
| Body mass index SDS | -1.28 (0.84) |
| Pre-transfusion hemoglobin (g/dL) | 7.05 (0.95) |
| Transfusion index (mL/kg/y) | 137 (34.97) |
| Deferasirox dose (mg/kg/d) | 15.68 (9.1) |
| Serum ferritin (ng/mL)[b] | 2000 (1010, 3237) |
| <2000[a] | 17 (45) |

*All values in mean (SD), [a]no. (%) or [b]median (IQR). SDS – standard deviation score.*

## RESULTS

The baseline characteristics of participants (*n*=37) are described in **Table I**. Data of metabolic bone disorder (patients older than 10 years, *n*=20) and endocrinopathies (*n*=37) are given in **Table II**. Backache and bone pain was seen in one patient, and low vitamin D (insufficiency/deficiency) was noted in 12 (60%) patients; two of these had hypocalcemia and one had hypoparathyroidism. Lateral thoracolumbar *X*-ray revealed the presence of vertebral fracture (3 biconcave, 1 crush) in four (20%) patients, two each had grade 1 and 2 fractures. None of the patients with vertebral fractures had a history of significant trauma. Two patients who had vertebral fractures were 16-

**Table II Metabolic Bone Disease and Endocrinopathies in Children With Transfusion-Dependent Thalassemia (*N*=37)**

| *Parameter* | *Value (%)* |
|---|---|
| *Metabolic bone disease, n=20* | |
| Vitamin D status [a] | |
| Sufficient | 8 (40) |
| Insufficient | 6 (30) |
| Deficient | 6 (30) |
| Vertebral fractures | 4 (20) |
| Bone mineral density status | |
| Normal | 8 (40) |
| Low bone mass | 8 (40) |
| Osteoporosis | 4 (20) |
| *Endocrine deficiency, n=37* | |
| Hypogonadism, *n*=24 | 15 (62) |
| Male | 10 (66) |
| Short stature | 12 (32) |
| Severe short stature | 3 |
| Proportionate | 3 |
| Disproportionate | 9 |
| Abnormal glucose metabolism | 10 (27) |
| Impaired fasting glucose | 5 (50) |
| Impaired glucose tolerance | 3 (30) |
| Diabetes mellitus | 2 (20) |
| Adrenal insufficiency | 9 (25) |
| Primary | 1 |
| Secondary | 8 |
| Hypothyroidism | 5 (13) |
| Subclinical | 3 |
| Overt primary | 1 |
| Secondary | 1 |
| Hypoparathyroidism | 1 (2) |
| At least one endocrinopathy | 25 (67) |
| Multiple endocrinopathies | 13 (35) |

*[a]serum 25-OH vitamin D: sufficiency, >20ng/mL, insufficiency, 12-20ng/ mL, deficiency, <12ng/ mL.*

**WHAT THIS STUDY ADDS?**

- We report high prevalence of asymptomatic vertebral compression fractures and osteoporosis among adolescents and young adults with transfusion-dependent thalassemia.

year-old with concurrent hypogonadotropic hypogonadism, short stature and IFG. Another 18-year-old with vertebral fracture had DM, hypogonadotropic hypogonadism, and vitamin D insufficiency. A 27-year-old male with hypogonadism, hypocalcemia, hypoparathyroidism and vitamin D insufficiency had multiple biconcave fractures from L4-L5. Among those with vertebral fractures, two each had normal and low BMD *z*-scores. When BMD and vertebral fractures were analyzed together, we observed low bone mass in 8 (40%) children, and osteoporosis in the four (20%) patients who had vertebral fractures, after adjusting for age, sex and height.

Twenty-five (67%) patients had at least one endocrinopathy, and 13 (37%) had multiple deficiencies. A seven-year-old male child, the youngest to have any endocrine deficiency, had impaired fasting glucose and secondary adrenal insufficiency. A 21-year-old male had four endocrine deficiencies (short stature, hypogona-dism, diabetes mellitus, secondary adrenal insufficiency).

Hypogonadism was the commonest endocrinopathy, followed by short stature, impaired glucose metabolism, adrenal insufficiency, impaired thyroid function and hypoparathyroidism. Among the 12 (32%) participants with short stature, 9 (75%) had disproportionate short stature (short upper segment: 8, short lower segment: 1), three had vertebral compression fractures. All the 12 patients with adrenal insufficiency were asymptomatic, with the 8 AM cortisol being significantly low (<5 mcg/dL) in only three patients, and another six patients were diagnosed by a stimulation test.

## DISCUSSION

Major findings of our study are the high prevalence of vertebral fragility fractures and low BMD, and early onset and high prevalence of multiple endocrine deficiencies, especially adrenal insufficiency.

Metabolic bone disease in TDT mostly affects vertebral bodies leading to vertebra fractures. However, vertebral fractures are mostly asymptomatic, making active screening the only way for early recognition and treatment [2,10]. The reported prevalence of vertebral fractures ranges from 2-14% in the few studies available, mostly in adults [4,10]. Earlier Indian studies were mostly limited to self-reporting of long bone fractures, and BMD was reported without adjusting for height and vertebral fracture status [2,3]. Recently, a study from Pune [4], which examined 179 children with TDT, found 21% asymptomatic long bone fractures and 4.5% vertebral fractures. However, BMD, pubertal status, or the presence of other endocrinopathies, which can impact bone health, were not reported in this study.

We found the vertebral fracture prevalence (20%) to be higher than in previous reports from India. Three of the four patients were under 18 years of age, unlike previous studies. Except for one, all others with fractures were asymptomatic, reiterating the need for active screening. All four patients had multiple endocrine deficiencies including hypogonadism. In an overburdened system like our country, meeting the ideal transfusion and serum ferritin targets is difficult, thus anemia and poor chelation, with resulting morbidity, including MBD, is likely to be common. As per ISCD guidelines [11], vertebral fractures alone are sufficient to diagnose osteoporosis, in the absence of trauma or local pathology. In our situation, carefully done *X*-rays of the lumbar spine, which are possible to do across the country, can help in early screening (after age 10 years) and detection of vertebral fractures. Where BMD is feasible, it will add to the overall assessment of bone health, but should be interpreted only after correcting for height and considering fracture history. BMD can still be normal in spite of vertebral fracture, as seen in two of our patients. A diagnosis of osteoporosis on uncorrected densitometry criteria alone, in the absence of vertebral or long bone fractures may be inappropriate [11]. Vitamin D deficiency, hypogonadism, and hypothyroidism are all known to have significant deleterious effects on bone health. They all can be easily and conveniently identified and corrected without much expense. Wherever patients with thalassemia are being treated, regular clinical screening at the time of transfusions for growth and pubertal staging must be emphasized. Regular supplementation of vitamin D and timely gonadal replacement would help improve bone mineral accrual.

Another important aspect of our study is early onset and high prevalence of multiple endocrinopathies and adrenal insufficiency compared to earlier reports [13]. Subclinical adrenal insufficiency among TDT patients varies widely (0-45%) [1,14], with very limited data from India. Despite the small sample size and wide age-range, the high prevalence (25%) in our patients is intriguing, and suggests need for routine testing. The incidence of other

endocrine deficiencies in our cohort is comparable with existing literature [13]. Disproportionate short stature was common, perhaps due to vertebral compression fracture, the disease itself, or direct iron toxicity of vertebrae.

Endocrine evaluation from a young age, and comprehensive MBD screening with serum vitamin D, BMD and vertebral fracture assessment are the highlights of our study. Lack of details about dietary intake of calcium-protein, physical activity which and unavailability of growth hormone stimulation test are limitation of our study.

The high and early occurrence of asymptomatic vertebral fractures in TDT underlines the need for early screening for vertebral fractures with at least spine x-rays. Wherever, BMD is estimated, interpretation of data must take into account, height of the patient and history of fracture. The finding of vertebral fractures being usually associated with hypogonadism and other endocrine deficiencies emphasizes the urgent need for greater awareness and timely preventive strategies.

*Ethics approval*: IEC, Kasturba Medical College and Hospital, Manipal; No. 235/2020, dated March 20, 2020.
*Contributors*: KH: conceptualized the study design, prepared the manuscript; KH, SA, GS, PK, RBY, SS: recruited patients, conducted endocrine studies; PS,KH: analyzed *X*-ray of spine. All the authors contributed to the final revision and approval of the manuscript.
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## Institute of Maternal and Child Health

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RESEARCH PAPER

# Premature Atherosclerosis in Children With Transfusion-Dependent Thalassemia: A Twin-Center Cross-Sectional Study

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**Objective** To analyze the risk of premature atherosclerosis in children with transfusion-dependent thalassemia (TDT) compared to controls by measuring carotid intima-media thickness (CIMT) and correlating it with clinical and biochemical parameters. **Methods:** Case-control study among children aged 2 to 15 years. **Results:** Significantly higher CIMT values were observed across all age groups. Mean (SD) CIMT in controls were 0.27(0.07) mm, 0.39 (0.03) mm, and 0.46 (0.05) mm in 2 to 5 years, 6 to 10 years, and 11 to 15 years age groups respectively, as against 0.43 (0.08) mm, 0.55 (0.07) mm and 0.63 (0.08) mm in cases in similar age groups ($P$<0.001). Mean triglycerides and liver enzymes were significantly elevated in cases. Logistic regression analysis demonstrated that older age group and higher serum ferritin levels, but not dyslipidemia, were significantly associated with high CIMT. **Conclusion:** Children with TDT are at increased risk for premature atherosclerosis.

**Keywords:** *Complications, Ferritin, Outcome, Survival*.

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The life expectancy and quality of life of children with transfusion-dependant thalassemia (TDT) have improved in recent years. However, non-hematological complications like atherosclerosis can cause severe morbidity and mortality [1]. Many studies have demonstrated an association between abnormal serum lipid levels and increased risk of premature atherosclerosis in these children [1-3]. Studies have also demonstrated an association between iron load and increased risk of premature atherosclerosis in them [4]. The conventional diagnostic tests to confirm atherosclerosis have been angiography and stress testing. Recently, these tests have been replaced by a more convenient and accurate test – the measurement of carotid intima-media thickness (CIMT) [5]. CIMT measurement has been widely used in many studies to analyze the risk of atherosclerosis in children and adults [5-8]. But there is a paucity of similar studies in children with TDT.

As the life expectancy of these children is improving, the early diagnosis of premature atherosclerosis should be a research priority. This study was planned to analyze the risk of premature atherosclerosis in children with TDT by measuring CIMT, a marker for atherosclerosis, and correlating it with clinical and biochemical parameters.

## METHODS

This cross-sectional study was conducted in the Thalassemia care units of two public sector medical colleges in Tamil Nadu, between January, 2022 and March, 2022. Children with TDT aged 2 to 15 years, and receiving a regular transfusion regimen for more than 6 months were considered for inclusion. Children with nephrotic syndrome or familial hypercholesterolemia were excluded. Age and sex-matched healthy volunteers were recruited from the outpatient department and taken as controls. Informed consent and clearance from institutional human ethics committee were obtained from both the centers.

*Invited Commentary: Pages 910-11.*

Baseline data of participants including age, sex, height, weight, body mass index (BMI), blood pressure (BP), and iron chelation history were recorded. Based on the BP, children were classified as normotensive, pre-hypertensive, or hypertensive [9]. Complete blood counts (CBC), lipid profile, C-reactive protein (CRP), serum ferritin, liver enzymes, and fasting blood sugar were estimated at enrolment. The common carotid arteries were analyzed for intima-media thickness at 1cm segment proximal to its bifurcation and expressed in millimeters using electronic calipers. CIMT was defined as the distance from the junction of the lumen and intima to the junction of media and adventitia [5]. The CIMT measurements were done using a Mind ray duplex ultrasound system with a linear array high-frequency transducer at 7.5 MHz scanning frequency in B mode by a trained radiologist who performed measurements in both the centers.

The sample size was estimated using nMaster software. In the study by Jindal, et al. [10] the reported mean difference of CIMT value between cases and control was 0.106 (0.058-0.153). Using pooled standard deviation of 0.09, with a least possible difference 0.058 for CIMT values between groups and to achieve a power of 80% at a level of significance of 5% (two sided), the required minimum sample size was 40 in each group. However, all eligible children were included in the study.

*Statistical analysis*: Data were analyzed using the R software. To study the association of clinical parameters between the groups, an independent sample *t* test or Mann-Whitney *U* test was applied for the continuous measurements, after checking the normality assumption. Chi-square test was applied for the categorical observations based on the expected frequency. Univariate and multiple linear regression analyses were carried out to examine the predictors of CIMT among cases. *P* value was considered significant at 5% level of significance.

**Table I General Characteristics of the Study Groups**

| *Parameters* | *Children without thalassemia (n=49)* | *Children with thalassemia (n=49)* |
|---|---|---|
| Age (y)[a] | 6.38 (3.65) | 6.38 (3.65) |
| Male gender | 20 (41) | 20 (41) |
| *Anthropometry* | | |
| Thinness | 2 (4) | 5 (10) |
| Normal | 41 (84) | 42 (86) |
| Overweight/obese | 6 (12) | 2 (4) |
| Pre hypertension | 0 | 2 (4) |
| *Laboratory values* | | |
| CRP (mg/L)[b] | 0.6 (0.2,1.2) | 2.1 (0.3,3.1) |
| WBC count ($X10^9$/L)[b,c] | 6.7 (6.2,9.2) | 9.2 (7.6,12) |
| SGOT (U/L)[a,c] | 24 (5.68) | 44.4 (12.39) |
| SGPT (U/L)[a,c] | 28.8 (6.9) | 45.7 (11.3) |
| SAP (U/L)[a,c] | 118.7 (37.0) | 190.6 (42.6) |
| Total cholesterol (mg/dL)[a,c] | 128.8 (15.8) | 90.5 (13.9) |
| HDL (mg/dL)[a,c] | 41.6 (7.6) | 25.4 (9.2) |
| LDL (mg/dL)[a,c] | 84.5 (6.6) | 71.2 (10.7) |
| Triglyceride (mg/dL)[a,c] | 84.3 (20.4) | 225.2 (59.9) |
| *Serum ferritin level (ng/mL)[a]* | | |
| 2-5 y | 83.7 (29.36) | 3740.2 (2120.96) |
| 6-10 y | 106.7 (55.87) | 5180.4 (3071.43) |
| 11-15 y | 87.8 (35.95) | 4222.6 (4467.93) |
| Overall | 91.7 (41.02) | 4316.8 (3072.47) |
| *Carotid intima-media thickness (mm)[a]* | | |
| 2-5 y[c] | 0.27 (0.07) | 0.43 (0.08) |
| 6-10 y[c] | 0.39 (0.03) | 0.55 (0.07) |
| 11-15 y[c] | 0.46 (0.05) | 0.63 (0.08) |
| Overall[c] | 0.35 (0.09) | 0.51 (0.11) |

*Values in no. (%), [a]mean (SD) or [b]median (IQR). [c]P<0.001. CRP-C-reactive protein, WBC-white blood cell, SGOT-serum glutamic oxaloacetic transaminase; SGPT-serum glutamic oxaloacetic transaminase, SAP-serum alkaline phosphatase, HDL-high density lipoprotein, LDL-low density lipoprotein.*

## RESULTS

We studied 49 children each with and without thalassemia. No statistically significant difference was observed between the cases and the control group in terms of age, sex, BP, and BMI (**Table I**). Significant differences were observed in the mean WBC count, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and serum alkaline phosphatase (SAP) levels between the two groups. The mean serum total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were significantly lower in cases than in the controls. On the contrary, the mean triglyceride levels were significantly elevated in cases. The mean (SD) serum ferritin was 4316.8 (3072.47) ng/mL in children with TDT against 91.7 (41.02) ng/mL in controls. All cases were receiving oral iron chelation with tablet deferasirox.

The mean (SD) CIMT in the thalassemia group was significantly higher than the control group [0.51 (0.11) vs 0.35 (0.09) mm; *P*<0.001]. Significantly higher values of CIMT were observed across all age groups. Mean (SD) CIMT in the controls were 0.27 (0.07) mm, 0.39 (0.03) mm, and 0.46 (0.05) mm in 2 to 5 years, 6 to 10 years, and 11 to 15 years age groups respectively, as against 0.43 (0.08) mm, 0.55 (0.07) mm and 0.63 (0.08) mm in cases in the similar age groups (*P*<0.001). These findings demonstrate that the risk of atherosclerosis in children with TDT is evident in all age groups.

