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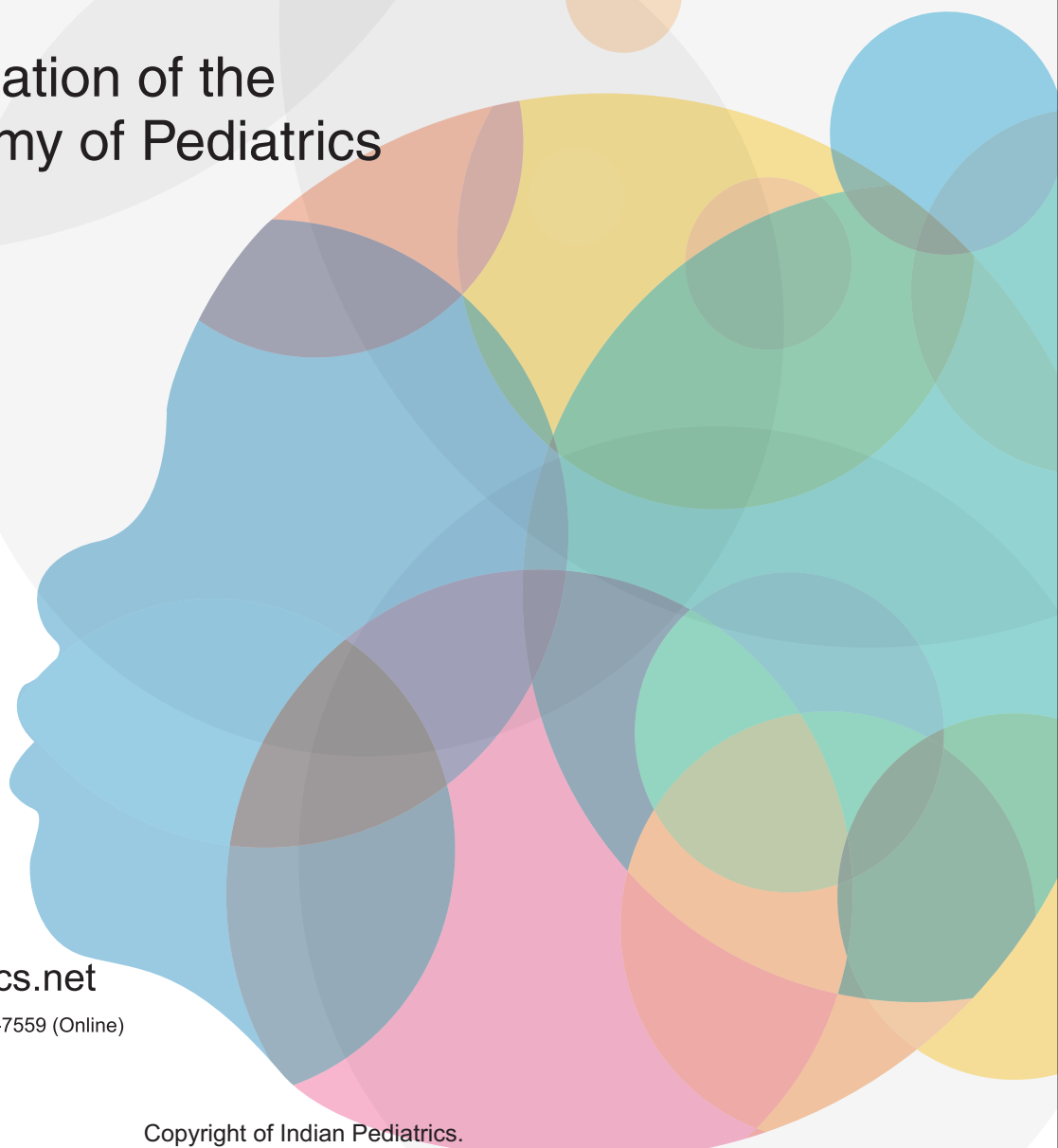

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IAP Guidelines for pediatric skincare

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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Substance Use: Focus on Adolescent Health

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"*Adolescence is a new birth, for the higher and more completely human traits are born now*"

G Stanley Hall

Adolescence is a promising stage in life when the child matures into an adult. All children are born with adorable innocence but their unique personalities find their footing in teenage only. This is a period of sudden and rapid physiological, psychological and behavioral change. Kids are prone to experiment with life and assert their independence in this phase. Very often a complete transformation can be seen in the personality. Those who were earlier noisy and hyperactive might suddenly become introverted, while the quiet ones might now seem more outgoing. A few may even turn rebellious. Along the way, we see their social life evolving with a new circle of friends. New hobbies and special interests take over. The real person is becoming born, developing character and traits that will stand by him or her for a lifetime.

On these grounds, adolescence is considered to be the most vulnerable phase of life. It can make or mar the life ahead. One of the big threats that afflict adolescence is substance use. They become exposed to addictive substances like tobacco, alcohol and psychotropic drugs like cannabis, cocaine and LSD. While some flirt with these temporarily, some others find it difficult to move on and get hooked. Withdrawal and isolation, or conversely aggressive behavior, emotional instability, neglect of studies and normal life activities and getting into trouble with authority figures and such other problematic issues might follow. Many such youth may end up in an adolescent clinic, when it becomes our duty to address the issue and lead them to a healthy life.

As a specialty discipline, Pediatrics has traditionally dealt with childhood diseases and disorders. There are well established protocols to deal with most of these, and as such the practicing pediatrician will rarely feel challenged. But the rapid expansion in the scope of our discipline has resulted in a bigger role for adolescent health. Many adolescent issues, such as substance use, fall in a gray area of medicine. They do not submit to black and white clinical analysis, but rather their scope spans other realms like psychology, behavioral science, sociology and the societal culture in general. Hence Pediatricians need to be well aware of these dimensions if they have to serve any useful role to help these young people and provide relief to their families as well.

CHILDHOOD – THE ENTRY POINT FOR SUBSTANCE USE

Substance use, also known as substance abuse, is the use of a drug in amounts or by methods which are harmful to the individual or others. According to Childline India, which is a nodal agency of the Union Ministry of Women and Child Development, the incidence of drug abuse among children and adolescents is higher than the general population [1]. This is notably because youth is a time for experimentation and identity forming. Many street children use cheap drugs to cope with the daily cycles of sexual, physical and mental abuse or as recreation to escape a life of poverty. Heroin, opium, alcohol, cannabis and propoxyphene are the five most common drugs being abused by children in India. The use of certain drugs such as whitener, alcohol, tobacco, hard and soft drugs is especially widespread among street children, working children and trafficked children but there is currently a lack of reliable data on drug abuse amongst children.

A survey undertaken by an NGO in India revealed that 63.6% of patients coming for treatment were introduced to drugs at a young age, as early as 12 years. According to another report 13.1% of the people involved in drug and substance abuse in India, are below 20 years. The use of tobacco is another major concern amongst children. In India, 20 million children a year and nearly 55000 children a day are drawn into tobacco addiction. The number is shocking when compared to the 3000 a day new child smokers in the US. While alcohol and tobacco are not to be sold to minors, other drugs are illicit and illegal. Strong aroma of substitute items like pain relief ointments, chemical adhesives, paint and paint thinners, gasoline and shoe polish are often inhaled to get a high. Cough syrup and certain prescription medicines and even snake venom and certain varieties of mushrooms might be taken for the sake of a kick. Children affected by substance abuse are considered as 'children in need of care and protection' under the Juvenile Justice Act, 2015 [1].