On univariate analysis, older age group and higher serum ferritin levels were significantly associated with high CIMT. The factors like BMI, pre-hypertension, CRP, and WBC count were not significantly associated. Multivariate analysis also demonstrated that the older age group and higher serum ferritin levels were found to be significantly associated (**Table II**).

**Table II Multivariate Analysis of Factors Associated With High Carotid Intima-Media Thickness in Children With Thalassemia**

| *Parameters* | *β coefficient (95% CI)* | *P value* |
|---|---|---|
| *Age group[a]* | | |
| 6-10 y | 0.07 (0.01,0.13) | 0.02 |
| 11-15 y | 0.13 (0.06,0.2) | <0.001 |
| *Serum ferritin[b]* | | |
| 5,001-10,000 ng/mL | 0.07 (0.02,0.12) | 0.01 |
| >10,000 ng/mL | 0.12 (0.04,0.21) | 0.004 |

*Reference for [a]age-group, 2-5y and for [b]serum ferritin, <5000 ng/mL.*

**WHAT THIS STUDY ADDS?**

- Children with transfusion-dependent thalassemia are at an increased risk of developing premature atherosclerosis and measurement of carotid intima-media thickness is a non-invasive tool for estimating it.

## DISCUSSION

Increased CIMT mirrors the risk of atherosclerosis and because of its ease of use; it has been extensively used. Many researchers consider high CIMT as a gold standard in the diagnosis of atherosclerosis in children [5-7]. In this study, we have included children from the 2 years of age and analyzed their risk for the development of atherosclerosis. There were significant differences in the lipid profile between the cases and the controls. The lower total cholesterol and HDL present in children with TDT in this study have been documented in many other studies [11,12]. Elevated triglyceride levels found in this study have also been documented in other studies [12]. Oxidative stress, iron overload, and deranged lipolytic activity have all been postulated to be the mechanisms of dyslipidemia in children with TDT which places these children at atherogenic risk [13,14]. Significantly higher mean serum ferritin levels were seen in children with TDT in the present study. Lack of local transport because of the prevailing coronavirus disease (COVID-19) pandemic during the study period has left many children with TDT without iron chelation for many months. There are contradicting studies that have documented a positive correlation and no correlation between high serum ferritin levels and risk for atherosclerosis in children with TDT [4,7].

In various other studies done in adults and children, the increase in CIMT in children with TDT has been well documented [2,7]. In a study by Dogan, et al. [14] (mean age 8 years), median CIMT in thalassemic patients was significantly higher (0.87 mm) than in controls (0.74 mm). In another study by Jindal, et al. [10] (mean age 7.33 years), the mean CIMT in thalassemic children was 0.69 (0.11) mm, and in controls, the CIMT was 0.51 (0.07) mm ($P$<0.001). This study has demonstrated that CIMT values are significantly higher even in younger children with TDT. Most of the studies of CIMT in patients with TDT had a higher mean age than this study [10,13,14]. To the best of our knowledge, there are no studies that have documented a significant difference in CIMT in children in the 2 to 5 years age group. Hence, it is evident that the process of atherogenesis in children with TDT starts at a very early age.

The older age group and higher serum ferritin were significantly associated with higher CIMT in regression analysis in this study. The association of serum ferritin with atherogenesis in children with TDT remains elusive, with contradicting observations as discussed earlier. This study had a few limitations. High serum ferritin levels observed in this study is a confounder in analyzing the risk of premature atherosclerosis. Prevalence of atherosclerosis could not be determined as normative values are not available for CIMT in Indian children below 10 years of age [15]. Also, due to the small sample size in this study, normative values for CIMT could not be defined. Further larger studies are needed to estimate normative values of CIMT in Indian children in all age groups, which will help in screening the children with TDT for the risk of premature atherosclerosis.

Children with TDT are at increased risk for premature atherosclerosis as evidenced by high CIMT in all age groups. Higher serum ferritin and a longer duration of disease were significantly associated with high CIMT. Measurement of CIMT in children with TDT is a convenient and non-invasive tool for estimating the risk of premature atherosclerosis.

*Ethics Clearance*: Institutional Human Ethics Committee clearance was obtained from both the centers (Center 1: GMKMC&H/4341/IEC/2019-561 dated December 29, 2021; and Center 2: EC No: 5/II/2021 dated November 05, 2021).
*Contributors*: VA, MH: involved in collection and interpretation of data; KSK: drafted and critically reviewed the manuscript; PP,BR,DS: designed the study and approved the final version; KSK: guarantor of the study and is in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the authors read and approved the final manuscript.
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RESEARCH PAPER

# Correlation of Transient Elastography With MRI T2* and Serum Ferritin Levels in Children With Transfusion-Dependent Thalassemia

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**Objectives**: We investigated the correlation of transient elastography (TE) with MRI R2* values and serum ferritin in patients with transfusion-dependent thalassemia (TDT) **Methods**: We reviewed hospital records of 59 patients with TDT aged ≥8 years without any evidence of chronic liver disease and who had fibroscan within 3 months of MRI T2*, who seen at our center between January, 2014 and December, 2019. Spearman correlation and linear regression analysis were used to evaluate the correlation between TE liver stiffness measurements and R2* MRI values and with serum ferritin. **Results**: Mean (SD) age of the subjects was 13.0 (3.1) years and body mass index was 16.6 (2.3) kg/m$^2$. Mean liver stiffness measurement, MRI T2*(3T), corresponding MRI R2*(3T), and ferritin values were 6.55 (3.10) kPa, 3.4 (4.6) milliseconds, 616.20 (383.9) Hz, and 2874.69 (1570.7) ng/mL, respectively. TE measurements correlated with MRI R2* values ($r$=0.61; $P$=*0.001*) and with serum ferritin level ($r$=0.59, $P$=0.001). **Conclusion:** TE is a reliable tool to estimate hepatic iron overload in patients with TDT.

**Keywords**: *Fibroscan, Iron overload, Liver iron, Prognosis.*

Iron overload mediated damage to various vital organs including liver, heart, and endocrine glands is the major cause of mortality and morbidity in patients with transfusion- dependent thalassemia (TDT) [1]. The liver is considered to be the first and major site of iron overload. The total body iron stores correlate well with the liver iron concentration (LIC), therefore LIC is often considered representative of overall iron overload in TDT patients [2].

Estimation of LIC by liver biopsy was previously regarded as the gold standard modality of iron overload estimation. However, being an invasive procedure and due to uneven distribution of iron, this method is now abandoned [3]. Being cheap and easily accessible, serum ferritin is the most practical method of estimation of iron overload in these patients. However, serum ferritin does not correlate with LIC, and being an acute phase reactant, gets affected by various systemic conditions such as infection, cancers, inflammatory states, and oxidative stress [4]. Presently, magnetic resonance imaging (MRI) T2* is considered as investigation of choice for iron estimation due to its high specificity and sensitivity [5]. However, MRI T2* has its own limitation like availability, affordability and also because of its poor ability to accurately ascertain very fast R2* signal decay occurring at very high overload [6]. Transient elastography (TE), a widely available, non-invasive, and relatively inexpensive tool to measure liver stiffness due to fibrosis, is emerging as a promising tool in estimating iron overload mediated liver fibrosis [7-9]. This study was conducted to evaluate the utility of TE in assessment of liver iron overload and also to correlate it with the serum ferritin, and liver MRI R2* values.

## METHODS

This was a review of hospital records at our public sector pediatric tertiary care hospital on patients evaluated between January, 2014 and December, 2019. Approval was obtained from the institutional ethics committee.

Data of TDT patients was retrieved from the hospital records. Patients aged ≥8 years with TDT and who had undergone fibroscan within three months of MRI T2* were enrolled for the study. All participants were receiving oral iron chelators regularly. At our center, monitoring of iron status is done with serum ferritin every three monthly and MRI T2* annually (starting at the age of 10 years or earlier, if persistent transaminitis and high serum ferritin).

Patients, who were hepatitis B antigen (HBsAg) positive, anti-HCV positive, human immune deficiency virus (HIV) positive or had any other chronic liver disease, were excluded. Obese children with BMI > 95th percentile for age and sex were also excluded. Any patient with any evidence of cirrhosis (imaging evidence, bilirubin >5 mg/dL, ascites, encephalo-pathy or variceal bleed), and cardiac insufficiency (which can increase venous pressure) were also excluded.

Data including anthropometry, hemoglobin, annual transfusion requirement (ATR), serum bilirubin (total and indirect), aspartate transaminase, alanine transaminase (AST, ALT), serum ferritin, hepatitis B surface antigen, anti-HCV antibody, ultrasonography of abdomen (if done), MRI T2* values, and fibroscan values were retrieved from records.

All TDT patients at our center undergo 3.0T MRI T2* (Philips Acheiva 3.0T, Philips Medical Systems) yearly. Liver iron overload was defined as mild, moderate and severe when T2* (1.5T) values (ms) were 4.5-15.4, 2.1- 4.5 and less than 2.1, respectively [10]. Corresponding R2*(1.5T) values (Hz) were 65-224, 224- 475 and more than 475, respectively.

Tissue elastography (Fibroscan 402, Echosens) was carried out by an experienced examiner in all patients (with at least 6 hours of fasting) in supine position in midaxillary line with right arm in full abduction. Median value of the 10 successful measurements fulfilling the criteria (success rate of greater than 60% and interquartile range / median ratio of <30%) were noted in kilo Pascals (kPa). Measure-ments that did not have a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software.

Serum ferritin was analyzed by chemiluminescence immunoassay (Beckman Coulter Unicel DX1\600 Serum).

*Statistical analysis*: Spearman correlation test and linear regression analysis were used to check for correlation between TE mean liver stiffness (LSM) values and R2*MRI, ferritin and LIC. Characteristics of four groups (no, mild, moderate and severe iron overload) were compared using one-way analysis of variance (ANOVA) test. Statistical significance was considered as $P$ <0.05. All analyses were done using SPSS software.

## RESULTS

Out of 102 patients with TDT (≥8 years of age), 97 were eligible for the study (3 patients who were HCV reactive and 2 patients who were HBsAg positive were excluded). Out of those 97 patients, 38 patients in whom the duration between MRI T2* and fibroscan was >3 months were also excluded from study. Finally, 59 patients (34 males) meeting the inclusion criteria were identified to participate in the study.

The mean (SD) age was 12.9 (3.1) years. The median time interval between the fibroscan and MRI T2* was 60 days (range 0-90 days). Baseline characteristics of patients are outlined in **Table I**. LSM, MRI T2*(3T), corresponding MRI R2*(3T), and serum ferritin values were 6.55 (3.1) kPa, 3.4 (4.6) milliseconds, 616.2 (383.9) Hz, 2874.7 (1570.9) ng/mL respectively (**Table I**).

Liver iron overload was defined on the basis of MRI R2* values, and was present in 96.6 % of patients. Based on MRI analysis, 8 patients (13.6 %) had mild iron overload, 10 patients (17%) had moderate iron overload, and 39 (66 %) patients had severe iron overload (**Table I**).

Mean LSM value (Kpa) was 6.55 (3.10). Using the Spearman correlation test, positive linear correlation was found between MRI R2* and LSM values by TE (correlation coefficient ($r$)=0.615; $P$=0.001) (**Fig. 1a**). We found significant correlation between serum ferritin and LSM values ($r$=0.587, $P$=0.001) (**Fig. 1b**).

Patients were stratified according to the degree of iron overload determined on the basis of MRI R2* values into four groups (**Table II**). Liver stiffness measurements (LPA) were 4.2 (0.8), 5.3 (1.3), 4.2 (1.01) and 7.5 (3.3) in patients with no, mild, moderate, and severe overload, respectively. Since the number of patients in no, mild and moderate group was very small hence correlation of LSM with the MRI T2* and ferritin values in each group could not be assessed.

## DISCUSSION

Transient elastography consists of an ultrasound transducer mounted on the axis of the vibrator, which produces vibration of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that

**Table I Baseline Characteristics of Children With Transfusion-Dependent Thalassemia Enrolled in the Study (*N*=59)**

| *Characteristics* | *Value* |
|---|---|
| Age (y) | 13.0 (3.1) |
| Body mass index | 16.6 (2.3) |
| Male sex[a] | 34 (57.6) |
| Hemoglobin (g/dL) | 9.3 (0.6) |
| Aspartate transaminase (U/L) | 53.1 (39.3) |
| Alanine transaminase (U/L) | 57.3 (52.1) |
| Annual transfusion requirement (mL/kg/y) | 136 (18) |
| Serum ferritin (ng/mL) | 2874.7 (1570.9) |
| MRI T2* liver (Hz) | 3.4 (4.6) |
| MRI R2* liver (Hz) | 616.2 (383.9) |
| Liver iron concentration (MRI T2*) | 18.9 (11.8) |
| Fibroscan (kPa) | 6.6 (3.1) |
| Cardiac MRI T2* (Hz) | 25.2 (10.7) |
| *Iron overload*[a] | |
| Mild | 8 (13.6) |
| Moderate | 10 (17) |
| Severe | 39 (66) |

*Data expressed as mean (SD) or [a]no. (%). MRI: magnetic resonance imaging.*

**Table II Profile of Iron Overload Documented by Magnetic Resonance Imaging in Children With Transfusion-Dependent Thalassemia (*N*=59)**

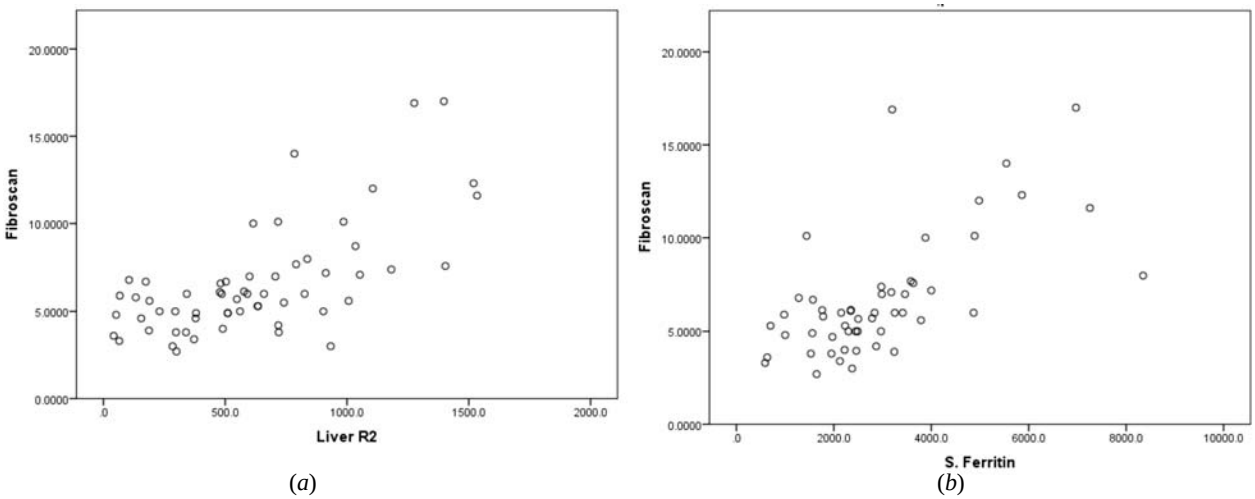
| *Parameter* | *No overload (n= 2)* | *Mild (n=8)* | *Moderate (n=10)* | *Severe (n=39)* | *P value* |
|---|---|---|---|---|---|
| Age (y) | 15.3 (2.8) | 12.8 (2.9) | 12.8 (2.5) | 12.8 (3.4) | 0.42 |
| Hemoglobin (g/dL) | 9.5 (0.6) | 9.4 (0.5) | 9.4 (0.5) | 9.3 (0.7) | 0.27 |
| Serum bilirubin, total (mg/dL) | 2.0 (1.4) | 1.1 (0.4) | 1.0 (0.4) | 1.2 (0.9) | 0.63 |
| Serum bilirubin, indirect (mg/dL) | 1.8 (0.9) | 1 (0) | 0.6 (0.6) | 0.7 (0.9) | 0.52 |
| Alanine transaminase (U/L) | 22.5 (11.4) | 23.8 (7.6) | 39.7 (29.8) | 76.1 (59.4) | 0.01 |
| Aspartate transaminase (U/L) | 27 (15.6) | 30.6 (10.5) | 41.7 (20.4) | 65.9 (45.8) | 0.02 |
| Serum ferritin (ng/mL) | 800.1 (220.1) | 1898.5 (636.9) | 2394.5 (807.0) | 3532.1 (1649.5) | 0.01 |
| MRI L2* (Hz) | 18.6 (3.9) | 5.5 (2.6) | 2.9 (0.9) | 1.3 (0.5) | <0.001 |
| MRI R2* (Hz) | 56.5 (11.7) | 255 (204.2) | 386.5 (134.2) | 854.9 (307.5) | <0.001 |
| LIC (MRI T2*) | 1.8 (0.5) | 7.8 (6.5) | 11.8 (4.5) | 26.3 (9.3) | <0.001 |
| Fibroscan (kPa) | 4.4 (1.9) | 6.1 (1.2) | 4.7 (1.3) | 7.6 (3.5) | 0.01 |
| ATR (mL/kg) | 134.8 (16.6) | 127 (11.3) | 135.6 (8.9) | 138.5 (21.5) | 0.24 |
| Body mass index (kg/m$^2$) | 17.5 (1.9) | 16.2 (2.2) | 16.2 (2.4) | 16.7 (2.4) | 0.76 |

*All values in mean (SD). MRI: magnetic resonance imaging; LIC: liver iron concentration; ATR: annual transfusion requirement.*

propagates through the liver. Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness, and is faster in fibrotic liver than normal liver [9].