The initial motivation for substance use could be as simple as natural curiosity or more complex like peer pressure, the need to fit into a particular group and influence of negative role models like celebrities in the news. Adolescence is characterized by independence from parents and older adults and seeking close ties with peers and friends. This age range is also characterized by experimenting with new ideas, life styles, and making choices that not always prove to be right. According to various studies, children who have at least one parent or an older sibling who has problems with substance use is more likely to develop these symptoms themselves [2]. Unhappy family background and history of child abuse is very often observed with substance use. Breakdown of joint family system into nuclear families, rapid urbanization and the evolution of new social structures are also identified as some of the other causative factors. College campuses and hostels are an important point of initiation to substance use.

According to a study from India in 2013-15, comprising 446 children and adolescents who reported for de-addiction, majority were in the age group 16-19 years (95.7%), 49.5% were from urban areas and 50.5% patients were from rural areas. Out of these, 36.1% were employed, 24.4% were unemployed and 39.5% were students. The results showed more involvement of males as compared to females. As far as educational status is concerned, 47.5% had studied up to matriculation, 24% up to secondary school, and 5.4% were illiterate [3].

IAP – NEED FOR A PROACTIVE ROLE

It is clear from the above that adolescence is the entry point for substance use. Hence, pediatricians of the future will definitely have an increasing role to play in dealing with this social evil. IAP Adolescent Chapter is propagating analytical and interventional tools to equip practicing pediatricians to appropriately understand and address the problem of substance use. Sensitive, enlightened and compassionate approach is required on the part of the clinician to deal with this. The chapter has also launched Mission Kishore Uday to ensure the well being of the youth of the country. This project includes addressing substance use as a major concern. One of the stumbling blocks is that substance use is a hugely neglected problem. There are very few specialized facilities to deal with it. The sheer complexity of the issue places it beyond the scope of clinical pediatrics. A collaborative approach might be needed involving all the stakeholders like pediatricians, parents, teachers, social workers, counselors and others.

In the years to come, we need to delve deeper into this topic as solving the problem of substance use will play a significant role in enhancing the general health of society.

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RESEARCH PAPER

Molecular Characterization and Management of Congenital Hyperinsulinism: A Tertiary Centre Experience

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Background: There is limited data from India regarding medical management of congenital hyperinsulinism (CHI).

Objective: To study the molecular diagnosis, medical management and outcomes of children with CHI.

Study design: Ambispective.

Participants: Children with CHI admitted in from December, 2011 till March, 2020 at a tertiary care referral hospital.

Outcomes: Clinical and genetic profile, treatment, and response

Results: 42 children with a median age of 3 days (range 1 day to 6 years) were enrolled, of which 23 (54.7%) were diazoxide-responsive. Mutations were identified in 28 out of 41 (68.2%) patients. The commonest gene affected was *ABCC8* in 22 patients. The pathogenic variant c.331G>A in *ABCC8* gene was identified in 6 unrelated cases from one community. Good response to daily octreotide was seen in 13 of the 19 (68.4%) diazoxide-unresponsive patients. Monthly long-acting octreotide was initiated and daily octreotide could be stopped or tapered in 9 patients. Sirolimus was tried with variable response in 6 patients but was discontinued in 5 due to adverse effects. Four patients had focal CHI, of which one underwent partial pancreatic resection. The disease severity reduced with age and neurodevelopment was good in the patients with identifiable genetic defects who were optimally managed. **Conclusions:** Medical management of CHI is effective, if compliance can be ensured, with good quality of life and neurological outcomes.

Keywords: *ABCC8 gene, Diazoxide, Hypoglycemia, Octreotide, Sirolimus*

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Congenital hyperinsulinism (CHI) results from inappropriate release of insulin from the pancreatic β-cells that causes persistent hypoglycemia in neonates and infants, with possible adverse neurodevelopmental outcomes [1,2]. It is a rare disorder with an incidence varying from 1 in 28 000-50 000 births in Western countries to 1 in 2 500 in the Middle East [3,4]. Mutations in around 15 key genes involved in pancreatic insulin secretion have been identified to cause CHI, the most common being *ABCC8* and *KCNJ11*genes, encoding the sulphonylurea receptor (SUR1) and K+ inward rectifying (KIR6.2) subunits of the K_{ATP} channel, respectively [3]. Identification of the underlying genetic etiology and the mode of inheritance is essential for management and counseling regarding the risk of recurrence.

Histopathologically, CHI can be categorized into diffuse or focal forms [5,6]. The focal forms are amenable to cure by resection of the lesion or partial pancreatectomy. In diffuse CHI, medical treatment with diazoxide and octreotide is the mainstay [7]; though, surgical modality was used in the past in non-responders [8]. In recent years, medical management with the use of newer options such as long-acting formulations of octreotide have emerged as the treatment of choice [7]. There is limited data from India regarding medical management and outcome of infants with CHI [9,10]. In this study, we present our long-term experience in the management of infants with CHI in India.

METHODS

This was an ambispective study of the clinical profile, biochemical and molecular diagnoses, drug response and follow-up assessment of children with a diagnosis of CHI, who were admitted or referred to the Pediatric Endocrine Division of the Department of Pediatrics at a tertiary care hospital in the last nine years between December, 2011, when genetic testing was incorporated in the CHI

management protocol, to March, 2020. Patient data was retrieved from records and also collected prospectively from 2017 onwards. Patients not under regular follow-up were contacted via telephone or email for collecting information on their current treatment, growth and development. The study was approved by the ethics committee of our institution.

The diagnosis of CHI was based on recurrent hypoglycemia, glucose requirement >8 mg/kg/min to maintain euglycemia in the newborn period, critical sample serum insulin of >2 mIU/L, inappropriately suppressed blood ketone (<2 mmol/L) or negative urinary ketone, and inappropriate glycemic response to glucagon challenge test (GCT). Other investigations included critical sample for growth hormone (GH), cortisol, lactate, galactosemia screen and serum ammonia levels.

Genetic testing of the proband (along with the parents in most cases) was performed either at Department of Molecular Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK or Department of Molecular Genetics, Madras Diabetes Research Foundation (MDRF), Chennai after taking informed consent from the parents. Sanger sequencing was performed for *ABCC8* and *KCNJ11* genes first, and for *GLUD1, GCK, HADH* in patients with specific suggestive features. Targeted next generation sequencing (tNGS) of the coding regions and exon/intron boundaries of known CHI genes (panel consisting of *KCNJ11*, *ABCC8*, *GLUD1*, *GCK*, *HADH*, *HNF4A*, *INSR*, *SLC16A1*, *TRMT10A* and *HNF1A*) was obtained (Agilent custom capture v5.3/Illumina NextSeq500) in patients with persistent diazoxide-unresponsive hypoglycemia in whom no pathogenic variants were identified in the common genes. Nuclear scan (18-F DOPA PET) was performed in-house to rule out focal pancreatic pathology where indicated.

Oral diazoxide was used as the first line of treatment in a dose of 5-15 mg/kg/day in 3 divided doses. Hydrochlorthiazide was added at a dose of 1.5-2.5 mg/kg/ day to prevent fluid overload. The patient was deemed diazoxide-responsive if the blood glucose normalized and glucose infusion could be tapered off. Minimum of 5 days of treatment at a maximum dose of 20 mg/kg/day was given before labeling the patient as diazoxide-unresponsive. The second line of treatment consisted of injection octreotide with a starting dose of 15-20 µg/kg/day (maximum 50 µg/kg/day). In case of sub-optimal response to octreotide, a trial of sirolimus was given in a dose of 0.05-1.8 mg/m^2 to keep the plasma drug level between 5-15 ng/mL with monitoring of side effects. Where feasible, patients on long-term octreotide were switched to long-acting release (LAR) octreotide intramuscularly monthly, at a dose calculated as daily dose multiplied by 30. After starting monthly injections, daily octreotide was tapered and stopped over the next few months, where feasible. A blood glucose value >70 mg/dL was considered normal. The treatment was considered effective if 90% blood sugar values were normal with no severe hypoglycemia (<30 mg/dL) or hypoglycemic seizures.

Most of the enrolled subjects were a few weeks old at the time of hospitalization. They were managed with frequent 2-3 hourly feeds (expressed breastmilk or formula) orally or via nasogastric tube. Feeds were supplemented with uncooked cornstarch at 1-2 g/kg/day, or with glucose 0.5 g/kg/feed, as needed.

Importance of compliance with medication and regular feeding, especially nocturnal feeds, was emphasized as part of education at discharge. Parents were taught to administer tube feeds, monitor blood glucose, manage hypoglycemia, and give subcutaneous octreotide (where indicated). Post-weaning, a balanced diet with avoidance of foods with high glycemic index was advised.

Patients were followed up monthly in the first year of life. Anthropometry and development assessment were performed in each follow-up visit. Children with delayed milestones with or without microcephaly were advised formal developmental assessment, sensory stimulation and magnetic resonance imaging (MRI) brain. Those on octreotide were monitored with liver function tests every three months and ultrasound abdomen for gall bladder stones every six months.

Statistical analysis: Statistical analysis was carried out using STATA version 14.0. Continuous variables were compared using student *t* test and proportions with chi-square test. A *P* value <0.05 was considered statistically significant

RESULTS

A total of 42 patients (23 males) were included in the study, 26 of whom had presented in the neonatal period. The median age of presentation was day 3 (range 1 day to 6 years). Consanguinity was present in 4 families. Two families had two affected siblings and three families had history of previous neonatal deaths. Hypoglycemic seizure was the most common presentation, and macrosomia was present in 15/26 (57.7%) neonates indicating inutero hyperinsulinism.

Mutations were identified in 28 (68.2%) patients, with *ABCC8* gene mutations in 22 (53.6%) patients. Of these, 14 had autosomal recessive mode of inheritance (homozygous and compound heterozygous in 8 and 6 patients, respectively), six had a paternally inherited heterozygous mutation, and two had de novo autosomal dominant mutations.

Twenty-three (54.7%) patients responded to diazoxide. Mutations could be identified in 9/22 (41%) of the diazoxide-responsive cases (1 could not be tested) and all the diazoxide-unresponsive patients. **Table I** presents the clinical comparison between diazoxide-responsive and unresponsive patients.

Web Table I summarizes the clinical presentation, genetic defects, F-DOPA PET results, treatment and follow-up of the patients. A total of 22 different pathogenic/likely pathogenic variants were identified in *ABCC8* gene, of which three variants were novel, namely c.3653+2T>G (abnormal splicing), c.2423_2424del (p.L808fs), and c.4411G>A (p.D1471N). All the novel variants were predicted to be pathogenic using prediction software, and were present in heterozygous state in clinically unaffected parents. The pathogenic variant c.331G>A (p.G111R) was common, and present in six patients; in homozygous state in two (cases 8, 14), compound heterozygous in three (cases 1, 3 and 13) and paternally-inherited heterozygous in one (case 20).

Two babies (patient 41 and 42) with prematurity and intrauterine growth retardation had transient but prolonged hyperinsulinism and succumbed at 1 month and 3 months of age, with prematurity and liver failure, respectively. One baby had no identifiable genetic mutation while the other could not be tested.

Subcutaneous octreotide was started in 19 patients with diazoxide-unresponsive disease (autosomal recessive or paternally inherited heterozygous pathogenic variants in *ABCC8*). Thirteen patients achieved good response at a median daily dose of 40 (range 35-50) µg/kg/day, while 4 continued to have hypoglycemia. Nine patients were started on monthly LAR octreotide injection at the median age of 6 month (range 3 month - 4 year). Daily octreotide was gradually stopped over the next 3-12 months in five patients, and the doses were reduced in remaining four patients.

Table I Response to Diazoxide in Children With Congenital Hyperinsulinism (*N*=42)

Characteristic	*Diazoxide responsive (n=23)*	*Diazoxide unresponsive (n=19)*
Male gender	10 (43.5)	11 (57.8)
Preterm birth	3 (13)	4 (21)
Birthweight[b,c]	2.86 (0.68)	3.61 (0.69)
Large for gestational age[c]	2 (8.7)	14 (73.6)
Neonatal onset[c]	7 (30.4)	19 (100)
Onset of hypoglycemia[a,c]	3 mo (1 d-6 y)	1 d (1-10 d)
Age of referral[a,c]	7 mo (1 mo-12 y)	1 mo (12 d-5 mo)
Genetic mutations[c]	9/22 (41)	19 (100)
Pathogenic variants	*ABCC8* (paternal), 1; *ABCC8* (AD), 2; *HADH* (AR), 2; *GLUD1*(AD), 3; *KMD6A,*1	*ABCC8* (AR), 14;*ABCC8* (paternal),5
Neurodevelopmental issues	12/20 (60)	3/17 (17.6)

Data expressed as n (%) or [a]median (range) or [b]mean (SD). AD: autosomal dominant, AR: autosomal recessive; neurodevelopmental issues - developmental delay or behavioral problems. [c]P< 0.05.

Sirolimus was started in six patients with partial response. However, it was discontinued in one patient because of inability to reach therapeutic blood levels on maximum dose, and in four other patients after a variable duration of treatment due to adverse effects. None of our patients received long term glucagon treatment.

Six patients had paternally inherited heterozygous *ABCC8* mutations (cases 15-20); three out of four patients had focal disease on18-F DOPA-PET, Of these, one patient (case 19) with a focal lesion at the junction of tail and body of pancreas underwent partial pancreatic resection at 7 months of age and has remained euglycemic till date. Second patient (case 16) was well controlled on octreotide and the treatment was stopped at 1 year of age. The third patient (case 17) had a lesion in the head and uncinate process of pancreas, which was deemed inoperable. She was continued on octreotide and sirolimus with few episodes of hypoglycemia related to poor compliance.

Hypertrichosis to a variable degree was noted in all infants receiving diazoxide, which reversed partially as the dose decreased on follow-up. One patient (case 6) developed congestive heart failure at initial trial. Case 39 developed neutropenia after 3 months of treatment and diazoxide had to be discontinued. One baby (case 42) with IUGR developed jaundice and liver failure after starting diazoxide.

Five patients developed gastrointestinal intolerance with octreotide. One patient had constipation and rectal bleeding with octreotide given at 55 µg/kg/day, and the dose had to be decreased. Transient mild elevation of transaminases was noted in three patients, but none had significant derangement needing withdrawal of the drug. One patient had asymptomatic gallstones and biliary sludge that improved with UDCA.

A derangement in liver function was seen in two patients on sirolimus. One patient (case 4) was euglycemic on sirolimus monotherapy, but developed life-threatening sepsis with shock at 4 years of age after which sirolimus was switched to LAR octreotide. Case 3 developed refractory anemia not responding to iron after which sirolimus was stopped. Case 17 was lost to follow-up during the Covid-19

lockdown and died at 1.7 years due to sepsis in another hospital.