Transient elastography; thus, is able to detect fibrosis and may indirectly assess the degree of iron overload. Fraquelli, et al. [8] demonstrated that TE is a reliable tool for assessing liver cirrhosis. Alavian, et al. [11], in a similar study, conducted on patients with TDT and hepatitis C, observed that fibroscan is an accurate and reliable method to diagnose liver fibrosis.

Our study showed that there is a significant correlation between TE and MRI R2* and also significant correlation between serum ferritin and TE values. Similar results have been also reported previously [7]. These authors [7] also found that TE is cheaper and more readily available than MRI, and might be used to estimate hepatic iron overload; however, they did not find any correlation between serum ferritin and LSM) values [7]. Similar results were also seen in other studies [12-14]. Atmakusuma, et al. [15], from their study on 45 patients with thalassemia intermedia from Indonesia, demonstrated that liver stiffness correlated with serum ferritin, liver MRI T2* and LIC and concluded that serum ferritin, liver MRI T2*and LIC correlated with liver elastography [15]. In contrast to our study results, no




(*a*) (*b*)

**Fig. 1** Scatter plot showing correlation between mean liver stiffness measurement values (LSM) measured by fibroscan and (*a*) MRI R2* ($r$=0.615, $P$= 0.001) and (*b*) serum ferritin ($r$=0.587, $P$= 0.001).

**WHAT THIS STUDY ADDS?**

- Transient elastography can be a useful adjunct to MRI T2* in assessment of iron overload related liver fibrosis in transfusion-dependent thalassemia.

correlation between LIC and TE war reported by Qu, et al. [16], who suggested that TE may not be sensitive enough to detect subtle changes in the hepatic parenchymal stiffness associated with liver iron deposition.

A small sample size is the major limitation of our study. We could not demonstrate a significant correlation of fibroscan values in different groups with no, mild, or moderate based on MRI T2* values as the number of patients in these different sub groups was very small. Moreover, applicability of our findings in children less than 8 years is uncertain.

We conclude that TE is a potential modality to estimate hepatic iron overload in patients with TDT.

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*Contributors*: Both authors have contributed, designed and approved the study and are accountable for all aspects related to the study.
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RESEARCH PAPER

# Comparison of Full Outline of Unresponsiveness Score and Glasgow Coma Scale for Assessment of Consciousness in Children With Acute Encephalitis Syndrome

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**Objectives:** To correlate the Full outline of unresponsiveness (FOUR) score and Glasgow coma scale (GCS) in the assessment of children with acute encephalitis syndrome (AES). **Method:** This observational study was conducted in the department of pediatrics of a public sector tertiary care center from January, 2019 to March, 2020. All consecutive patients of AES admitted during the study period ($n$=150) were recruited. Subjects were analyzed using the FOUR score and GCS on admission, and then 12-hourly till discharge/ death. Treatment-related and demographic variables were collected and analyzed. Correlation between FOUR score and GCS scores was calculated using spearman correlation coefficient. **Results:** Positive correlation was observed between the GCS score and the FOUR score ($n$=0.82; $P$<0.001). **Conclusion**: FOUR score and GCS were comparable to assess the level of consciousness in patients with AES. The possibility of using FOUR score as an alternative to GCS in children with AES needs to be considered.

**Keywords:** *Emergency department, Febrile encephalopathy, Pediatric intensive care unit*.

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Acute encephalitis syndrome (AES) is defined as "acute onset of fever, with acute change in mental condition which includes confusion, disorientation, coma, and inability to talk or new onset of seizures (excluding simple febrile seizures) in a person of any age" [1]. It is a group of clinical symptoms and signs, proposed by the World Health Organization (WHO) for surveillance purposes, to screen patients with viral encephalitis, including Japanese encephalitis.

Glasgow coma scale (GCS) was initially developed to assess consciousness after head injury [2,3]. Now, it is also used for outcome prediction in patients with stroke, as a neurosurgical prognostic indicator, and for cerebral dysfunction measurement [2-5]. Limitations of GCS are its low efficiency in intubated patients, inability to evaluate brainstem reflexes, and its poor use in case of language disorder [6-8].

The full outline of unresponsiveness (FOUR) score was developed to overcome these limitations [9]; however, its accuracy and precision have been evaluated only in a few studies [10]. This study was performed to correlate the GCS and FOUR score for assessment of consciousness in patients admitted with AES.

## METHODS

This observational study was conducted at a pediatric intensive care unit (PICU) of an academic, tertiary care center between January, 2019 to March, 2020. All patients aged five to 12 years fulfilling the WHO definition of AES, were recruited to the study after taking informed consent from their legal guardians. The study was approved by the institutional ethics committee. Children with a head injury, chronic neurological illness, known cases of epilepsy, brain tumor, or febrile seizure, and suspected metabolic disorder were excluded.

Demographic data, including age, gender, and clinical features were collected at admission to the PICU. FOUR score and GCS were evaluated by the on duty resident in each patient at the time of admission, and then 12-hourly throughout the PICU stay. The statistical analysis was performed using scores of the initial 48 hours. Patients were categorized into three groups viz., the mean GCS was classified as severe [3-8], moderate [9-12], and mild [13-15] while the mean FOUR score was divided into three groups (0-7), (8-13) and (14-16).

*Statistical analysis*: The collected data were coded and analyzed using IBM SPSS Statistics for Windows, version 21 (IBM Corp.). Chi-square test was used for analysis of the statistical difference between proportions. Spearman correlation coefficient was used to evaluate the correlation between the FOUR score and GCS. A $P$ value less than 0.05 was considered statistically significant.

## RESULTS

The study was conducted among 150 children. Baseline demographic characteristics are depicted in **Table I**. The mean (SD) age of children with AES was 8.82 (2.33) years and most children belonged to 8 to 10 years of age (47.3%). Fever (100%) was the most common presenting clinical feature followed by altered sensorium (75.3%).

The mean (SD) GCS score at the time of admission was 8.82 (2.33), and most children had a score between 8 and 12. After 12 hours, the GCS score improved in majority of children, and at the end of 48 hours, GCS was less than 8 in only four children. The mean GCS at admission amongst children, who were discharged and died, was not statistically different [9.5 (1.88) vs 9.7 (2.33); *P*=0.74]. However, the GCS at 48 hours was significantly lower in children who died than in children who recovered and were discharged [14.7 (0.49) vs 3.75 (0.50), *P*=0.001].

The mean (SD) FOUR score at admission was 11.03 (2.63) and was in the range of 8 to 14 in the majority of children. At the end of 48 hours, FOUR scores were low only in four children. At admission, the FOUR score was also comparable amongst patients who died and those who were discharged [11.12 (2.51) vs 10.3 (3.10) *P*=0.16]. The mean (SD) FOUR score was significantly lower at 48 hours in children who died than in children who recovered and were discharged [16.0 (0) vs 2.5 (0.57); *P*=0.001] **(Table II)**. A strong positive correlation was observed between GCS score and FOUR scores (r=0.82; *P*<0.001) **(Fig. 1)**.

## DISCUSSION

In this study, we observed that the FOUR score correlated well with GCS in the monitoring of consciousness among children with AES. Both FOUR scores and GCS were significantly low at 48 hours among the children who died, as compared to those who were discharged.

Fever was documented in all the children and altered sensorium was noted in 75.3% of patients. Khinchi, et al. [10] observed fever and altered sensorium in all the children with AES, seizures in 90%, and vomiting in 30% of the children. The difference in the etiology and severity of AES could be the possible reason behind these differences in both studies.

None of the previous studies have assessed the predictive value of the FOUR score in AES. We found that both GCS and FOUR scores at admission were poor predictors of outcome; however, the change in GCS and FOUR scores at subsequent time intervals were the better determinants of outcome. In our study, both GCS and FOUR scores showed a similar performance, and both tools were good at predicting the outcome in children with AES.

**Table I Baseline Characteristics of Children With Acute Encephalitis Syndrome Enrolled in the Study (*N*=150)**

| *Characteristics* | *n (%)* |
|---|---|
| Age (y) | 8.82 (2.33) |
| Male gender | 79 (52.7) |
| *Clinical features at presentation* | |
| Fever | 150 (100) |
| Altered sensorium | 113 (75.3) |
| Seizures | 54 (36.0) |
| Glasgow Coma Scale[a] | 8.82 (2.33) |
| Full Outline of Unresponsiveness Score[a] | 11.03 (2.63) |
| Discharged | 126 (84) |

*Values in no.(%) or [a]mean (SD).*

**Table II Glasgow Coma Scale Scores and Full Outline of Unresponsiveness (FOUR) Scores and Outcome in Children with Acute Encephalitis Syndrome (*N*=150)**

| *Characteristics* | *Discharged alive* | *Death during hospital stay* |
|---|---|---|
| *Glasgow coma scale scores* | | |
| At admission, *n*= 150 | 9.5 (1.88) | 9.7 (2.33) |
| 12 h after admission,[a] *n*=149 | 11.2 (2.39) | 7.8 (2.07) |
| 24 h after admission,[a] *n*=135 | 12.6 (2.85) | 5.5 (2.28) |
| 48 h after admission,[a] *n*= 126 | 14.7 (0.49) | 3.7 (0.50) |
| *Full outline of unresponsiveness scores* | | |
| At admission, *n*=150 | 11.2 (2.51) | 10.3 (3.10) |
| 12 h after admission,[a] *n*=149 | 12.1 (3.38) | 6.3 (3.31) |
| 24 h after admission,[a] *n*= 135 | 13.8 (3.65) | 4.6 (2.94) |
| 48 h after admission,[a] *n*= 126 | 16.0 (0) | 2.5 (0.57) |

*Values in mean (SD). [a]P<0.001.*

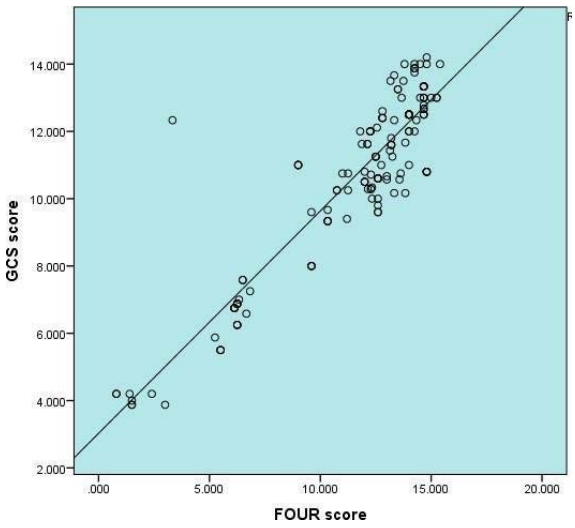


**Fig. 1** Scatterplot showing correlation of full outline of unresponsiveness score with Glasgow coma scales score ($r^2$=0.827).

**WHAT THIS STUDY ADDS?**

- Full outline of unresponsiveness (FOUR) scores correlated well with Glasgow coma scale scores in children with acute encephalitis syndrome.

However, GCS has certain disadvantages, such as the verbal component cannot be assessed in intubated patients, and it does not reflect the severity of coma. FOUR score provides information about brainstem function and respiratory drive by which severity of coma can be assessed. It is also useful in intubated patients, comatose patients, and the pediatric population as the verbal response is not a component of the FOUR score.

In our study, a strong positive correlation was observed between GCS and FOUR scores. Many previous studies also documented a similar predictive value of the GCS and FOUR scores [11-15]. McNett, et al. [13] concluded that the predictive ability of the FOUR score was comparable to GCS while assessing the functional status and cognitive outcome amongst children admitted with a traumatic injury. Stead, et al. [14] concluded that inter-rater reliability was excellent for the FOUR score in predicting the functional outcome and overall survival among children. The authors documented that the performance of the FOUR score was comparable to that of GCS; however, the FOUR score provided more neurological details that helped in the triaging and the management of these patients.

The limitations of the present study include a small sample size and limited generalizability of these results as we included only AES patients; thus, the results of this study cannot be extended to all patients admitted to PICU. We also did not calculate the inter-rater reliability of the residents for the FOUR score.

FOUR scale and GCS scores have a good correlation for the assessment of children with AES. These results, if confirmed in different settings, suggest that FOUR score may be used as an alternative to GCS while assessing the level of consciousness; especially, in children with AES.

*Ethics clearance*: Institution ethics committee, GMC, Bhopal; No. 35673-75 MC/IEC/2018, dated November 5, 2018.
*Contributors*: NM: Acquisition and interpretation of data and literature review, BM: Acquisition and interpretation, data analysis, and literature review; UP: Concept, interpretation of data and data analysis, literature review, and drafting the article; SR: Interpretation of data and data analysis, literature review and drafting the article; AA: Editing the article, literature review, and revising the article critically for important intellectual content. All the authors approved the final manuscript.
*Funding*: None; *Competing interests*: None stated.

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RESEARCH PAPER

# Abdominal Manifestations of Multisystem Inflammatory Syndrome in Children: A Single-Center Experience

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**Objectives:** We reviewed the cases of probable multisystem inflammatory syndrome in children (MIS-C) to identify those cases that mimicked surgical emergencies. **Methods:** Records of children managed for MIS-C during a 15-month period between March, 2020 and April, 2021 were retrieved. Data on clinical presentation, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR report, SARS-CoV-2 antibody status, blood investigations, radiological investigations and management were collected. **Results**: A total of 28 out of 83 children with probable MIS-C had acute abdominal symptoms and signs. Fifteen children had mild features like diffuse abdominal pain or non-bilious vomiting, and the remaining 13 (46.2%) had severe abdominal signs or bilious vomiting. Four children worsened with conservative treatment for MIS-C and were detected with perforated appendicitis. Two more children developed recurrent appendicitis on follow up. One child with appendicitis who underwent laparoscopic appendectomy, later manifested with MIS-C. **Conclusion:** Surgical abdominal emergencies may be confused with or occur concurrently in children with MIS-C that should be identified with a high index of suspicion.

**Keywords**: *Acute abdomen, Appendicitis, COVID-19, SARS-CoV-2, Surgery*.

Multisystem inflammatory syndrome in children (MIS-C) is a dreaded complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Abdominal pain can be a presenting feature of both coronavirus disease 2019 (COVID-19) and MIS-C. There exists a diagnostic dilemma in managing children with COVID-19 or MIS-C presenting with abdominal symptoms. This study aimed to identify management challenges of MIS-C mimicking surgical emergencies and delay in surgical management with probable MIS-C characteristics.

## METHODS

This study retrieved records of children hospitalized with probable MIS-C from March, 2020 to April, 2021. Institutional review board (IRB) approval was obtained for the study.

MIS-C was diagnosed as per World health Organization (WHO) criteria [1]. The abdominal symptoms were graded mild for generalized abdominal pain and non-bilious vomiting, and severe for bilious vomiting, guarding and rigidity. All the children underwent tier 1 investigations like complete blood count (CBC), renal function test (RFT), liver function test (LFT), and C-reactive protein. Other tests like SARS-CoV-2 antigen, SARS-CoV-2 IgG and IgM antibody levels, serum ferritin, D-dimer levels, blood culture, echocardiogram and coagulation profile were done as tier 2 investigations. Ultrasonography (USG) of the abdomen was done when children had severe abdominal symptoms/ signs or when they had worsening of abdominal features. Data were collected on need for surgical manage-ment; and outcome and follow up data were collected in children with severe abdominal symptom/signs.

## RESULTS

A total of 83 children were hospitalized as probable MIS-C. Twenty eight (33.7%) children had abdominal symptoms. Of these, 15 (53.6%) had mild symptoms and 13 (46.4%) had severe abdominal symptoms **Table I.**

Among 13 children with severe symptoms, dilated appendix and peri-appendicular inflammation was seen in nine children, and bowel wall edema in four children on sono-graphy. Six of these children were diagnosed with MIS-C and improved with conservative management; three of them required intravenous immunoglobulin, steroid and anticoagulant; and one child required steroid alone and two recovered with supportive care. Among those with severe symptoms, two children presented after 1-2 months with recurrent appendicitis and underwent laparoscopic appendectomy.

**Table I Characteristics of Children With Abdominal Symptoms (*N*=28)**

| *Features* | *Mild abdominal symptoms (n=15)* | *Severe symptoms (n=13)* |
|---|---|---|
| Age, y[b] | 9 (5-14 ) | 10 (6-15) |
| Males | 9 (60) | 4 (30.8) |
| Interval till diagnosis, d[b] | 7 (4-11) | 6 (2-10) |
| Leucocyte count, $x10^9/L$[a] | 2.4-17.4 | 12.2-26.8 |
| CRP, mg/L[a] | 50-480 | 12.4-282 |
| D-dimer, ng/mL[a] | 998 – >10,000 | 761-7331 |
| Ferritin, mcg/L[a] | 116-1967 | 227-846 |
| SARS-CoV-2 positive[c] | 15 (100) | 9 (69.2) |

*Data presented as no. (%), [a]range or [b]median (range). [c]Either of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antigen, IgG, or IgM positivity.*

Four children with severe abdominal symptoms had a delay (range 2-8 days) in surgical management due to an underlying suspicion of MIS-C. In all four children, diagnosis was confirmed with radiological investigations like USG or CT abdomen. Surgical management was necessary for successful treatment; two had appendicular phlegm and two had acute perforated appendicitis that was managed with open appendectomy.

One other child who underwent appendectomy for suspected appendicitis had persistent fever spikes post-operatively. Investigations revealed high D-dimer, CRP and SARS-CoV-2 IgG positivity, and he was treated with single dose of intravenous immunoglobulin. A six-year-old male child presented with acute orchitis, which settled with conservative management. There were no deaths in these 28 children.

## DISCUSSION

In this retrospective study, equal number of children with severe abdominal complaints were subsequently diagnosed as MIS-C or acute surgical abdomen. Children with severe abdominal complaints had a delay in surgical management with an initial suspicion of MIS-C. This was probably as these children were initially managed elsewhere as MIS-C and then transferred to our center.

The incidence of gastrointestinal manifestations like vomiting, abdominal pain and diarrhea in COVID-19 is reported between 6-13% [2]. There are reported cases of pseudo-appendicitis, appendicitis or complicated appendicitis with COVID-19 [3-6]. The postulated cause for this association was SARS-CoV-2 binding with ACE-2 receptors in the gastrointestinal tract, resulting in hyper-inflammation, dysregulation of immune cells, and a prothrombotic state with organ ischemia [5].

Acute abdomen has been reported in one-third children with MIS-C, postulated to be due to underlying severe intestinal vasculitis [7]. Children with suspected acute appendicitis were noted to develop postoperative fever and shock following appendectomy [8,9]. They required immunomodulators, steroids and rarely, repeat surgical exploration [10]. Histopathological examination of the resected specimens showed transmural chronic inflammation, extensive venous microthrombi, and markedly inflamed mesentery, that favored MIS-C as an etiology.

A systematic review of acute abdomen in MIS-C reported that abdominal surgery was unnecessary in half of the children with MIS-C [11]. Conversely, one-fourth of children with MIS-C had a surgical pathology. The imaging findings were discriminatory for surgical abdomen in MIS-C unlike laboratory markers, similar to the present study.

Appendicitis or terminal ileal thickening is common during the inflammatory phase of COVID- 19 infection or in children with MIS-C. Most of them improve with conservative management. Instead, operative management may lead to stormy postoperative period and high morbidity [9,10]. As a corollary of intestinal ischemia (hypothesized as a complication due to intestinal vasculitis), we may consider ruling out cardiac involvement in MIS-C by an echocardiogram, before operating upon children with surgical complications [12].

A multinational experience from Latin America [13] reported age more than 5 years to be associated with a higher risk of appendicitis. However, contrary to our study, they did not note a delay in diagnosis of acute appendicitis in their patients [13].

Testicular torsions have been reported during COVID-19 pandemic [14], similar to a single case of acute orchitis in the present study. This could result from higher expression of ACE2 receptors in the testes and can be related to inflammatory and vasculitis changes occurring during COVID-19 or MIS-C. Acute pancreatitis has also been reported as one of the causes of abdominal pain in children with MIS-C [15]. There was no child with acute pancreatitis in this study group.

To conclude, MIS-C and surgical abdomen are close mimickers. Severe illness, shock out of proportion to the clinical findings, presence of high-grade fever, contact history with COVID-19 positive patient, and COVID IgG positivity can help in differentiation of these two. A multidisciplinary team with physician, surgeon, radiologist and intensivist can help in managing these children timely and effectively.

**WHAT THIS STUDY ADDS?**

- Severe abdominal signs may occur in a significant proportion of patients with multisystem inflammatory syndrome in children (MIS-C).
- Surgical abdominal emergencies may mimic MIS-C and should be identified timely.

*Ethics clearance*: Ethical clearance obtained from institutional review board
Contributors: AKU-manuscript writing and data analysis; RP-data collection; LS-review of the manuscript and corrections; JS-manuscript review and corrections. All authors aproved the final version of the manuscript.
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RESEARCH PAPER

# Serum Ferritin for Predicting Outcome in Children With Severe Sepsis in the Pediatric Intensive Care Unit

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**Objectives:** To evaluate the prognostic ability of serum ferritin when estimated within 5 days of onset of illness in children with severe sepsis admitted to a pediatric intensive care unit. **Methods:** This observational study enrolled children aged 1 month to 12 years with severe sepsis. Hemoglobin, serum ferritin and C-reactive protein levels were measured within five days of illness. Final outcomes were recorded in all enrolled children. **Results:** 70 children with median (IQR) age of 27 (8,108) months were enrolled during the study period (July, 2019 to August, 2021). 28 (40%) of these had poor outcome (non-survival). The median (IQR) level of serum ferritin was 1369 (558-5607) ng/mL in non-survivors and 282 (129-680) ng/mL in survivors ($P$<0.05). A significant correlation was seen between serum ferritin and Pediatric Risk of Mortality III (PRISM III) score ($r$=0.364 $P$=0.002) and pediatric Sequential Organ Failure Assessment (pSOFA) score ($r$=0.246 $P$=0.04) at 48 hours of admission. 54 (77.1%) children were anemic. Serum ferritin levels in children with anemia also had a good predictive ability for poor outcome [AUC: 0.764, 95% CI: 0.634, 0.894]. **Conclusions:** Serum ferritin levels, within five days of onset of illness, predicted poor outcome in critically ill children with severe sepsis and in children with microcytic anemia.

**Keywords:** *Anemia*, *C-reactive protein, Infection, Mortality*.

Sepsis is a major cause of morbidity and mortality in children worldwide [1], with high fatality rate. Biomarkers can diagnose, monitor, stratify, predict outcomes and aid in evaluating therapy response and recovery in sepsis [2]. C-reactive protein (CRP) and procalcitonin are the two extensively studied biomarkers [3]. Although CRP is widely available, its ability to accurately predict outcomes is yet to be established, while the use of procalcitonin is limited in developing countries. Elevated levels of serum ferritin in sepsis has been linked with poor outcome in children aged 28 days to 18 years [4,5]. Serum ferritin, when used as a biomarker to risk-stratify hospitalized children, would be helpful in clinical management [3]. The role of serum ferritin as a biomarker to prognosticate severe sepsis in children with concurrent iron deficiency; however, still needs to be studied.

The primary objective of this study was to predict the outcome in children with severe sepsis, using serum ferritin. The secondary objectives were to find the correlation between serum ferritin levels and Pediatric Risk of Mortality (PRISM) III score as well as pediatric Sequential Organ Failure Assessment (pSOFA) score. The predictive ability of serum ferritin and CRP for outcomes in children with severe sepsis were also compared.

## METHODS

This was an observational study conducted at the pediatric intensive care unit (PICU) of our institution from July, 2019 to August, 2021, after approval from the institutional ethics committee.

Children aged 1 month to 12 years with severe sepsis were included. Severe sepsis was defined as sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions [6]. Children with chronic organ dysfunction like chronic liver, kidney, lung or heart disease, beyond five days of onset of illness, family history or previous diagnosis of hemophagocytic lymphohistiocytic syndrome (HLH), recipient of a blood transfusion in the last four months, children with proven or suspected genetic malformation or inborn error of metabolism and children diagnosed/suspected with childhood malignancy and autoimmune disease were excluded. Definitions of the terms used in the study were as per standard definitions [6-10].

Enrolled children were treated according to standard PICU protocols. At admission to PICU, an additional 2 mL of venous sample was collected for serum ferritin, that was estimated using Beckman Coulter kit by chemiluminescence method. Serum CRP levels were estimated using immunoturbidimetry principle in Horiba Microsemi CRP LC-667G Hematology Analyzer. PRISM III score was calculated within 24 hours of admission. pSOFA score was calculated every 48 hours from admission till discharge of the patient from the PICU. Children enrolled in the study were followed up till discharge to record the outcome, which was classified as survival or non-survival.

Sample size was based on a previous study [4], where the predictive sensitivity was observed to be 64%. With an absolute precision of 10% and type 1 error of 5% (0.05), the estimated sample size was 96.

*Statistical analysis*: Data were analyzed using SSPS software version 23. Non-parametric continuous variables were compared using Mann-Whitney test while categorical variables were compared using Chi-square test or Fisher exact test. The receiver operating characteristic (ROC) curve for serum ferritin levels were plotted to derive the cut-off value and estimate the area under curve (AUC) to predict mortality in children with severe sepsis. Statistical significance was taken at *P* value of <0.05.

## RESULT

During the study period, we could enroll only 70 children, whose baseline data is shown in **Table I**. Of these, 54 (77.1%) children had septic shock at admission, while 16 (22.9%) had multiple organ dysfunction syndrome (MODS) at the time of admission. An additional 41 children developed features of MODS during their PICU stay. Pneumonia was found to be the most common cause of severe sepsis, followed by acute meningoencephalitis.

The median (IQR) duration of PICU stay was 4 days (2,9) and pSOFA score at end of 96 hours of PICU stay was 9 (6.5,12). The median (IQR) vasoactive inotrope score was 30 (10,80). Ventilatory support was required in 54 (77%) children, and renal replacement therapy in 13 (19%) children in the form of peritoneal dialysis.

The median (IQR) duration for the development of poor outcome (non-survival) was 3 days (2,10) **Table II**. A cut-off value of serum ferritin of 558 ng/mL had a sensitivity of 74.1% and specificity of 67.7% to predict the development of poor outcome (non-survival) [*n*=70; AUC (95% CI): 0.731 (0.599,0.864)]. The best cutoff of CRP to predict non-survival was 3.08 mg/dL with a 63% sensitivity and 41.9% specificity [*n*=58; AUC (95% CI): 0.458 (0.308, 0.608)] **Fig. 1).**

Fifty four (77.1%) of children had microcytic anemia; however, their median levels of serum ferritin were higher than non-anemic children (**Table II**). Serum ferritin levels in anemic children with severe sepsis were found to have a good predictive ability to detect poor outcome [(AUC (95% CI): 0.764 (0.634, 0.894); **Fig.1b**] compared to non-anemics [AUC (95% CI): 0.450 (0.150, 0.750)]. The

**Table I Baseline Characteristics of Children With Severe Sepsis Enrolled in the Study (*N*=70)**

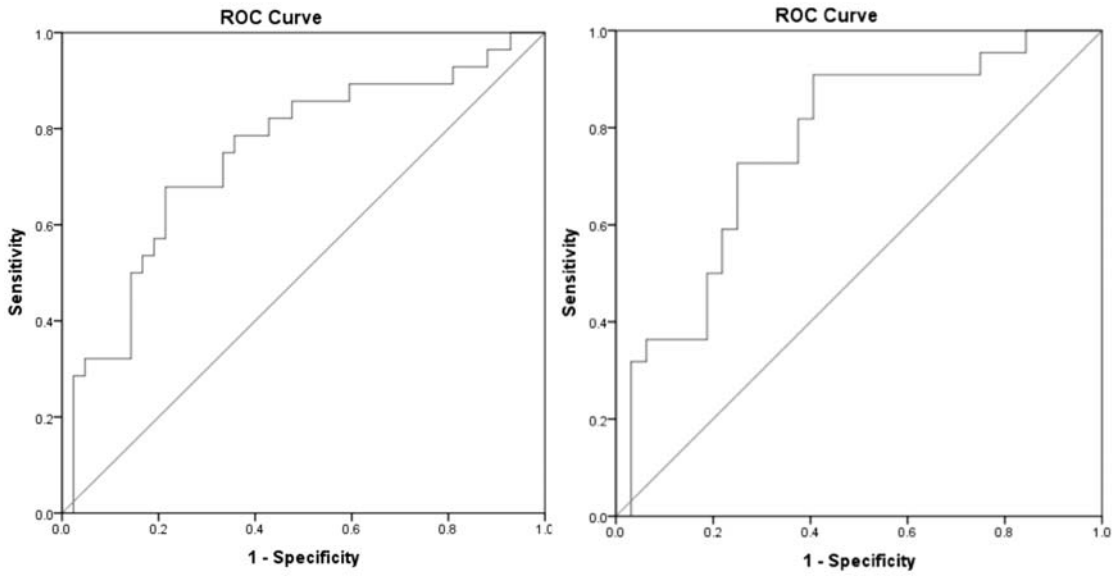
| *Characteristics* | *Value* |
|---|---|
| Age (mo) [a] | 27 (8,108) |
| Male gender | 41 (59) |
| Day of illness | 2 (1,4) |
| Stunting | 16 (23) |
| Severe stunting (%) | 10 (14.2) |
| Wasting | 20 (53) |
| Severe wasting | 11 (55) |
| Thinness [b] | 6 (19) |
| Severe thinness | 3 (50) |
| pSOFA score at admission [a] | 9 (6.5,12) |
| Pediatric risk of mortality (PRISM III) score [a] | 17 (10,20) |
| Pediatric intensive care unit stay (d) [a] | 4 (2,9) |
| Ventilated | 55 (78.6) |
| Renal replacement therapy | 13 (18.6) |

*Data expressed as no. (%) or [a]median (IQR). [b]in children aged 5-12 years. pSOFA - Pediatric sequential organ failure assessment.*

**Table II Outcome Characteristics in Children With Severe Sepsis Enrolled in the Study (*N*=70)**

| *Characteristics* | *Value* |
|---|---|
| Serum ferritin (ng/mL) [a] | 558 (192,1505) |
| C-Reactive protein (mg/dL) (*n*=58) [a] | 5 (2,13) |
| Elevated CRP | 36 (62) |
| Multiple organ dysfunction syndrome | 57 (81) [b] |
| Septic shock | 13 (19) |
| *Outcome* | |
| Survivors | 42 (60) |
| Non-survivors | 28 (40) |
| Multiple organ dysfunction syndrome [b] | 57 (93) |
| Septic shock | 2 (7) |
| *Serum ferritin (ng/mL)* [a] | |
| Anemic group (*n*=54) | 627.7 (198.23, 1885.5) |
| Non-anemic group (*n*=16) | 360.03 (219.08, 800.07) |
| Survival group (*n*=42) | 282.2 (129, 680) |
| Non-survival group (*n*=28) | 1369.15 (558,5607) |

*Values in no. (%) or [a]median (IQR). [b]16 children had features of MODS at the time of admission,41 more developed MODS during PICU stay.*




(*a*) (*b*)

**Fig. 1** Receiver operating characteristics (ROC) curves of serum ferritin levels for predicting non-survival in *a*) all children with severe sepsis, and *b*) anemic children with severe sepsis.

correlation between serum ferritin and PRISM III score ($P$=0.002) or pSOFA score ($r$=0.246, $P$=0.04) was statistically significant.

## DISCUSSION

The present study concluded serum ferritin as a good predictor of poor outcome in children with severe sepsis. Hyper-ferritinemia, has been suggested to identify patients with sepsis-induced macrophage activation syndrome [11]. Management of hyper-ferritinemic sepsis is usually preferred with immunomodulation including IVIG [12].