The median age till follow-up was 3.9 year (range 3 month - 15 year) and 3.5 years (range 3 month - 9 year) in diazoxide-responsive and unresponsive disease, respectively. On follow-up, the growth parameters of all patients on diazoxide and most patients on octreotide were within normal range. Two patients on octreotide had height <-3SD with short mid-parental height where causal role of octreotide with short stature could not be established. Case 3, with height at -3.8 SD at 3 year showed improvement to -3.1 SD over the next 1.5 years after stopping octreotide. Three patients developed obesity in infancy. Of the 14 patients with autosomal recessive *ABCC8* mutations (P1-14), two children had died, seven had normal development, three had initial mild motor delay (which improved with time), and two had global developmental delay. Of note, 9 out of 11 alive patients had normal neurodevelopment in follow up. Among the 6 patients with paternally inherited heterozygous *ABCC8* mutations, five had normal neuro-development, while one had frequent hypoglycemic seizures with global delay, and died at 1.7 year. Among the diazoxide-responsive cases, the neurodevelopmental outcomes were highly variable.

DISCUSSION

In this series of children with CHI from India, mutations could be identified in the majority, the commonest being autosomal recessive *ABCC8*, similar to the observations in previous Indian data [9]. The response rate to diazoxide in our study was similar to the reported rate of 50-65% [11,12]. The positivity rate of mutations in this study was similar to the previously reported rate, suggesting that the etiology of diazoxide-responsive CHI was very heterogeneous and not fully elucidated [11,12].

All the six patients with the pathogenic variant c.331G>A (p.G111R) in *ABCC8* gene, although unrelated and from different states of Northern India, belonged to the Aggarwal community. This is interesting as caste endogamy is prevalent in this community and it is known to harbor founder mutations for other rare autosomal recessive disorders such as panthothenate kinase associated neuro-degeneration, and megalencephalic-leukodystrophy with cysts [13].

Our observations suggest that medical therapy can be used in focal disease if euglycemia is achieved on a single drug, as there are chances of spontaneous remission. Non-availability of surgical expertise and family's preference are also relative indications of medical management in focal CHI [14]. 18-F DOPA-PET is highly useful for localizing focal lesions [15]; however, its availability is limited.

Majority of patients with homozygous *ABCC8* mutations and diffuse CHI responded well to octreotide, in consonance with previous literature [14,16], and nine of these patients were shifted to long-acting formulations. Lanreotide and sandostatin-LAR are two long-acting somatostatin analogues [17], of which only the latter is available in India. It is used in parallel with daily octreotide therapy for few months, till blood levels of octreotide reach adequate levels [18]. There are limited reports on use of long-acting octreotide in CHI suggesting better glycemic control [18,19].

Diazoxide can lead to multiple side effects including pulmonary hypertension (PH) [7,20]. PH is reported in 2.4-7% patients, especially in children with congenital heart disease [21], but we did not routinely monitor for this. Long-acting octreotide formulations should be used only beyond the neonatal period. Suppression of growth hormone and growth failure are occasionally reported with somatostatin analogues, but catch-up growth occurs in follow-up after octreotide is weaned [14,16], as was observed in one of our patients. Octreotide therapy can lead to suppression of thyroid stimulating hormone to recommend regular monitoring of thyroid function [7], though none of our patients had deranged thyroid function on follow-up. Sirolimus, an mTOR inhibitor, has been reported to reduce the proliferation of pancreatic β-cells and inhibit insulin secretion [22], was found to be effective in conjunction with octreotide in two patients, and as monotherapy in one. However, it had to be discontinued in most patients due to serious side effects; as also reported recently in a follow-up study in 22 patients [23].

There were multiple challenges in the medical management, the foremost being cost of daily octreotide and LAR preparations. Lack of free availability of diazoxide, frequent feeding and monitoring of blood sugar, and compliance to multiple daily injections were additional challenges faced by the families. The use of LAR octreotide helped in improving compliance to treatment. Non-response to diazoxide and post-surgical diabetes requiring insulin therapy have been identified as major drivers of cost in a previous study [24]. Medical therapy although expensive in the short-term, can help reduce overall costs as clinical disease remits with age.

Neurodevelopmental outcomes were highly variable in diazoxide-responsive patients, depending on age of diagnosis and referral, underlying molecular mechanism and compliance to therapy. Overall, in our study, developmental outcomes were poorer in those with low compliance or delayed diagnosis. Hypotonia, fine motor problems, clumsiness and speech problems were reported in medically treated diazoxide-unresponsive children,

which resolved by 4-5 years of age with subsequent normal neurodevelopment [14].

The limitations of our study are that compliance could not be formally documented in all patients, and detailed neurodevelopmental assessment for subtle issues in behavior, learning, attention and speech was not done in all patients.

To conclude, in this series of medically treated Indian children with CHI, the main challenges were related to frequent monitoring, feeding, compliance to medication and high cost of therapy. Good neurodevelopmental outcomes were observed in those with optimal care and appropriate medical therapy. Remission or reduction in severity after the first two years of life was noted, which is a silver lining in the management of this difficult disease.

Ethics clearance: Ethics committee of AIIMS, New Delhi; No. IEC 109/5.2.21, RP-26/2021, dated February 05, 2021.
Contributors: RS, KR: prepared the manuscript; RS, KR, AS, PMN, AK, ND, VJ: involved the diagnostic work up, clinical management of patients and data collection; SEF, JALH, VR, VM: performed the genetic studies; VJ: conceived the study, initiated the collaborations for genetic testing, critically reviewed the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work.
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Competing interests: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I: Summary of Genetic Mutations, Treatment and Follow-Up in Patients with Congenital Hyperinsulinism (*N*=40)