Earlier, few studies from developing country settings have evaluated the serum ferritin levels and its predictive utility for outcome in children admitted with sepsis [12-16]. Two studies [4,14], had a similar study design, developing country setting and survival outcome as the present study. The median level of serum ferritin in this study was similar to an earlier study [14], where both studies had a high proportion of children with septic shock at admission. The median levels of CRP were higher [14] than the present study, for reasons that are not clear. The association between serum ferritin levels and outcome was statistically significant [4,15], as seen in this study. Serum ferritin was observed to be a better predictor of outcome than serum CRP in the present study, probably as there were lesser proportion of children with elevated CRP than those with elevated ferritin.

A high prevalence of anemia was earlier reported in a similar study [14]; however, the number of children with elevated ferritin was approximately 30% lower compared to our study. In hyperinflammatory state like severe sepsis, the interaction between serum ferritin levels and iron deficiency can be complex. Children with iron deficiency anemia are more immunosuppressed than non-deficient children. As a result, iron-deficient individuals are likely to progress to a hyperinflammatory state when challenged by infection, resulting in higher levels of serum ferritin than non-deficient children. Iron deficiency can be the cause of higher serum ferritin levels in anemic group [17]. Children who reach hyperinflammatory state either because of agent or immunological or treatment related factors can have significant activation of macrophage-monocyte system. CD163, a marker of macrophage activation and hemoglobin scavenger receptor, is elevated in these hyperinflammatory states. The rate and severity of hemo-globin scavenger function by macrophages-monocyte system by CD 163, is increased in these hyperinflammatory states, thereby resulting in anemia. Here, anemia is the end result of the hyperinflammatory state [18]. It is difficult to ascertain the likely pathology in our study group as other inflammatory markers and CD 163 levels were not performed. These could be responsible for better predictive function of serum ferritin and its higher levels in the anemic group.

Our study had several limitations. The initial targeted sample size of 96 could not be achieved due to slower recruitment amidst the COVID 19 pandemic. We were able to test CRP levels only in 58 children as the sample taken at admission was hemolyzed in the rest. We were unable to

**WHAT THIS PAPER ADDS?**

- Serum ferritin estimated before fifth day of illness is predictive of poor outcome in children with severe sepsis.

estimate the iron profile of anemic children in our study.

The present study adds further evidence to the predictive and prognostic ability of serum ferritin for poor outcome in pediatric sepsis. A large proportion of children in developing countries is anemic and has iron deficiency. In this context, it is noteworthy that serum ferritin was a predictor of poor outcome even in children with anemia.

*Ethics clearance*: Institutional ethics committee, JIPMER; No. JIP/IEC/2019/0136, dated June 24, 2019.
*Contributors*: GNS: collected and analyzed data, drafted the manuscript; JGR: concept and designed the study, analyzed the data and supervised the study; NP: managed the cases, analyzed the data and supervised the study; GPS: performed biochemical investigation, analyzed the data and supervised the study. JGR: guarantor of the paper. All authors approved the final version of manuscript and are accountable for all aspects related to the study.
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RESEARCH PAPER

# Cerebrospinal Fluid Polymerase Chain Reaction in the Diagnosis of Neonatal Bacterial Meningitis: A Single-Center Experience From Vietnam

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**Objective:** To compare the performance of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) with bacterial culture for the diagnosis of neonatal bacterial meningitis (NBM). **Method:** The CSF analysis of neonate with confirmed bacterial meningitis was performed with PCR and bacterial culture, and results were compared. **Result:** Among 24 neonates, the pathogens Identified included *E. coli K1*, GBS, *Streptococcus pneumoniae* and *Listeria*. PCR identified 20 (83.3%) pathogens, and culture 4 (16.7%) pathogens. Prior antibiotics were administered to 20 (83.3%) neonates in whom PCR identified 17 (85%) and culture 3 (15%) pathogens. **Conclusion:** CSF PCR had a higher yield of pathogens than CSF culture in confirmed neonatal bacterial meningitis with a high rate of prior antibiotic therapy.

**Keywords:** *Bacterial culture, Molecular assay, Neonatal ICU, Sepsis.*

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Neonatal bacterial meningitis is a devastating infection in neonates, with a mortality rate of up to 58%. The most common causative pathogens in developed countries are Group B *Streptococcus* (GBS) and *Escherichia coli*. The incidence of neonatal meningitis is significantly higher in developing countries where the common causative pathogens are Gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli* [1,2]. Neonatal bacterial meningitis is confirmed by microscopic, chemical, and bacteriological analyses of the cerebrospinal fluid (CSF), with culture as the gold standard. However, CSF analysis is unreliable in case of exposure to antibiotics during the birthing process [3], or before a lumbar puncture is performed [4]. A sterile CSF culture does not rule out neonatal bacterial meningitis and, precludes the identification of the causative pathogen.

Bacterial nucleic acid-based polymerase chain reaction (PCR) assays have been developed for the detection of common pathogens with a rapid turnaround time compared to conventional culture [5,6]. There are limited studied on comparison between CSF PCR testing and bacterial culture in developing countries, where antibiotics are often adminis-tered before the diagnosis is made and bacterial profile is different. We evaluated the diagnostic value of CSF PCR in neonatal bacterial meningitis in this study.

## METHODS

This was a cross-sectional study on neonates aged between 0 and 28 days of life, who were admitted to the Neonatal Centre, National Children's Hospital, Hanoi, Vietnam, the main pediatric referral center between July, 2019 and June, 2020.

Neonatal bacterial meningitis was suspected in the presence of suggestive clinical features with or without risk factors for sepsis. Neonates with confirmed meningitis, where the organism was identified in the CSF by culture or by PCR, were included. Probable cases of meningitis were not included. Diagnosis made in the first three days of life or between days 4 and 28 of life was defined as early-onset and late-onset neonatal meningitis, respectively.

The study was approved by the Institutional Ethics Committee. Written informed consent to participate in the study was obtained from parents or legal guardians. The following data were extracted from the medical records: gestational age at birth, birth weight, gender, prior administration of antibiotics before lumbar puncture, maternal risk factors for infection, clinical features, peripheral total leukocyte count, platelet count, and serum C-reactive protein (CRP) concentration. The CSF was collected and sent for biochemical analysis (protein and glucose content), cell count, culture, and PCR testing.

While the results of the CSF culture were available within three days, the PCR testing result was reported within 24 hours.

CSF culture was performed by inoculating 100 µL of CSF onto each bacterial culture plate containing blood agar, chocolate agar, Mac Conkey agar, and brain heart infusion agar. A negative result was defined by the absence of bacterial growth after 5 days. DNA extraction was performed using MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche Inc). Multiplex real-time PCR was accomplished using the Allplex Meningitis-B Assay kit for *H. influenzae, S. pneumoniae, L. monocytogenes, N. meningitidis,* Group B *Streptococcus,* and *E. coli K1*.

*Statistical analysis*: SPSS software version 22.0 (IBM) was used. Categorical variables were expressed as numbers (percentages), and median (interquartile range) for continuous variables with a skewed distribution. The Fisher exact test was used for the univariate comparison of the frequency of variables. A two-tailed *P* value < 0.05 was considered statistically significant.

**Table I Clinical and Laboratory Findings of Neonates With Confirmed Bacterial Meningitis (*N*=24)**

| *Parameter* | *Value* |
|---|---|
| Males | 13 (54.0) |
| Gestational age <37 wk | 12 (50.0) |
| Birth weight <2500g | 10 (42.0) |
| Maternal infection | 6 (25.0) |
| Premature rupture of membranes | 6 (25.0) |
| Temperature instability | 12 (50.0) |
| Poor perfusion | 14 (58.3) |
| Jaundice | 14 (58.3) |
| Lethargy | 12 (50.0) |
| Irritability | 8 (33.3) |
| Hypertonia | 3 (12.5) |
| Convulsion | 1 (4.2) |
| Bulging fontanelle | 9 (37.5) |
| Poor feeding | 23 (95.8) |
| Feeding refusal | 18 (75.0) |
| Abdominal distension | 13 (54.2) |
| Hepatomegaly | 3 (12.5) |
| Vomiting | 8 (33.3) |
| *Blood*[a] | |
| White cell count ($\times 10^9$/L) | 18.5 (9.9, 26.7) |
| Platelet count ($\times 10^9$/L) | 292 (98, 387) |
| Serum C-reactive protein (mg/L) | 33.8 (6.9, 123.9) |
| *Cerebrospinal fluid*[a] | |
| Leukocytes | 445 (96, 2000) |
| Protein (g/L) | 2.0 (1.1, 2.9) |
| Glucose (mmol/L) | 1.8 (0.9, 2.8) |

*Values expressed as no. (%) or [a]median (IQR).*

## RESULTS

During the study period, 4318 neonates were hospitalized, of whom 324 underwent lumbar puncture with suspected neonatal meningitis. Twenty four neonates met the diagnostic criteria for confirmed neonatal bacterial meningitis. The clinical and laboratory findings in blood and CSF are shown in **Table I**.

A total of 20 (83.3%) pathogens were identified by PCR, and 4 (16.7%) by culture. Prior antibiotics had been administered to 20 (83.3%) neonates (**Table II**). Five of these neonates had early onset and 15 had late-onset infection (*P*=0.54).

## DISCUSSION

The present study demonstrated a higher rate of bacterial identification by PCR than conventional bacterial culture in CSF samples in neonatal meningitis. Most infections were late onset with non-specific clinical manifestations, conforming to an earlier report [7].

CSF culture is traditionally considered to be the gold standard for diagnosis. However, the yield of positive culture was very low in this study, similar to an earlier study [8]. The low yield of CSF culture was related to the high rate of prior exposure to antibiotics (83.3%) at the local hospital before transfer to referral hospital. Prior antibiotics were administered in early-onset infections that commonly occur in preterm neonates where the risk of sepsis is high. In addition, performing a lumbar puncture before initiating antibiotic therapy may have been contraindicated in clinically unstable neonates.

PCR has been used for pathogen detection in neonatal sepsis and meningitis, allowing rapid bacterial identi-

**Table II Pathogens Identified by Cerebrospinal Fluid (CSF) Culture and/or Polymerase Chain Reaction (PCR) in Neonatal Meningitis (*N*=24)**

| *Organism* | *CSF PCR* | *CSF Culture* |
|---|---|---|
| *All (n=24)* | | |
| *E. coli* | 8 | 2 |
| *GBS* | 5 | 1 |
| *Listeria* | 3 | 0 |
| *S. pneumoniae* | 4 | 1 |
| *Prior antibiotics (n=20)* | | |
| *E. coli* | 7 | 1 |
| *GBS* | 4 | 1 |
| *Listeria* | 3 | 0 |
| *S. pneumoniae* | 3 | 1 |

*Values expressed as no. (%). GBS-group B streptococcus.*

**WHAT THIS STUDY ADDS?**

- Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) outperformed CSF culture to identify bacterial pathogens causing neonatal bacterial meningitis, even in babies with prior antibiotic exposure.

fication with a higher detection rate (58%) compared with culture (29%) [9]. The present study also reported a higher percentage of positive PCR than culture, as described earlier [8]. The higher prevalence of GBS meningitis in this study than in other reports may be attributed to the absence of routine GBS screening during pregnancy and inadequate intrapartum antibiotic prophylaxis.

The study had few limitations. The bacterial coverage of the PCR kit was narrow and included only six bacteria. Neonates with suspected neonatal meningitis who did not undergo lumbar puncture were not included..

CSF PCR is useful in suspected neonatal bacterial meningitis who have prior exposure to antibiotics before lumbar puncture, or when it is contraindicated, and with sterile CSF cultures. PCR allows identification of the causative pathogen, thus permitting appropriate antibiotic selection and duration [10].

In conclusion, CSF PCR had a higher yield of patho-gens than culture even with prior antibiotic therapy. How-ever, unlike culture, PCR does not allow testing antibiotic sensitivity of identified pathogens that is a limitation of this test.

*Ethics clearance*: IEC, National Children's Hospital, Hanoi; No. 1565/BVNTW-VNCSKTE.
*Contributors*: TQNN,AS,HN: conceptualized and designed the study; TQNN,TVN,MDT: collected the data and performed laboratory analyses; HN,TQNN: analyzed the data and composed the first manuscript. The document was critically reviewed and approved all authors who are accountable for the totality of the work.
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# Feasibility of Pulse Oximeter Derived Respiratory Parameters in Young Children: A Pilot Study

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## INTRODUCTION

Clinicians are familiar with the need to monitor vital signs including heart rate (HR), respiratory rate (RR), pulse volume, blood pressure (BP), and transcutaneous oxygen saturation ($SpO_2$), in infants and children with diverse conditions. Among these, all except RR are recorded using mechanical or electronic devices. However, RR is generally measured by (manually) counting the chest wall (or abdominal movement) over a fixed duration of time. Despite its inaccuracies and inconsistencies, this has served as an important 'monitoring tool' used to determine clinical status, response to therapy, need to escalate (and de-escalate) therapy, and even decisions to hospitalize (or discharge) sick children; in diverse clinical settings ranging from primary healthcare facilities to tertiary care centers. The World Health Organization (WHO) criteria for the diagnosis of pneumonia hinges on the accurate determination of tachypnea by field workers with limited skills and training [1,2]. The United Nations Children's Fund (UNICEF) developed special timer devices to assist healthcare workers to count RR accurately [3]. Manual counting has several major drawbacks viz., the impossibility of continuous monitoring; tying up valuable human resource(s) with the consequent tendency to count for shorter durations of time (than prescribed), thereby reducing accuracy and reliability; inter-observer variation(s); and inability to store the recordings for later review (unless videography is used).

Therefore, there is a need to develop devices that can accurately monitor respiratory rate in infants and children. The UNICEF Office of Innovation website [4] describes two such devices; one uses a strap around the torso of infants/children, and the other is a device that measures RR and $SpO_2$. Another UNICEF document [5] details the proposed technical specifications for such devices. A thesis published in 2017 also discussed various technologies for the accurate determination of RR in children [6]. Later, a systematic review evaluating technologies to measure RR, identified 15 automated methods, including several devices using pulse oximetry signals to derive RR [7]. More recent work focused on clinical validation of some of these tools [8-10].

## SUMMARY

Wertheim, et al. [11] examined the pulse plethysmography (PPG) tracings from a standard (i.e., unmodified) pulse oximeter, to calculate respiratory rate (rr), and examined its feasibility for continuous RR monitoring. The investigators built on their previous work that showed its feasibility in normal newborn infants, and preterm babies with chronic lung disease. In the current study [11], they evaluated the method in a cohort of infants and children (1-7 y) with acute wheezing (of any cause) after the first hour of initial bronchodilator therapy (10 puffs salbutamol, every 20 minutes). They did this in a systematic manner, encompassing *i*) comparison of RR derived from PPG tracings against a 'gold standard' method, *ii*) estimation of respiratory modulation of the PPG tracing, as a surrogate for pulsus paradoxus, *iii*) exploration of feasibility of using PPG data reflecting RR and pulsus paradoxus, in a real-world clinical setting, and *iv*) determination of PPG-derived data to predict clinical response(s).

Briefly, PPG tracings were (retrospectively) filtered to eliminate the heart rate component, and comparing the derived RR, to the rate obtained by another method called respiratory inductive plethysmography using thoracic and abdominal bands. The simultaneous tracings from the PPG and the comparison method were visually inspected for respiratory modulation of the pulse tracing (as a surrogate for pulsus paradoxus).

The clinical parameters evaluated included: need for escalation of therapy to intravenous bronchodilator; duration requiring hourly (or more frequent) inhaled bronchodilator; hospitalization (ward or high-dependency facility); and length of hospitalization. A priori sample size calculation was performed, and appropriate statistical treatment of data was undertaken.

In 35 of 44 enrolled children (wherein a 'satisfactory' 5-minute simultaneous recording of the RR from the PPG, as well as gold standard method, were available), the mean (SD) RR by both methods were exactly the same viz. 44 (10) per minute. The mean difference from the gold standard was -0.5 (SD 1.4), although confidence intervals were not presented. The Bland-Altman plot confirmed limits of agreement ranging from -3.4 to +2.3 per minute, confirming that the RR calculated by both methods were very similar. However, a little over half the PPG tracings had artefacts of >10 seconds duration in 1-minute epochs, suggesting that the quality of the derived RR data could be compromised. The duration of the longest segment with artefacts ranged from 7 to 31 minutes.