S. no.	*Age at onset*	*Pathogenic variant*				*F-18 DOPA PET*	*Initial treatment*	*Follow-up*			
		Gene, zygosity	*Nucleotide change*	*Protein change*	*Type of variant*			*Age*	*Treatment*	*Growth*	*Development*
P1	Day 8	*ABCC8,* Compound hetero	c.331G>A/ c.3979G>T	p.G111R/p.E1327*	Missense/ Nonsense	Diffuse	Octreotide 35 µg/kg/day LAR started at 3 y	9 y	LAR 7.5 mg every 45 days	Normal	Initial motor delay Average school performance
P2	Day 1	*ABCC8,* Compound hetero	c.1330C>T/ c.3653+2T>A	p.Q444*/p.?	Nonsense/ Aberrant splicing variant^	Diffuse	Octreotide 40 µg/kg/day LAR 10 mg per month from 2.5 y, stopped at 3.5 y	4.5 y	None	Normal	Mild motor delay Delayed speech
P3	Day 1	*ABCC8,* Compound hetero	c.221G>A/ c.331G>A	p.R74Q and p.G111R	Missense/ Missense	Diffuse	Octreotide 50 µg/kg/day; Sirolimus added but stopped due to severe anemia. Octreotide tapered and stopped at 2 y	4.5 y	None	Ht -3 SD Rest normal	Normal
P4	Day 2	*ABCC8,* Homo	c.522dup/ c.522dup	p.L175fs/p.L175fs	Frameshift	Diffuse	Poor response and compliance to octreotide Sirolimus 1.8 mg/m^2 Developed sepsis at 4 y, shifted to octreotide LAR	4 y	LAR10 mg monthly	Normal	GDD, DQ 70, epilepsy on AED
P5	Day 1	*ABCC8,* Compound hetero	c.4480C>T/ c.(4414+1_4414-1)_(*4749+34_?) del	p.R1494W/p.?	Missense/ Deletion	Not done	Octreotide 40 µg/kg/day	Lost to FU after 6 mo	-	Normal	Global delay
P6	Day 1	*ABCC8,* Homo	c.3653+2T>G/ c.3653+2T>G	p.?/ p.?	Aberrant splicing^	Diffuse	Octreotide 40 µg/kg/day LAR 12 mg monthly since 2 y of age Sirolimus trial; stopped due to low plasma drug levels	3.5 y	Daily octreotide at 10 ug/kg/day LAR 12 mg monthly	Height -3.5 SD Rest normal	Initial mild motor delay Normal in FU
P7	Day 1	*ABCC8,* Homo	c.2423_2424del/ c.2423_2424del	p.L808fs/p.L808fs	Frameshift^	Diffuse	Octreotide 35 µg/kg/day LAR 10 mg monthly since 6 mo of age	2.5 yrs	LAR 10 mg monthly	Height -2 SD	Normal
P8	Day 1	*ABCC8,* Homo	c.331G>A/ c.331G>A	p.G111R/p.G111R	Missense	Diffuse	Octreotide35 µg/kg/day. Sirolimus tried but stopped due to deranged LFT. LAR 5 mg monthly started at 4 mo, daily octreotide stopped after 1.5 y.	2.5 yrs	LAR 10 mg q 2 monthly	Weight for height 97th centile Rest normal	Normal, h/o myoclonic jerks controlled on AED
P9	Day 1	*ABCC8,* Homo	c.3653+2T>G/ c.3653+2T>G	p.?/ p.?	Aberrant splicing^	Diffuse	Octreotide40 µg/kg/day. Sirolimus tried but stopped due to deranged LFT. LAR 10 mg monthly started at	2 yrs	LAR 10 mg monthly	Obese Wt for height 99th cent Rest normal	Normal

							4 months of age				
P10	Day 1	*ABCC8*, Homo	c.2675_2679del/c.2675_2679del	p.Q892fs/p.Q892fs	Frameshift	Not done	Octreotide50 µg/kg/day Planned for near-total pancreatectomy	LAMA, expired	-	-	-
P11	Day 2	*ABCC8*, Compound hetero	c.267delT and c.619-629 del CCCGAGGACCT	p.(Ile89MetfsTer10)/ p.(Pro207AlafsTer61)	Frameshift	Not done	Octreotide 40 µg/kg/day	Expired at 4 mo due to hypoglycemia at night	-	-	-
P12	Day 1	*ABCC8*, Homo	c.1138del	p.(Ala380fs)/ p.(Ala380fs)	Frameshift	Diffuse	Octreotide 40 µg/kg/day LAR started at 5 months of age	1 y	LAR 10 mg monthly Octreotide 10 ug/kg/day	Wt for Ht + 2SD Rest normal	Normal
P13	Day 1	*ABCC8*, Compound hetero	c.331G>A/ c.4411G>A	p.Gly111Arg/p.Asp1471Asn	Missense/ Missense^	Diffuse	Octreotide50 µg/kg/day LAR 5 mg monthly started at 2 mo	4 mo	Octreotide 40 µg/ kg/ day, LAR 5 mg monthly	Normal	Normal
P14	Day 2	*ABCC8*, Homo	c.331G>A/ c.331G>A	p.G111R/p.G111R	Missense	Not done	Octreotide 40 µg/kg/day	3 mo	Octreotide 40 µg/ kg/ day	Normal	Normal
P15	Day 1	*ABCC8*, Paternally inherited hetero	c.3871-1G>A	p.?/N	Aberrant splicing	Diffuse	Octreotide10 µg/kg/day	9 mo	LAR 2 mg monthly	Normal	Normal
P16	Day 1	*ABCC8*, Paternally inherited hetero	c.4024C>T/ N	p.Q1342*/N	Missense	Focal	Octreotide 10 µg/kg/day	2.5 y	Off treatment since 1.2 y	Normal	Normal
P17	Day 1	*ABCC8*, Paternally inherited hetero	c.4256G>A/ N	p.R1419H/N	Missense	Focal	Octreotide40 µg/kg/day Sirolimus 0.3 mg/m^2	1.5 y Lost to FU: Expired at 1.7 years due to sepsis	Octreotide 40 µg/ kg/day sirolimus Poor compliance	Normal	Moderate GDD
P18	Day 10	*ABCC8*, Paternally inherited hetero	c.1330C>T	p.Q444*/N	Nonsense	Not done	Octreotide20 µg/kg/day till 2 years of age	7 y	Off treatment since 2 years of age	Normal	Normal
P19	Day 3	*ABCC8*, Paternally inherited hetero	c.4415-13G>A	p.?/N	Aberrant splicing	Focal	Octreotide 12 µg/kg/day Partial pancreatectomy done at 7 months of age	3 y	None	Normal	Normal
P20	Day 6	*ABCC8*, Paternally inherited hetero	c.331G>A/ N	p.G111R	Missense	Not done	Diazoxide	4.5 y	4 mg/kg	Normal	Normal
P21	Day 3	*ABCC8*, Hetero (de novo)	c.4377G>C/ N	p.Q1459H	Missense	No focal lesion	Diazoxide	8 y	Stopped after 6 years	Normal	Mild MR
P22*	Day 1	*ABCC8*, Hetero (de novo)	c.4519G>A	p.Glu1507Lys	Missense	Not done	Diazoxide	18 mo	3.5 mg/kg	Normal	Mild GDD

P23	3 mo	*HADH,* Homo	c.550A>T	p.I184F	Missense	Not done	Diazoxide	5 y	5 mg/kg	Normal	Normal
P24	4 mo	*HADH,* Homo	c.550A>T	p.I184F	Missense	Not done	Diazoxide	6.5 y	5 mg/kg	Normal	Mild delay
P25	7 mo	*GLUD1,* Hetero [#]	c.943C>T/N	p.H315Y	Missense	Not done	Diazoxide	4 y	4 mg/kg	Normal	Autism
P26	6 mo	*GLUD1,* Hetero [#]	c.1334C>T/N	p.S445L	Missense	Not done	Diazoxide	7 y	7 mg/kg, stopped at 6 yrs due to non-availability Octreotide 15 ug/day	Microcephaly	GDD, Epilepsy
P27	4 mo *	*GLUD1,*[#] Hetero	c.820C > T/N	p.R274C	Missense	Diffuse	Diazoxide	10 mo	7 mg/kg	Normal	Fine motor delay
P28	6 yrs	None by tNGS	-	-	-	Not done	Diazoxide	15 y	2 mg/kg	Obese	-
P29	3 mo	None in ABCC8/ KCNJ11	-	-	-	Not done	Diazoxide	Lost to follow-up at 3 y	Poor compliance	-	GDD Epilepsy
P30	4 mo	None in ABCC8/ KCNJ11	-	-	-	Not done	Diazoxide	6 y	0.4 mg/kg Poor compliance	Normal	GDD, poorly controlled epilepsy
P31	9 mo	None by tNGS	-	-	-	No focal lesion	Diazoxide	6.5 y	5 mg/kg	Normal	GDD, epilepsy
P32	6.5 mo	None by tNGS	-	-	-	Not done	Diazoxide	5 y	5 mg/kg	Normal	Normal
P33	3 mo	None in *ABCC8/KCNJ11*	-	-	-	Not done	Diazoxide	Lost to FU	-	-	-
P34	5 mo	None in *ABCC8/KCNJ11*	-	-	-	Not done	Diazoxide	Lost to FU after 3 y, Expired at 4 y due to hypoglycemia	-	-	-
P35	9 mo	None by tNGS	-	-	-	Not done	Diazoxide	5 y	2 mg/kg	Normal	Normal
P36	Day 6	None by tNGS	-	-	-	Not done	Diazoxide	3 y	4 mg/kg	Normal	GDD, epilepsy
P37	Day 3	None by tNGS	-	-	-	Not done	Diazoxide	2.2 y	2.5 mg/kg	Normal	Mild GDD, epilepsy
P38	5 mo	None by tNGS	-	-	-	Not done	Diazoxide	1.5 y	10 mg/kg	Normal	GDD, epilepsy
P39	2 mo	*KMD6A* mutation causing Kabuki syndrome Mosaic	ChrX:g.(?_44873552)_(44873987_?)del	De novo	-	Not done	Diazoxide, stopped due to neutropenia, Started Octreotide	Lost to FU after 1 y	Octreotide 20 ug/kg/day	Length < -2SD	GDD, epilepsy
P40	2 yr	None by tNGS					Diazoxide	8 y	1.5 mg/kg	Normal	Normal