The attempt to identify 'pulsus paradoxus from PPG tracings' was compromised in nearly a quarter of the participants, as good quality traces could not be obtained during the simultaneous recording. Rather than presenting the aggregate data of the remainder, the authors presented sample 20-second sample tracings demons-trating the presence as well as absence of beat-to-beat variation in the amplitude of the PPG tracing- the presence signifying pulsus paradoxus. They calculated that nine children without the surrogate marker of pulsus paradoxus were discharged; compared to 14 of 22 having it. The median duration of hospitalization in the former was about half of that in the latter.

As expected, children with less favorable clinical course/outcome had higher respiratory rate, as also the clinical asthma score. However, there was no difference in the heart rate or SpO2 at the end of the second hour of therapy, suggesting that RR could be a better indicator of clinical response. Using an arbitrary cut-off of 55 breaths per minute, children with higher rates at the end of the second hour, stayed longer in hospital.

## COMMENTARIES

### *Evidence-based Medicine Viewpoint*

### Critical Appraisal

This study [11] does not fit into the usual type of study designs appraised in the Journal Club section of *Indian Pediatrics*. This is perhaps because multiple objectives were pursued to confirm the validity of PPG derived data, its feasibility in an acute care setting, and its impact on clinical course and outcome. Therefore, this study provides rich opportunities for learning. Overall, the study was conducted well, and there were no major methodological red flags. However, the following considerations could have enhanced confidence in the data presented.

A major objective of this study was to validate the RR derived from PPG tracings against the gold standard method for RR, in a cohort of infants and children with acute wheezing. Therefore, a comparison over only five minutes using both methods, in a clinical scenario involving several hours of care, appears inadequate. This is further substantiated by the fact that comparative data from one-fifth of the enrolled children could not be evaluated, due to unsatisfactory simultaneous recordings. It is unclear whether longer (even continuous) comparative evaluations were challenged by technical or logistical reasons. The former seems unlikely because several multiple-parameter monitors used even in resource-limited settings are able to provide (at least crude) respiratory tracings and RR values. Further, the patients in this study had manual (i.e., visual) counting of respiratory rate. Despite its flaws and limitations, comparison against this readily-available data would also be useful. In a research study, these limitations could have been mitigated to a large extent by videographed simultaneous manual counting by two (even multiple) independent observers, blinded to each other as well as the PPG data.

The same limitation exists for the data on the pulsus paradoxus surrogate derived from the PPG tracings. In addition, this set of data is also incomplete as (unlike RR) there is no information on two of the four clinical outcomes viz., need for intravenous bronchodilator and the duration of hourly (or more frequent) inhaled bronchodilator.

The lack of longer duration of comparative data makes it difficult to determine whether PPG derived data on RR and pulsus paradoxus, are affected by factors such as patient movement, healthcare interventions, irritability of sick children, etc. It is also unclear whether chest and abdominal movements associated with increased work of breathing could compromise the RR calculated from either the PPG tracings or the gold standard method.

Fourth, in this study, both RR and pulsus paradoxus (derived from the PPG) have been used as 'predictors' of clinical course and outcome. However, this is a somewhat circular argument, because both are 'indicators' of the clinical status and used for clinical decision making. For example, tachypnea (derived by any method) 'indicates' lack of normalcy and 'dictates' escalation of therapy, rather than 'predicts' it. In this study, the fact that PPG derived RR is close to the gold standard RR (despite the limitation noted above) means that to use it as a 'predictor' (rather than 'indicator') of clinical course/ outcome, the study should have evaluated the result(s) of clinical decisions based on it.

The study is silent about the correlation (or otherwise) between PPG derived RR and pulsus paradoxus data. For example, were there similar clinical outcomes observed in children with abnormalities in RR and pulsus paradoxus? Additionally, did the same (or different) children have less favorable outcome, if they had abnormalities?

For some reason, the investigators decided to examine PPG tracings only after the first hour of bronchodilator therapy. As significant variations in RR and clinical scores are expected within this period, exclusion of this merits explanation. Of course, logistic issues in obtaining consent may have precluded data collection from the beginning. However, given that the PPG data were extracted retrospectively, it seems feasible to have obtained consent to analyze the first hour data also. This may have provided valuable information on indicators for escalation of therapy, clinical course, and outcome.

As mentioned previously, over half the PPG tracings were compromised by 'artefacts'. This has several implications. On the one hand, it perhaps mimics the real-world scenario wherein RR measurement (by any method) is often compromised. However, on the other hand, some may argue that the proportion of data with artefacts is unacceptably high, for reliable interpretation. From the methodological perspective, it is perhaps more important to ascertain the cause(s) of the tracings with artefacts, in order to determine their clinical impact. In a research setting like this study, videography of the patient would have helped to determine whether the artefacts were temporally associated with patient and/or caregiver factors, or technical problems with the PPG device.

The authors acknowledged some methodological limitations, notably their use of a uniform RR cut-off of 55/minute (across all ages) to determine 'tachypnea' after the first hour of therapy. In a research setting using retrospective data, it should have been feasible to examine multiple cut-off values, and also age-appropriate values, to construct receiver operating characteristic (ROC) curves to identify the best cut-off value indicating the clinical course.

## CONCLUSION

This study suggests the tantalizing possibility of an accurate method to determine respiratory rate, using standard pulse oximeters, in an acute care setting. However, further studies with the suggested methodological refinements are required to confirm this.

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### *Pediatric Pulmonologist's Viewpoint*

Acute asthma exacerbation is a significant contributor for emergency visits in children [1]. Appropriate assessment of severity and monitoring of response to therapy in children with asthma exacerbations is crucial in improving their treatment outcomes. There are various severity assessment scores that help the clinician in the assessment and monitoring of response to therapy, and these include the childhood asthma score, pediatric asthma severity score, pulmonary index score, pediatric respiratory assessment measure etc [2]. Respiratory rate assessment is an important component of many such scores and is an important clinical skill taught to medical students during their initial clinical posting in pediatrics. It is also a simple skill based on which guidelines for management of pneumonia by health care workers in the periphery have been formulated by the World Health Organization. Another important clinical sign that is seen in severe asthma exacerbations is pulsus paradoxus. It is not yet convincingly known to what extent these two clinical signs are reliably checked or utilized in the management of children with severe asthma exacerbations. Pulse oximetry is an indispensable tool used in pediatric emergency to rapidly determine pulse rate and oxygen saturation in sick children.

In this exploratory research paper [3], the authors describe a method of reliably assessing respiratory rate and pulsus paradoxus through pulse oximetry plethysmography tracing using appropriate software in a sample of 44 children (1-7 years of age) with asthma exacerbation. Their hypothesis being, poor recording and underutilization of respiratory rate assessment and pulsus-paradoxus in clinical practice. The authors were able to demonstrate that respiratory rate can be reliably assessed using pulse oximeter by comparing it with respiratory inductive plethysmography. They also could demonstrate that respiratory modulation of plethysmography trace as a surrogate marker of pulsus paradoxus can be visualized and documented.

The clinical utility of these observations; however, remains speculative, and there are challenges that need to be addressed. Having a pulse oximeter probe attached securely to the digit in a crying/ agitated child and hoping to get an artefact free continuous tracing for the algorithm to calculate the respiratory rate could be challenging. It is also unclear at present whether continuous respiratory rate monitoring affects outcomes in children with asthma exacerbations. However, it has been shown in earlier studies that pulse oximetry detected pulsus paradoxus can be used to predict severity and response to treatment [4,5]. It will be interesting to compare how well these predictions fare vis-à-vis clinical prediction scores. Unfortunately, there is not much literature in this regard. Therefore, there is a need for further validation of the current study's results in larger cohorts of children belonging to different age groups, before it can be used in clinical algorithms in the care of children with acute asthma exacerbations. The landscape of wearable techno-logies to improve health is changing very fast and there may be machine learning and artificial intelligence derived algorithms that change the way we practice medicine in the near future. Until then, the age-old yet simple clinical observation skill of respiratory rate counting will need to be practiced, and the clinician should continue to rely upon clinical severity assessment scores to assess and monitor response to treatment in children with acute asthma exacerbations.

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### *Pediatrician's Viewpoint*

Pulse oximeter is routinely being used to measure SpO2 in young children with respiratory disorders and can be a useful bed side tool to provide continuous real time measurements of pulsus paradoxus (PP) and respiratory rate (RR).

Respiratory rate (RR) is a key clinical indicator for assessing severity as well as treatment outcome for young children with respiratory distress and wheezing.

RR is a non-specific parameter but is sensitive parameter for various pathophysiologic changes of respiratory system in young children. It is often difficult to accurately count RR in a tachypnoeic or crying child. In this study [1], it has been measured using pulse oximeter and has been validated with respiratory inductance plethysmography (RIP). Some other studies have also demonstrated validity of RR using pulse oximeter in comparison with RIP [1]. In the current study, RR was used to assess treatment outcome. RR can be used as a marker for improvement for various respiratory conditions such as acute asthma and wheezing.

PP is traditionally measured using sphygmomanometer, which is difficult in a tachypneic child [2]. Plethysmograph wave can be used to quantify PP as has been done in this study. PP obtained from plethysmograph waves has been shown to correlate with lung functions [3]. PP assessment can be a helpful tool in assessment of asthma severity and response to treatment in children who are unable to perform spirometry.

These two parameters incorporated with pulse oximeter may provide clinicians improved assessment of severity of respiratory condition and also help in predicting treatment outcome. However, presence of artifacts can hinder accurate measurement. The device may require modifications such as better probe fit, and improved user interface [4]. Further, use of these parameters in clinical settings would require larger studies.

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SPECIAL ARTICLE

# Empowered Nurses: A Win-Win Situation in Pediatric Critical Care

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The atmosphere of a pediatric intensive care unit (PICU) is charged, fast paced, stressful, and tiring with emphasis on precision of care. Pediatric critical care nursing is still in its infancy stage in India and other low middle income countries. The lack of resources, staff shortage, migration and brain drain are persistent issues in India. There is lack of career advancement as well as exposure to research activities. Keeping these barriers in mind, over the years, we have adopted certain multipronged strategies in our PICU with the objective of empowering, and motivating our nursing personnel. We have been able to 'build a horizontal team' where each member feels wanted and works to his/her maximum capacity. This model of nurse empowerment may be reproduced by other institutions especially in low middle income countries that are also struggling with similar problems.

**Keywords:** Advocacy, Fellowship, Innovation, Leadership.

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Nursing is the backbone of any healthcare system and nurses constitute about 60% of the global health-care work force [1]. They are the first point of contact for health-care service seekers and often the first responders for health emergencies. Working on the front lines, nurses play an important role in the delivery of high-quality care and bringing about favorable patient outcomes. Among the various nursing disciplines, pediatric nursing is extremely challenging given that they attend to patients belonging to a wide range of age groups. The pediatric nurses balance both the uncooperative children and their anxious families. Within pediatric nursing, the subset of pediatric critical care nursing is more demanding and challenging. Pediatric intensive care unit (PICU) environment is charged, fast paced, stressful, and tiring with emphasis on precision of care. Attention to details cannot be over emphasized as the smallest of errors can be life threatening. Globally the concept of pediatric critical nursing has evolved significantly [2]. In India, pediatric critical care nursing is still in its infancy, although the sensitization about its need is catching up fast.

In developed countries, nurses have evolved from being subordinates to doctors into independent health-care professionals practicing technology guided and evidence-based care. There are clear laid down policies and legislations for minimum recommended nurse- patient ratios. Key organizations like World Health Organisation (WHO) and International Council of Nurses (ICN) are voicing the need for nurses to become more involved in leadership, advocacy and policymaking [3,4].

The scenario in low- and middle-income countries (LMICs) is different. India is amongst the most populated countries with growing health care needs. Public sector hospitals are overcrowded and have myriads of challenges and barriers [5]. These become impediments to nurse empowerment and their autonomy to work as independent stake holders.

## PROBLEMS

*Staff shortage*: A lower nurse-patient ratio results in lower mortality rates, shorter hospital stays, and decreased readmissions [6]. However, there is disparity in the availability of nurses in different regions of the world, including India, with only 6.0 active nurses/midwives per 10,000 population, that is far below the expected [7]. In India, the deployment of nursing personnel is as per the Staff Inspection Unit (SIU) norms that were framed in 1991-92, and are obsolete in the face of changing patient needs and complexity of treatment [8].

The ideal nurse:patient ratios according to SIU norms, should be 1:4 and 1:2 for pediatric general wards and neonatal nurseries, respectively; but even in tertiary referral multispeciality hospital like ours, with no cap on admissions, the ratios are dismal (1:15 for wards and 1:30 for emergencies). Similarly, for the pediatric ICUs, the recommended nurse:patient ratio of 1:1 is seldom

achieved, challenging the ability to care with precision [9]. Adverse events related to medication errors, needle stick injuries and breach in care bundles compromises patient safety, results in healthcare associated infections (HAI), and prolongs hospital stay [10].

*Migration and brain drain*: Excessive work load coupled with meagre salaries and lack of incentivisation for specialised nursing care in neonatal and pediatric critical care units, result in poor job satisfaction [11,12]. Better salaries and higher standard of living in developed countries attracts nurses towards job opportunities overseas [11,13]. There is a passive acceptance of health care worker migration by the policy makers [14,15]. Lack of policy, guidelines or legislation to check migration of nurses or other health care workers only adds to this brain drain.

*Non-existent concept of specialty nurses*: Nurses are rotated from one specialty to another and are expected to perform with the same acuity, passion and commitment in each random rotation. Nurse administrators with no clinical experience of the particular specialty are expected to lead and produce results. The importance of specialty nurses as an asset for an ICU is lost, while striking a balance between individual interests and hospital needs [4,5,16].

*Non-nursing jobs*: Nurses in India are required to perform a host of non-nursing jobs which include maintenance of drug inventory, central sterile supply department (CSSD) inventory, medical equipment log-books, linen stock, admissions and discharges, supervising ward and sanitary attendants. Performing these non-nursing jobs curtails time for actual patient care, and can lead to exhaustion [15].

*Lack of career advancement and recognition*: Our health care systems are predominantly doctor driven and nurses are usually considered subordinates to the doctors. The intellectual capabilities of nurses are rarely recognized. The idea of team concept seldom gets translated to practice, and due credit and recognition to nurses is denied [16,17].

Concept of lateral entries for promotions in nursing administration is missing; promotions in clinical nursing, appraisals or salary raise are seniority based and not performance based. There are limited opportunities for career progression and in-service education [5,17].

*Research exposure and opportunities*: Research opportu- nities are confined to the academic nurses who are usually not directly involved in patient care. The clinical bedside nurses lack knowledge and awareness about research methodology and nursing research is barely utilised to improving the nursing care. Lack of nurses' involvement in parental counselling and communication barriers within heath care team are other issues which need to be addressed.

## A PICU MODEL OF NURSE EMPOWERMENT

The above barriers can only be addressed by empowerment of existing nurses. Empowerment has a positive impact on employees; it motivates them to perform better and deliver quality care. A healthy work environment is important to achieve this empowerment. An intensive care unit is a good place to practice nurse empowerment and inclusiveness.

Our PICU is a 16 bedded level 3 ICU with a nurse-to-patient ratio of 1:2 for ventilated and 1:3 for non-ventilated children. However, the ratios exceed to 1:3 for ventilated patients many a times. Nurses provide comprehensive care to the critically sick children, which involves attending to personal hygiene needs, assessing, monitoring, assisting doctors for various procedures, preparing for admissions and discharges, indenting medications or surgical supplies, supervising the jobs of hospital and sanitary attendants, performing and supervising the cleaning and disinfection procedures, parent education for parental participative care etc.

Over the years, we have adopted certain strategies with the objective of addressing the shortage and empowering our nurses, thus circumventing some barriers over time.

*Nurse as a primary driver*: We identified certain core areas where nurses can be primary drivers. The tasks that require stringent supervision and monitoring are better executed by nurses as they are in a position to ensure continuity and adherence to established protocols like infection control. Our nurses were made the primary drivers for infection control program and one PICU nurse is re-designated as infection control nurse (ICN) by rotation. This nurse in addition to his/her other nursing tasks is responsible to maintain good hand hygiene compliance, check adherence to all preventive bundles, and assess the daily need for an invasive device. Low-cost simple device reminders (colorful balloon) are pasted at the head end of a patient's bed once the duration of an indwelling catheter exceeds 7 days. He/she is given autonomy to ensure that strict aseptic techniques during various procedures and device maintenance bundles are followed religiously. Cohort nursing is practiced for children infected with multidrug resistant organisms to avoid cross-contamination. A separate sepsis board was created to keep a count of hospital acquired infections (HAI) in real time. Appreciation for '0' count of HAI and best hand hygiene compliance are acknowledged on unit pin up boards. However, breach in hand hygiene compliance or infection

control bundles are communicated to the concerned healthcare providers on individual basis.