*Abbreviations: Homo: homozygous; Hetero: heterozygous; tNGS: Targeted next generation sequencing; LAR: Long-acting release octreotide; FU: follow-up; LAMA: Left against medical advice; Wt: weight; Ht: height, SD: Standard deviations, AED: antiepileptic drugs; DQ: Development quotient; GDD: global developmental delay; *One affected elder sibling diagnosed at 5 years of age and having epilepsy; **sibling of 23; [#]Hyperinsulinism-hyperammonemia syndrome; ^Novel pathogenic/ likely pathogenic variants*

RESEARCH PAPER

Predictive Performance of Different Diagnostic Criteria for Overweight and Obesity Between 2008-2015 in Adolescents

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Background: The reference cut-offs for overweight and obesity have evolved from the use of International obesity task force (IOTF) to extended IOTF and revised Indian Academy of Pediatrics (IAP) growth charts. **Methods**: Secondary analysis of anthropometric data of school-going children from Delhi in the year 2008, 2013 and 2015 was performed. The proportions of children with overweight, obesity, and undernutrition were checked for agreement using different diagnostic cutoffs, and compared at three-time points. **Results**: Among 8417 adolescents, weighted Kappa statistics showed good agreement between extended IOTF and IAP cutoffs (k=0.933; 95% CI 0.93-0.94), between eIOTF and IOTF (k=0.624; 95% CI 0.619 - 0.629) and between IAP and IOTF (k=0.654; 95% CI 0.645-0.662). A higher proportion of adolescents were diagnosed with obesity with extended IOTF and IAP charts than IOTF charts (P<0.001 for both genders). The mean (SD) BMI showed a rising trend for adolescents overall from 19.61 (3.89) kg/m^2 in 2008, 20.44 (4.37) kg/m^2 in 2013 and 20.88 (4.60) kg/m^2 in 2015 (*P*<0.001). 158 adolescent (97 girls) were undernourished using combined IAP and extended IOTF criteria. **Conclusion:** Both extended IOTF and IAP charts showed good agreement for diagnosing overweight and obesity in adolescents. A secular trend in malnutrition was observed in adolescent girls.

Keywords: *BMI, Extended IOTF, IAP growth charts, Secular trend, Undernutrition*.

Obesity has emerged as a pandemic across all age groups. Lifestyle including nutritional transition has been identified as a major risk factor for overweight and obesity in South-east Asia, including India [1]. A systematic review of 2416 population-based studies with 128.9 million children (5-19 years) showed plateauing of change in BMI from 1975-2016 in northwestern Europe, high-income groups of English speaking countries and Asia-Pacific regions, unlike east and south Asia which still showed an increasing trend [2]. In addition, undernutrition was listed among the top ten global contributors to disability-adjusted life years [3].This highlights the dual burden of over-nutrition and undernutrition in children.

Adolescents remain a vulnerable population for nutritional problems with their physiological and psychosocial changes [4]. The present study compares the performance of different diagnostic criteria for underweight, overweight and obesity in school-going adolescents from northern India over the last decade.

METHODS

A secondary analysis of previously collected cross-sectional anthropometric data of school-going adolescents (10-18 years) from five different zones (North, South, East, West, and Central regions) of Delhi in the last decade was done. Data were collected in 2008, 2013, and 2015 as three separate time points and not as longitudinal data (**Supplementary material**).

The schools were selected based on their geographical location and permission granted by the school managements. The detailed written protocol was provided to all parents through the school administration, requesting them to give written consent for their children to participate in the study. Assent was taken from the subjects before conducting the examination. Any child with a known chronic systemic disorder or taking any treatment for more than one month in the last three months based on school's medical records and parental proforma was excluded from the study. As per the education policy of Delhi Government, a mandatory 25% reservation for economically weaker sections (EWS) of students in schools was implemented with effect from 2011 [5].The ethical clearance was taken from the institutional ethics committee for the respective studies as done separately.

The anthropometric evaluations were made by trained

staff with subjects dressed in minimal light clothing and without footwear, as detailed before (**Supplementary material**). Body mass index (BMI) was calculated as weight/(height)^2 in kg/m^2 and interpreted according to criteria given by the World Obesity Federation as International obesity task force (IOTF) [6], extended IOTF [7] and revised IAP growth charts 2015 [8]. The IOTF criteria defined overweight and obesity at six-monthly age intervals separately for boys and girls [6]. Overweight and obesity were defined as BMI more than ≥23 kg/m^2 and ≥ 27 kg/m^2 cutoff for respective age and gender interpreted at six monthly age interval in the extended IOTF classification [7]. IAP 2015 charts defined overweight as BMI ≥23kg/m^2 of adult equivalent (more than 71st and 75th percentile in boys and girls, respectively) and obesity as ≥27 kg/m^2 of adult equivalent (more 90th and 95th percentile in boys and girls, respectively) [8]. Undernutrition was classified as per extended IOTF as BMI less than 16 kg/m^2 of adult equivalent (thinness grade 3) [7] and as BMI less than 3rd centile (<-2SDS) as per IAP 2015 charts, separately for both genders [8]. The category of overweight was inclusive for obesity in all three definitions.

Statistical analysis: All statistical analyses were carried out using STATA V15.1 (StataCorp LLC). Data normality was checked by normal probability plot and Kolmogorov - Smirnov test. Undernutrition, overweight and obesity were compared between the groups by chi-square test. One way analysis of variance was used to compare the mean BMI between three different time points followed by Bonferroni correction for multiple comparisons. Weighted Cohen's Kappa coefficient was used to measure the degree of disagreement between the scales used. For testing of hypothesis two-tailed test was considered, and a *P* value of <0.05 was considered to be statistically significant.

RESULTS

Data of total 3401 boys and 5016 girls were evaluated across three time points. The weighted Kappa (95% CI) statistics showed good agreement between extended IOTF and IAP cutoffs (0.933 (0.93- 0.94); *P*<0.001), between eIOTF and IOTF (0.624 (0.619-0.629); *P*<0.001) and between IAP and IOTF (0.654 (0.645-0.662); *P*<0.001).

Using the combined criteria of extended IOTF and IAP charts (*n*=8417), undernutrition was seen in 158 (1.9%; 97 girls), overweight in 1809 (21.5%; 1137 girls) and obesity in 1300 (15.4%; 713 girls) adolescents. **Table I** shows the proportion of adolescents with underweight, overweight, and obesity for 2008, 2013, and 2015 for boys and girls as per three different criteria.