The autonomy to handle infection prevention and control measures gives our nurses a better sense of belonging to the unit, and increases their overall morale.

*Nurse driven unit huddles*: All health care workers posted in PICU gather for about 15-20 minutes daily morning for an update regarding the PICU patients. Daily unit huddles are conducted by the PICU nurses by rotation. The whole team is apprised about the last 24 hours patient census, new admissions, shift outs, critical incidents, planned procedures and patient transport for the day, count of HAI, number of children on antibiotics and devices, reminder for de-escalation of antimicrobials and removal of devices, and reinforcement of hand hygiene and care bundle compliance. A separate huddle board has been created to put all summary points that need attention during the unit huddle. The unit huddles help plan their activities in advance and provide an opportunity to introspect critical incidents or HAIs.

*Parental participative care:* Parents being natural care providers to their child at home are allowed to stay with the child and help in patient care activities like feeding, cleaning, measuring urine output, changing diapers, providing emotional comfort etc. They are counselled and educated by the PICU nurses to perform these familiar tasks in unfamiliar setting through daily morning small group sessions, printed pamphlets and videos in vernacular languages. Repeated rounds of reinforcement are done. Parental participation in care decreases the workload of nurses and enables them to focus on more important tasks like assessment and monitoring, and preparation and administration of drugs and medication.

*Resource persons for capacity building*: Our PICU nurses are actively involved in capacity building of nurses working at district level hospitals in the State of Madhya Pradesh as a part of the Integrated Module for Pediatric Acute Care Training (IMPACT), a collaborative project between our institute, UNICEF and State National Health Mission. The nurses trained in these workshops, visit our institute as observer for further skill training. Grassroot level nurses gain precious skills and knowledge while our nurses find this collaboration meaningful and motivational for their professional growth. The IMPACT program was awarded the Innovation in Education Award for 2021 by the Society of Critical Care Medicine (SCCM),USA.

*Simulation training*: It has been seen that only 50% graduating nurses could perform basic nursing care skills and less than 10% independently practiced few of the advanced nursing skills [18]. Learning critical care skills through simulation is a safe, less time-consuming method to avoid harm to patients. In our unit, new entrants (doctors and nurses) are trained on simulators before they perform procedures on patients. Nurses are amongst the first to be trained in simulation and participate as a team to practice scripted scenarios. Many procedures are videographed and shared with other team members, for a continued learning experience.

*Nurse driven quality improvement initiatives*: As bed-side care providers, nurses are the best for identifying quality improvement opportunities [19]. A number of bedside nurse-driven quality improvement initiatives have been conducted in our PICU like implementation and adherence to VAP and CLABSI bundle care, critical incident reporting, sepsis and equipment audit, and device reminders. Maintenance of equipment in the absence of a full time ICU technician is a tedious task that was streamlined with the involvement of nurses.

*Ongoing education and research activities*: Nurses from our unit actively participate in various conferences and workshops as faculty members. Many are certified Basic and Advanced Life Support instructors. They are contributors in pediatric critical care nursing and Advanced Life Support manuals and also involved in conducting research projects on parental participation in patient care activities, reducing HAIs and use of simulation.

A one-year fellowship program in pediatric critical care nursing has been started at our institute. This program entails recruitment of three nurses biannually for training in pediatric critical care. This will encourage more nurses to get formally trained in the discipline of pediatric critical care.

## CONCLUSION

Nurses call for active participation and leadership roles from the medical team. The traditional vertical leadership and hierarchical team is outdated in today's scenario [20].

**Box I Recommendations for Empowered Nurses in the Pediatric Intensive Care Unit (PICU)**

- To shoulder responsibilities beyond their usual subordinate roles.
- To lead health care teams looking after infection control and critical incidents.
- To minimize out-of-PICU rotations for specialty nurses.
- To participate in capacity building of grassroot level nurses (PHC/CHC) while working in tertiary hospitals, for nurse empowerment and addressing staff shortage.
- To involve nurses in research collaborations for them to understand local problems and gain professional satisfaction.

*PHC-primary health center, CHC: community health center.*

Through our multipronged interventions, we have endeavored to build a horizontal team, where each member feels wanted and works to his/her maximum capacity despite the shortage of nursing staff. Participation in the process of decision making provides a sense of responsibility. Our model of nurse empowerment has created a healthy work environment and interpersonal relationship between doctors, nurses and other health care workers. A team that has respect, trust and care for each other survives longer.

This model of nurse empowerment (**Box I**) may be replicated in other institutions, especially in LMICs, which are also struggling with similar problems, especially shortage of nurses and brain drain of skilled staff.

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# Health Promoting Schools in India: The Time Has Come!

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A health promoting school is a school that consistently strengthens its capacity as a safe and healthy setting for teaching, learning and working [1]. Such a school helps promote health and educational attainment in schools to better physical, social-emotional, and psychological conditions for health as well as for positive education outcomes [2]. Worldwide, schools are getting converted into health promoting schools, and India cannot be left behind in this ongoing advancement.

On 12 October, 2021, at Delhi, World Health Organization (WHO), along with several specialized agencies of the United Nations viz., United Nations Educational, Scientific and Cultural Organization (UNESCO), United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA) and World Food Programme (WFP), gave a call for action for "*Making every school a health promoting school: Scaling up implementation of comprehensive school health programs for promoting health and well-being of students and staff* [3]." India is also a signatory to the same [3].

## HEALTH PROMOTING SCHOOLS INITIATIVE OF IAP-NCDPA

It is a standards-driven school health program and system for accreditation of schools in India, developed by the Non-Communicable Disease Prevention Academy (NCDPA), the statement of 10 commandments of which was endorsed by the Executive Board of Indian Academy of Pediatrics (IAP) in its meeting on 19-20 March, 2022. This was done with the conviction that it will be help to provide quality education and to ensure the safety and wellbeing of each child exposed to the school environment, and it was envisaged that the proposal document of NCDPA may become a role model in the formation of standards norms for "Child Friendly School" initiative. The commandments (an abridged version is listed in **Box I**), lay high focus on cultivation of healthy lifestyle early in life, and prevention of non-communicable diseases over the life span, especially those originating in childhood and adolescence.

Further details to operationalize these ten points are as follows:

1. Conducting age-appropriate activities every three months, aimed at building among all students, awareness and skills related with primary prevention of diseases (esp. healthy lifestyle, hygiene and sanitation).
2. General health check-up including assessment of vaccination status and annual body mass index (BMI) recording, tracked serially. Any deviation from normal should be reported to a health care provider, and the parents.
3. A 30-45 minutes session of age-appropriate physical activity after adequate warm-up exercises. Between successive classes, a short, around 2 minute break for few stretch exercises/moderate-vigorous physical activity.

**Box I Ten Points for IAP-NCDPA-HPS Accreditation of Schools in India**

1. Healthy Lifestyle awareness sessions targeted at primary prevention of behavioral risk factors skills every 3 months.
2. Annual BMI recording, serial tracking and referral if required.
3. Physical activity daily 30-45 minutes and for two minutes in between the classes.
4. Traffic light system based availability of foods in canteen.
5. Food should never be a part of reward or punishment.
6. Weight of the school bag should always be <1/10th of weight of child.
7. A peer-based school squad should exist and be available for all students alike.
8. At least one teacher trained and certified Basic Life Support (BLS) provider.
9. At least one teacher trained in screening for learning disorders (LD), and one counsellor.
10. A safe and secure environment for all students

4. Full compliance of traffic light based availability of foods in the canteen [4.]. Unhealthy food should be strictly prohibited from distribution in any event in the school, including sponsored events.
5. Food should never be a part of any reward or punishment.
6. The weight of school bag should be less than 1/10th of the weight of the child with lowest body weight in that class.
7. A peer group based 'School squad' should be engaged in ongoing surveillance for prevention, early detection, reporting and management of students getting into substance abuse, mental harassment/ bullying/depression.
8. On each working day, availability of at least one teaching staff trained and certified as a Basic Life Support (BLS) provider.
9. Availability of least one teacher trained and certified in screening children for learning disabilities.
10. A safe and secure environment for all students, including: strict compliance with fire safety norms and national building safety norms; global positioning system (GPS) and closed-circuit television (CCTV) in school buses; Installation of CCTV in school premises covering all sensitive areas, with footage preserved for 60 days; and, Compliance with all the directions of the Hon. Supreme Court of India [5] and Government of India [6] with respect to school buses, as well as responsibilities of parents in respect thereof, must be strictly enforced.

Undoubtedly, and more so in the wake of the Covid-19 pandemic, time is now ripe to carve out a greater role for schools in preventive healthcare with e standards-driven approach, and IAP and NCDPA are geared up to deliver an efficient system for the same.

*"Nothing else in the world…not all the armies…is so powerful as an idea whose time has come."*

– Victor Hugo, The Future of Man.

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# Minoxidil Ingestion in a Toddler

Minoxidil is a direct arterial vasodilator used in the treatment of hypertensive emergencies. Minoxidil use can also cause hypertrichosis, and hence is widely used in treatment of male pattern baldness [1]. It is available over the counter as 2% and 5% topical hair formulation. Accidental ingestion of this topical solution even in lesser quantities can lead to significant cardiovascular toxicity. We report the youngest case of accidental ingestion of 5% topical minoxidil hair formulation in a toddler.

A developmentally normal one-and-a-half-years-old male child presented to pediatric casualty with history of accidental ingestion of 5% topical minoxidil hair formulation while playing. The child ingested around 3 -5 mL (150-250 mg of minoxidil) of the formulation and presented to hospital 45 minutes post-ingestion in a drowsy state. He did not have any history of vomiting or breathlessness at presentation. On examination, child's temperature was - 99.8° F, BP-90/62 mm of Hg ($50^{th}$-$75^{th}$ centile), pulse rate - 150 /min with good volume and perfusion. His respiratory rate was 44/min, oxygen saturation - 99% in room air with bilaterally equal and reacting pupils. Cardiac examination revealed tachycardia with no murmurs, rubs or gallop rhythm. Examination of other systems was normal. Oxygen was supplemented at 2 L/min during initial stabilization. His BP dropped to 66/46 mm of Hg ($<5^{th}$ centile) within 3 hours post-admission and his pulse rate was 176 beats per minute. He received 20 mL/kg of intravenous normal saline bolus followed by maintenance fluids. Child was transferred to pediatric intensive care unit where dopamine infusion was started and titrated to a maximum dose of 12 mcg/kg/min. Child's sensorium improved after 6 hours. His blood pressures stabilized gradually within 12 hours and dopamine was tapered and stopped by 20 hours. His blood counts and electrolytes were within normal limits. Chest *X*-ray was taken 6 hours post ingestion, which did not show any features of aspiration. Initial cardiac markers showed negative TROP-I, CK- total : 196 IU/L and mildly elevated CK MB : 38 IU/L. ECG showed sinus tachycardia, flattening and inversion of T waves but no features of myocarditis. At 24 hrs post ingestion, repeat cardiac makers were within normal limits. Echo-cardiography done on day-4 showed normal LV function and EF: 65%. Renal function was normal throughout the course. During the course of hospital stay, the child had tachycardia around 170 to 180 per minute 3 hours post ingestion, which gradually reduced to 140-150 per minute on Day 2, and 100 to 110 per minute on Day 3. Child was normotensive after stopping dopamine, and tachycardia gradually reduced over next two days. He was discharged on day 4 of admission.

Minoxidil has a direct effect on arteriolar smooth muscles by opening of intracellular potassium channels that hyperpolarizes cell membranes resulting in marked vasodilation. The plasma half-life is around 3-4 hours. It causes reflex increase in myocardial contractility and cardiac output due to decreased peripheral resistance, which enhances venous return to heart and in turn decreases the blood pressure [1,2]. Minoxidil also stimulates renin secretion, which is mediated by renal sympathetic stimulation, resulting in sodium and water retention. Topical minoxidil preparations often contain denatured alcohol. In our case, the composition of each mL of ingested formulation had 95% alcohol equivalent to absolute alcohol 40% v/v.

In children, the usual therapeutic dose of minoxidil is 0.25-1 mg/kg to maximum dose of 50 mg/day [1]. Our index case consumed approximately 3 to 5 times of daily maximum dose. The toxic dose of minoxidil is not known but ingestion of few mL of solution will cause hypotensive effect and cardiovascular involvement in children. After ingestion, it gets absorbed quickly from gut and reaches the peak plasma level in first hour. Gastric decontamination or activated charcoal cannot be given because of its high absorption rate. Hypotension and cardiac effects usually develop 30 minutes after ingestion, peaking at 3 to 4 hours and can persist for 30 to 70 hours depending on the ingested dose [1-3]. This unusually prolonged cardiovascular action is thought to be due to persistence of the minoxidil in the vascular smooth muscle [4]. As expected, our index case developed hypotension and tachycardia 3 hours after ingestion and while hypotension settled 20 hours post ingestion, tachycardia reduced gradually over a period of 50 hours.

Since minoxidil 5% hair preparation is widely available over the counter drug for the treatment of alopecia, it should be marketed with child resistant packing and also kept away from the reach of children. Parents should be educated regarding the risk of accidental poisoning even with small quantity of minoxidil in children.

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# Considerations for Diagnosis in Potential Cases of Monkeypox

The World Health Organization (WHO) designated monkey pox a public health emergency of global significance on July 23, 2022 [1]. The emphasis is on methods to slow the spread of the disease as the number of cases is increasing exponentially in non-endemic areas. These initiatives comprise making a prompt diagnosis, quickly identifying close contacts, and taking immunization precautions. In order to help clinicians evaluate a suspected case of monkeypox, the main screening techniques and diagnostic procedures are addressed here briefly.

According to the Centers for Disease Control (CDC) case criteria, a patient is classified as having 'suspected monkeypox' if they meet any one epidemiological requirement and exhibit a distinctive rash without a plausible explanation [2,3]. The recognizable monkeypox rash develops centrifugally from macules to umbilicated vesiculopustules (**Box I**). Patients who present with fever and vesiculopustular exanthem may have painful lesions and frequent involvement of lymph nodes. This constitutes the so-called 'vesiculopustular phase'. The term "pseudo-vesiculopustules" is more aptly used to describe the stiff, challenging-to-deroof monkey pox vesiculopustules that lack fluid contents after deroofing [4].

In addition to the exanthem, monkeypox can result in an enanthem, which can be difficult to treat. The oropharyngeal mucosa is involved, which causes pharyngitis and tongue ulcers. At times, the sole presenting characteristic of the disease may be anogenital mucosal involvement. Rectal discomfort, diarrhea, proctitis, tenesmus, or isolated genital ulcers are common first signs in patients [5,6]. Differential diagnoses include clinical conditions which manifest with similar-looking rashes viz., varicella zoster, measles, rubella, scabies, bacterial skin infections, syphilis, and drug-rash [7,8].

**Box I Mucocutaneous Manifestations of Monkeypox**

*Exanthem*

- Onset of rash on face, palms, soles or anogenital area
- Evolution from painful macules to papules to vesiculopustules
- Umbilicated vesiculopustules progressing to crusted lesions healing with scar formation
- Interval of 2 weeks between prodrome and scab• Often <20 evolving lesions in different stages of evolution

*Enanthem*

- Ano-genital ulcers
- Nasal or ocular lesions
- Oral or tonsillar lesions

It is also important to understand how monkeypox specimen collection differs from those of other morphologically comparable vesiculopustular eruptions. Swabs can be taken from intact vesiculopustules and scabs/crusts in the case of monkeypox [2]. In contrast, herpetic exanthems require thorough base swabbing before specimens are taken from deroofed fluid-filled vesiculopustules. To confirm the diagnosis, non-variola orthopoxvirus DNA and monkeypox virus DNA isolation tests using polymerase chain reaction (PCR) are conducted sequentially. Testing must be done in Biosafety Level 2 facilities by personnel who have received their vaccinations.

A skin biopsy is not necessary for diagnosis because the results are often not specific. Other tests such as immuno-histochemical staining, anti-orthopoxvirus IgM antibodies, atomic force microscopy and viral cultures are useful [2]. In ambiguous cases and atypical findings, clinicians must take into account further testing in addition to sampling cutaneous, oral mucosal and rectal mucosal areas to rule out sexually transmitted diseases, which may be seen concurrently or may mimic monkeypox.

An understanding of the clinical characteristics and diagnostic procedures, and being aware of monkeypox imitators will prepare professionals to quickly and correctly arrive at a diagnosis.

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# Emerging Socioeconomic Trends in Pediatric Liver Transplantation in India

Pediatric liver transplantation (LT) in India has come a long way since its inception in 1998. The program has now matured with multiple centers in the country treating patients coming in from various parts of the world. The initial years saw a very slow growth due to multiple factors including financial constraints, reservations about organ donation and donor safety, in a largely living related program. The initial successes fueled growth with greater acceptance noted in the next decade and finally a boom manifested in the last five years or so due to advent of crowd funding platforms that use social media to reach out to a vast and varied population base of conscientious donors to raise funds, making the modality a feasible option even for the poor.

Apart from the medical advancements and achievements that have made India a regional hub for liver transplantation in South East Asia, the progressive and exponential increase in female recipients and male donors is most encouraging. At our centre, from the year 1998 to 2007, only 16 transplants were performed with 13 males (81%) recipients; amongst these, 10 (62%) were Indian. After 2007, 341 transplants have been performed with 126 (58%) patients being domestic and 215 (42%) international, reflecting the need for greater acceptance and reach for Indian children (total domestic 136/357=38%); 64% of the recipients were males.

In contrast, the proportion of donors was initially largely skewed towards females with as many as 87% ($n$=14) being female in the years 1998-2007. The ensuing years have shown a dramatic shift with the male-female gap becoming significantly narrower. The proportion of female donors was 55% ($n$=189) post 2007 to mid-2022 ($P$=0.01), reflecting an encouraging statistically significant rise in male donors.

Another heartening development has been the funding support that has now become available for transplantation. In our program, about 7 crore rupees were raised through domestic crowdfunding platforms and individual philanthropic organizations that fund liver transplants in India. About 13 crore rupees were granted by international organizations to recipients from South East Asia who travelled to India for a liver transplant. Only about 20% of the transplants in the last 5 years were fully financed by the family, and the rest all received partial or total financial support. Acute liver failure (11 transplanted in last 5 years out of total 41) constitutes the cohort for which funding is most challenging, due to paucity of time.

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# COVID-19 in Children With Tuberculosis: Methodological Issues

I read with interest the recently published research paper highlighting COVID outcomes in children with tuberculosis [1]. I have the following concerns related to the study.

The study methodology is unclear. Was this a retrospective chart analysis? The number of children with no tuberculosis is surprisingly low (as compared to those with tuberculosis), when we look at other pediatric coronavirus disease 2019 (COVID-19) studies [2]. The authors have stated "*Only a few studies have highlighted the association between tuberculosis and COVID-19*"; however, no references have been cited for this statement. In fact, there are multiple studies on this aspect of COVID-19 [3,4]. A meta-analysis [4] suggests that in adults COVID with tuberculosis patients are at an elevated risk of mortality than non-tuberculosis COVID patients. Authors should elaborate on possible differences between pediatric and adult tuberculosis that could explain their different outcomes.

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## AUTHORS' REPLY

We thank the reader for the interest in our work. Many of the queries raised have already been addressed in two previous communications [1,2].

This was a retrospective study in which data on patients were extracted from the database. This was described in brief in the methods section, due to word limits. For references to other coronavirus diseases 2019 (COVID-19) studies, due to the reference limit in the brief research section, we could not add the references.

We had submitted a brief discussion on tuberculosis and COVID-19 in adults vs children. However, it was removed in subsequent revisions due to word limits and references limit. An upcoming publication from our center will report on the adult-pediatric differences in COVID-19 and tuberculosis co-infection.

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# NEWS IN BRIEF

### Monoclonals for Malaria

A new tool in our armamentarium against malaria is born. CIS43LS is a monoclonal antibody against a major protein of the sporozoite stage of falciparum malaria - *P. falciparum* circumsporozoite protein (PfCSP). This protein is important during the entry of the sporozoites into the hepatocytes.

A recent trial in healthy adults in Mali demonstrated a proportional efficacy of 88.2% (in the high dose 40 mg/kg) vs 75% (in the low dose 10 mg/kg) when compared to placebo. A total of 330 healthy adults were randomized into the three groups and followed up for 6 months. *P. falciparum* was detected on smears in 18.2% of the high dose antibody group, 35.5% in the low dose antibody group and 78.2% of the placebo group.

What could be the role of monoclonals in the fight against malaria? Currently the WHO has approved the use of the malaria vaccine (RTS,S ) in children living in moderate to high *P. falciparum* transmission areas like in sub-Saharan Africa. This four dose vaccine (0, 1, 2, 20 mo) in children above 5 months has a vaccine efficacy of 36% over four years. Additionally, bed nets and chemoprophylaxis during the malaria season is recommended.

The newly tested monoclonal antibody appears to have high efficacy in preventing infections over a 6-month period and could be advised at the onset of the malaria season. The major logistic problem would be the fact that it is an intravenous drug to be given over 30 minutes. To circumvent this a subcutaneous injection has been developed and is undergoing trials. It may also be an attractive alternative for travelers to malaria endemic regions. (NEJM 31 October 2022)

### Deaths in Gambia Related to Cough Syrups

In July and August this year, physicians in Gambia noticed a sudden spike in children developing vomiting and fatal renal failure. Nearly 70 children died. Investigations have implicated four cough syrups - Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup and Magrip N Cold Syrup; all manufactured by Maiden Pharmaceuticals Limited in Haryana, India. Investigations are under way in India and Gambia.

The renal failure is suspected to be due to contamination with diethylene glycol and ethylene glycol. They are considered to be cheaper substitutes of the normal solvents like glycerine and propylene glycol. Similar deaths have been reported in the past from India, USA, Bangladesh and Nigeria. Last year, 12 children died in Udhampur after ingesting a cough syrup called Coldbest-PC due to diethylene glycol contamination, which was then withdrawn from the entire country. Stringent quality control at every step is required if we are to avoid these preventable deaths. (*The Hindu, 17 October 2022*)

### Medical Education in Hindi

Madhya Pradesh (MP) has become the first state to introduce undergraduate medical education in hindi. Medical textbooks for anatomy, physiology and biochemistry have been translated into Hindi. It took 97 medical college teachers more than 5000 hours of brainstorming and hard work to translate the books. Students enrolling this year for an undergraduate course in medicine will have the option to learn in Hindi or English in all 13 state government colleges of MP. Textbooks in Hindi for the senior batches will become available from next year.

Ninety percent of people in MP speak Hindi, and higher education may become more accessible to the poor. However, critics have said that the textbooks are merely full of English medical terms written in Hindi without any fundamental contribution by the translators. Some others have prophesized that medical education other than in English will result in distancing of Indians from the global medical community. (*The Economic Times, 17 Oct 2022*)

### Pompe Disease Treated In-Utero

Children with infantile Pompe disease develop hypertrophic cardiomyopathy in utero. So even if enzyme replacement is started at birth, it may be somewhat late. In a dramatic story, a baby who was diagnosed to have Pompe disease was treated with enzyme replacement (Alglucosidase alpha) in utero from 24 - 34 weeks. It was infused via the umbilical vein 2 weekly at a dose of 20 mg/kg. One of the chief investigators of the study was Priya Kishnani, an Indian origin physician-scientist in Duke's University, who has been working for children with Pompe for the past several decades.

At birth, her left ventricular mass index was normal. Enzyme replacement was continued from day 4 of life every 2 weekly. At one year follow up, she had a normal CPK and normal echocardiogram. The child also mounted a lower immune response to enzyme replacement compared to children who are treated postnatally – antenatal therapy appears to have this added benefit. This case report in the NEJM highlights that timing is everything in medicine. Sometimes even the day of one's birth may be too late! (*NEJM, 9 November 2022*)

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**Dietary intakes and eating behavior between metabolically healthy and unhealthy obesity phenotypes in Asian children and adolescents** (Nutrients. 2022;14:4796)

This study aimed to evaluate the dietary food groups, nutrient intakes and eating behaviors of metabolically healthy and unhealthy obesity phenotypes in an Asian cohort of children and adolescents. Participants (*n*=52) were asked to record their diet using a 3-day food diary and intakes were analyzed using a nutrient software. Eating behavior was assessed using a validated questionnaire. Metabolically healthy obesity (MHO) or metabolically unhealthy obesity (MUO) were defined based on criteria of metabolic syndrome. Children/adolescents with MUO consumed fewer whole grains [median: 0.00 (IQR: 0.00-0.00 g) vs 18.5 g (0.00-69.8 g)] and less polyunsaturated fat [6.26% kcal (5.17-7.45% kcal) vs 6.92% kcal (5.85-9.02% kcal)], and had lower cognitive dietary restraint [15 (13-17) vs. 16 (14-19)] compared to children/adolescents with MHO. Deep fried food, fast food and processed convenience food were positively associated with both systolic (β: 2.84, 95%CI: 0.95-6.62) and diastolic blood pressure (β: 4.83, 95%CI: 0.61-9.04). Higher polyunsaturated fat intake (OR: 0.529, 95% CI: 0.284-0.986) and cognitive dietary restraint (OR: 0.681, 95%CI: 0.472-0.984) were associated with a lower risk of the MUO phenotype. The authors concluded that a healthier diet composition and positive eating behavior may contribute to favorable metabolic outcomes in children and adolescents with obesity.

**Serum 25-OH vitamin D and fatty acids in relation to the risk of microbial infections in children: The TRIGR Divia study** (Clin Nutr. 2022 2022;41:2729-39)

Nutrient status may affect the risk of microbial infections and play a role in modulating the immune response against such infections. This study was conducted with the aim to determine whether serum 25(OH)D and serum fatty acids in infancy are associated with microbial infections by the age of 18 months. 576 newborn infants from Trial to Reduce IDDM in the Genetically at Risk (TRIGR), born between 2002 and 2007 were included. Concentration of 25(OH)D vitamin and proportions of 26 fatty acids were analyzed in cord blood serum and in sera at 6, 12, and 18 months of age. The cord blood samples and mean of 6-18 month values were used as exposures. Infections were detected by screening IgG antibodies against 10 microbes using enzyme immunoassay and antibodies against 6 Coxsackievirus B serotypes at 18 months of age. A higher proportion of *n*-3 polyunsaturated fatty acids (PUFAs) and especially long-chain n-3 PUFAs at birth and at the age of 6-18 months was associated with decreased risk of coxsackievirus B2 infection. Higher proportion of docosapentaenoic acid (DPA, 22:5 *n*-3) at birth was associated with a decreased risk of respiratory syncytial virus infection. 25(OH)D vitamin concentration was not consistently associated with the risk of infections. The authors concluded that in young children with increased susceptibility to type 1 diabetes, long-chain *n*-3 PUFAs may influence the risk of viral infections and immune response against the infections.

**Anemia in Indians aged 10-19 years: Prevalence, burden and associated factors at National and regional levels** (Matern Child Nutr. 2022;18:e13391)

The aim of this study was to describe the national and subnational prevalence, severity and burden of anemia among Indian adolescents; and to examine factors associated with anemia at national and regional levels. Data (*n*=14,673 individuals aged 10-19 years) were from India's Comprehensive National Nutrition Survey (CNNS, 2016-2018). Anemia was present in 40% of girls and 18% of boys, equivalent to 72 million adolescents in 2018, and varied by region (girls 29%-46%; boys 11%-28%) and state (girls 7%-62%; boys 4%-32%). Iron deficiency (ferritin < 15 µg/L) was the strongest predictor of anemia [odds ratio (OR): 4.68, 95% CI: 3.21,6.83], followed by hemoglobinopathies (HbA2 >3.5% or any HbS) (OR: 2.81, 95% CI: (1.66,4.74), vitamin A deficiency (serum retinol <20 ng/mL) [(OR: 1.86, 95% CI: 1.23,2.80] and zinc deficiency [(serum zinc <70 µg/L) (OR: 1.32, 95% CI: 1.02,1.72). The authors concluded that adolescent anemia control programs in India should continue to address iron deficiency and strengthen strategies to identify hemoglobinopathies and other micronutrient deficiencies.

**Serum ferritin, zinc, and copper levels in children with *H. pylori* gastritis and the effect of the treatment** (J Pediatr Gastroenterol Nutr. 2022;75:e88-93)

This study aimed to assess the serum levels of iron, zinc, and copper in symptomatic children with *H. pylori* infection, and to evaluate the effect of *H. pylori* treatment on their levels. Seventy children were with upper gastrointestinal tract symptoms. *H. pylori* infection was diagnosed by the H. pylori antigen test in the stool and histopathologic findings during upper gastrointestinal endoscopy. Hemoglobin, serum ferritin, transferrin (sTfR), zinc, and copper were assessed. *H. pylori*-infected children had low serum ferritin and zinc levels, high sTfR level and no effect on serum copper levels. After treatment, the hemoglobin, serum ferritin and zinc significantly increased in *H. pylori*-positive patients, especially in those who responded to treatment. The authors concluded that *H. pylori*-infected children had low serum ferritin and zinc levels but high sTfR level with no effect on serum copper levels. Gastric histologic findings correlated significantly with hemoglobin, serum ferritin, zinc, and sTfR levels.

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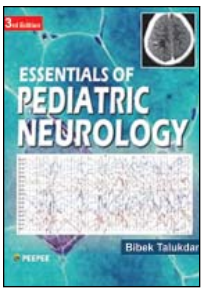
# AUTHOR INDEX 2022

## INDIAN PEDIATRICS

*Volume 59, January-December, 2022*

# SUBJECT INDEX 2022

# BOOK REVIEW




**Essentials of Pediatric Neurology**

**BIBEK TALUKDAR**
*Peepee Publisher, New Delhi*
*Pages*: 584; *Price*: Rs. 795/-.

This book is a valuable addition to Indian medical literature. Pediatric Neurology is a relatively new discipline and is in the process of consolidation, with DM and DNB programs being initiated in different parts of India. There is need for new trained manpower to maintain and develop pediatric Neurology. Effective teachers and books are necessary, to draw young residents and students to this upcoming discipline. An Indian book on Pediatirc Neurology is needed, which not only makes the reader interested but also address to the regional pediatric neurology issues. The book nicely fills this gap.

The book has six sections which naturally flow from one to the other. The first section details the clinical evaluation and investigations, imaging, stroke, electro-encephalogrpahy, nerve conduc-tion and evoked potential study and special issues with neonatal neurophysiology. The second section deals with developmental disorder including congenital malformation, attention and hyper-kinetic disorders, autism, learning disorders, intellectual disability disorders and finally a chapter on approach to a child with neurodevelopmental delay. The third section deals with seizures and epilepsies and describes various types of seizure in children. There is also a chapter on pediatric status epilepticus.This section concludes with a chapter on approach to children with seizure and epilepsy. The fourth section deals with encephalopathy, neuropathy and neuromuscular disorders which deals with a wide variety of subjects like cerebral palsy, movement disorders, demyelinating disorders, Guillane Barre syndrome, Spinal muscle atrophy and neuromuscular junction disorders. The fifth section deals with infections and includes chapters on bacterial meningi-tides, viral meningitis, encephalitis, including Japanese encephalitis, polio, malaria and neurocysticercosis. The sixth section includes the miscellaneous disorders such as headache, stroke, neuromuscular syndrome neuro-degenerative disease, hydrocephalus.The last chapter of this section is about dosageof drugs in pediatric practice. Most of the sections have a concluding chapter by the editor himself giving an overview based on his rich clinical experience on the respective subject thereby maintaining uniformity and conveying a mature clinical approach directly to the readers. Multiple authors are necessary in the increasingly complex medical specialty and con-veying different view points and diversity of approaches whereas single author books convey a more focussed personalized approach, directly to the readers.This book has contribution from a large number of authors and overview of editor in a concluding chapter which has complimentary dual advantage. Each chapter is well referenced and amply illustrated with numerous clinical photographs, imaging findings and tables which make the reading effective and add to the value of book. The main focus of the book is clinical bedside application although basic issues have also been given due importance. Most of the conditions important in Indian context have been given due importance. Time is determinant of growth and development which applies to this book also; the present edition is larger than earlier ones, and the future editions are likely to be bigger to accommodate the growing information and developments. I hope to see a section of pediatric neurocritical care and cost effective medicine in subse-quent edition of this book.

The authors of different chapters are mainly from New Delhi but are experienced, knowledgeable and have taken great care to write their chapters. This book will be useful for pediatrics, neurology and neurosurgery residents, student and consultants and anyone dealing with neurological disorders in children.

This book will not only be useful for Indian readers but also to neighboring SARC and south Asian readers where clinical requirements and practice conditions are similar to ours.

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