The mean (SD) BMI showed a rising trend for adolescents overall from 19.61 (3.89) kg/m^2 in 2008, 20.44 (4.37) kg/m^2 in 2013 and 20.88 (4.60) kg/m^2 in 2015 (*P*<0.001). The gender-wise mean (SD) BMI across these three years is shown in **Table II**. **Web Table I** shows age-wise BMI values across three years where significant secular changes were seen mostly between 10-15.5 year age-groups in boys, and in most age-groups in girls.

Table I Proportion of Underweight, Overweight and Obesity According to IOTF, Extended IOTF and IAP Criteria (2008-2015)

	2008	*2013*	*2015*
Boys	*n*= 1595	*n*= 1371	*n*= 435
IOTF			
Overweight	265 (16.6)	294 (21.4)	105 (24.1)
Obese	77 (4.8)	131 (9.6)	22 (5.1)
Extended IOTF			
Underweight	24 (1.5)	41 (3)	5 (1.2)
Overweight	350 (21.9)	335 (22.2)	119 (27.4)
Obese	209 (13.1)	305 (22.2)	75 (17.2)
IAP 2015			
Underweight	22 (1.4)	43 (3.1)	4 (0.9)
Overweight	298 (18.7)	277 (20.2)	108 (24.8)
Obese	243 (15.2)	352 (25.7)	86 (19.8)
Girls	*n= 1577*	*n= 1636*	*n= 1803*
IOTF			
Overweight	208 (13.2)	427 (26.1)	371 (20.6)
Obese	53 (3.4)	162 (9.9)	115 (6.4)
Extended IOTF			
Underweight	24 (1.5)	35 (2.1)	50 (2.8)
Overweight	374 (23.7)	472 (28.8)	471 (26.1)
Obese	144 (9.1)	370 (22.6)	296 (16.4)
IAP 2015			
Underweight	20 (1.3)	35 (2.1)	44 (2.4)
Overweight	338 (21.4)	456 (27.9)	440 (24.4)
Obese	122 (7.7)	321 (19.6)	273 (15.1)

All values in no. (%). P value calculated for gender-wise difference in proportion of nutritional categories for each respective year using each of the three BMI criteria separately. P <0.05 in 2008 and 2013 for all three criteria and in 2015 using extended IOTF and IAP criteria.

DISCUSSION

The present analysis demonstrated a good agreement between IAP 2015 and extended IOTF cutoffs for defining

Table II Body Mass Index of Adolescents (2008-2015)

	n	*Boys*	*n*	*Girls*
2008	1595	19.47 (4.03)	1577	19.74 (3.73)
2013	1371	20.11 (4.37)	1636	20.72 (4.36)
2015	435	20.36 (4.94)	1803	21.0 (4.51)

Data expressed as mean (SD). P<0.001 for year-wise comparison in boys and girls; P <0.05 for comparison between 2008 and 2013, and between 2008 and 2015, for both boys and girls.

WHAT THIS STUDY ADDS?

- Extended IOTF and IAP 2015 charts showed good agreement for detecting malnutrition in Indian adolescents.
- Mean BMI showed a secular trend in adolescents of both genders from 2008 to 2015.

overweight and obesity. A secular trend in obesity and overweight in the last decade (2008-2015) among school-going adolescents in northern India was also observed.

The lack of prospective longitudinal data was the main limitation of the study. Fewer boys in 2015 (as per school selection) and fewer adolescents stratified across different ages were difficult to be compared within subgroups for age-wise secular trends. The retrospective study design could not identify the effect of nutrition or socioeconomic status and associated risk factors for this trend.

The difference between old and new IOTF cutoffs was between -0.1 to +0.3 SDS when tested for data from China and the US-NHANES 20005 [7]. However, an earlier Indian study [9] showed double the proportion of obesity with the use of revised IAP growth charts than IOTF 2000 charts in both boys and girls, similar to the present study findings. The proportion of obesity as per revised IAP charts in boys in 2015 was marginally lower (16.2%) than the present study. The proportion of obese girls was lesser (5.8%), probably because of fewer representative girls in their study [9]. An excellent agreement between IAP 2015 and extended IOTF charts as seen in the present study was also shown earlier [10]. However, a difference in the proportions of nutritional categories between extended IOTF and IAP (even with excellent agreement) in the present study reiterates the need to use country- specific reference charts.

A secular trend in growth trajectories among children and adolescents has been documented globally [11,12]. A systematic review of 52 studies from India also reported an increase in the combined prevalence of overweight and obesity from 16.3% in 2001-05 to 19.3% in 2010 [13]. A pooled analysis on 2416 population studies (5-19 years) from 200 countries showed flattened BMI trends in Western countries, unlike South-East Asia where the prevalence of obesity increased from 0.9% and 0.7% in 1975 to 7.8% and 5.6% in 2016 in boys and girls, respectively [2]. The present study showed a significant rise in mean BMI in both genders in the last decade (2008-2015) as reported previously between 2006-2009 in New Delhi [14]. However, the proportion of obesity in both genders (and overweight in girls) showed a decline from 2013 to 2015. This implies that even though mean BMI showed a secular trend, the proportion of obesity reduced, which could possibly be due to increased awareness on obesity prevention in schools and communities, the impact of which cannot be deduced in the present study. Moreover, a longitudinal study design would have better substantiated the decline in burden of overweight/ obesity even though the mean BMI showed a marginal increase over time. The percentage of adolescent girls who additionally became obese (as per IAP criteria) from 2008 to 2015 was; however, higher than boys, which highlighted the gender-wise trend of over-nutrition in this study.

An increase in undernutrition from 2008 to 2013 (both genders) and in 2015 (in girls) in this study was probably because children from EWS category were admitted to 25% of seats in schools during these years. This may also be reflective of a nutritional transition where under-nutrition is increasingly being recognized in adolescents [3]. An increase in the proportion of undernutrition in girls with time was seen in this study, which highlights the need for nutritional strategies for adolescent females; the numbers of boys were meagre for a similar comparison. An overall declining proportion of children with moderate to severe underweight were reported globally albeit with India having the largest prevalence of underweight children. The mean BMI of adolescents (10-19 years) in south Asia were even lower than their African peers [2]. A modified BMI screening tool [15] has been recently validated to screen for undernutrition and over-nutrition in Indian children, which may help screen for dual burden of malnutrition.

The present study establishes a good agreement between extended IOTF and revised IAP charts to detect malnutrition. The need to identify both obesity and undernutrition as significant expansive health problems during school years with an emphasis on promoting healthy lifestyles in Indian children and adolescents is also highlighted.

Ethics clearance: No separate ethical clearance taken for the present analysis, IEC permission was available for all included studies.

Contributors: RK: conceptualization, manuscript review and editing; AD,VR: data analysis, manuscript preparation; RKM: manuscript review and editing; RK: will act as final guarantor of the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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

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CLIPPINGS

Severe obesity caused by GNAS mutations and clinical heterogeneity associated with impairment of various molecular pathways *(N Engl J Med 2021;385:1581-92)*

GNAS regulates G-protein coupled receptor (GPCR) signalling, and its mutations are known to be associated with obesity and hormone resistance in pseudohypopara-thyroidism. The present study was conducted on 2548 children (aged <10 year) with early onset severe obesity. Exome sequencing was performed and *GNAS* mutations were identified in 22 of them. Investigators aimed to study the molecular pathways explaining obesity and clinical variability associated with these mutations. They revealed that all GNAS mutations caused impairment of melanocortin (MC4R) pathway, explaining the obesity. Six out of 22 patients, having poor growth, had disruption of growth hormone–releasing hormone receptor signaling caused by GNAS mutations, but growth remained unaffected when this pathway was not impaired. Mutations disrupting thyrotropin receptor signaling, led to developmental subnormality and high thyrotropin levels. GNAS mutations can differentially affect GPCR pathway leading to the clinical variability. Since presentation as isolated obesity and clinical heterogeneity is evident for these mutations, authors advocate the screening of children with severe obesity for GNAS mutations. Unbiased genetic analysis may aid in early detection and better clinical outcome of such patients.

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Web Table 1A Body Mass Indices of Boys 10-18 Year Age Across Three Years

	2008 (N= 1595)		*2013 (N= 1371)*		*2015 (N= 435)*		***P value***
Age, y	*n*	*BMI, kg/m²*	*n*	*BMI, kg/m²*	*n*	*BMI, kg/m²*	
10-10.5	112	17.6 (3.6)	109	19.5 (4.3)	24	19.3 (4.4)	0.001
10.5-11	17	18.6 (3.6)	112	18.0 (3.5)	23	18.95 (3.4)	0.44
11-11.5	212	18.3 (3.6)	155	19.4 (4.3)	13	17.6 (3.4)	0.02
11.5-12	17	19.1 (3.6)	140	19.7 (4.4)	23	20.2 (8.8)	0.80
12-12.5	215	18.5 (3.5)	121	20.1 (4.3)	45	20.0 (3.7)	<0.001
12.5-13	18	17.2 (2.2)	138	19.9 (4.0)	40	19.0 (3.8)	0.02
13-13.5	225	18.7 (3.1)	108	20.4 (3.9)	27	19.9 (3.0)	<0.001
13.5-14	13	18.6 (2.8)	103	21.0 (4.6)	38	19.0 (4.7)	0.03
14-14.5	256	20.0 (4.2)	99	21.3 (4.6)	38	19.9 (3.0)	0.03
14.5-15	25	19.0 (3.3)	85	21.0 (4.4)	38	20.4 (4.0)	0.11
15-15.5	156	20.4 (4.4)	62	22.4 (4.8)	31	21.6 (4.1)	0.01
15.5-16	16	19.9 (3.6)	50	20.7 (4.1)	34	23 (8.7)	0.14
16-16.5	182	21.3 (4.4)	30	20.5 (4.8)	22	22.0 (4.6)	0.48
16.5-17	16	22.1 (5.2)	28	20.7 (5.1)	12	22.6 (4.7)	0.48
17-18	115	21.6 (4.2)	31	19.0 (3.7)	27	22.2 (3.9)	0.003

Data expressed as Mean (SD)

Web Table 1B Body Mass Indices of Girls 10-18 Year Age Across Three Years

	2008 (N= 1577)		**2013 (N= 1636)**		**2015 (N= 1803)**		**P value**
Age, y	*n*	*BMI,*	*n*	*BMI, kg/m²*	*n*	*BMI, kg/m²*	
10-10.5	84	18.0 (3.5)	195	19.2 (4.0)	53	17.0 (3.0)	<0.001
10.5-11	-	-	149	19.4 (4.0)	45	17.5 (3.5)	<0.001
11-11.5	217	18.1 (3.3)	195	19.6 (4.0)	88	19.3 (4.5)	<0.001
11.5-12	-	-	167	21.0 (4.1)	70	17.5 (3.3)	<0.001
12-12.5	236	18.8 (3.5)	152	20.4 (4.2)	140	19.8 (4.8)	<0.001
12.5-13	12	17.7 (3.4)	137	21.1 (4.3)	110	19.2 (3.5)	<0.001
13-13.5	242	19.6 (3.5)	111	21.5 (5.1)	152	21.1 (5.1)	<0.001
13.5-14	16	19.98 (3.4)	102	21.4 (4.2)	96	21.1 (4.3)	0.446
14-14.5	219	20.2 (3.6)	99	21.5 (4.1)	127	21.0 (4.1)	0.014
14.5-15	15	19.8 (3.5)	76	22.7 (4.4)	119	21.9 (4.0)	0.04
15-15.5	200	20.5 (3.5)	65	22.6 (4.6)	171	22.2 (4.4)	<0.001
15.5-16	19	21.5 (4.3)	75	21.6 (3.6)	117	21.9 (4.6)	0.86
16-16.5	182	21.1 (3.7)	62	23.0 (5.0)	142	22.2 (4.1)	0.003
16.5-17	26	21.9 (3.8)	23	18.7 (4.3)	99	22.9 (4.7)	<0.001
17-18	109	21.4 (4.0)	28	19.9 (4.2)	274	22.1 (4.4)	0.02

Data expressed as Mean (SD); -Less than five entries (data not computed)

RESEARCH PAPER

Opioids for Pediatric Pain Management

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Objectives: To study the efficacy and adverse effects of opioids in management of pain in children. **Methods**: A descriptive study was conducted in children aged below 15 years with moderate to severe pain, and response to opioids and adverse effects were assessed at 24, 48 and 72 hours after administration. **Results**: 100 children (68% males) with median (IQR) age of 6.5 (3.5,10) years were studied. 81% (*n*=81) children with moderate pain and 78.9% (*n*=15) with severe pain responded to opioids in 72 hours. Among children with severe pain of non-malignant origin, 80% (*n*=8) responded in 48 hours compared to 11.1% (*n*=1) with malignancy and this difference was statistically significant at 24 hours (*P*=0.005). Of children with severe pain 73.7% (*n*=14) developed adverse reactions compared to 30.9% (*n*=25) with moderate pain. **Conclusions**: Children with moderate-severe pain, either of malignant or non-malignant origin could be managed effectively with opioids without severe adverse effects.

Keywords: *Analgesia, Analgesic ladder, Malignancy.*

Despite the relatively high prevalence of pain and its distressing implications for children and their families, it is often under-recognized and under-treated. Lack of awareness and misconceptions regarding use of opioids has led to suboptimal use of this class in children [1]. Opioids are indicated for moderate to severe pain when other measures have failed. The present study was conducted to ascertain the efficacy of opioids in both malignant and non-malignant conditions in children.

METHODS

This study was conducted after Institutional Ethics Committee clearance, among children under 15 years with moderate to severe pain at a tertiary centre in India over 24 months from January, 2012. Critically ill children with unstable vital parameters, obtunded sensorium, intellectual disability and whose parents refused consent were excluded. Severity of pain was assessed using age appropriate tools (3 years and below - FLACC scale, 3-7 years- Wong Baker Faces Scale, 7 years and above - Numerical Rating Scale) and grading was done as 0 - no pain, 1-3: mild pain, 4-6: moderate pain,7-10: severe pain [2-4].

Children with moderate pain were treated with a weak opioid (codeine) and those with severe pain were given a strong opioid (morphine) along with step 1 analgesics and adjuvants, when indicated according to WHO three step ladder [5]. Follow up by one of the four trained observers was done at 24, 48 and 72 hours, when the severity of pain and adverse effects were carefully assessed and dose of drug titrated. Reduction in severity of moderate-severe pain to no pain/mild pain was considered as response to treatment.

Statistical analysis: Data were entered into a semi-structured proforma, and statistical analysis was done by SPSS 16.0 software. The analysis of the data was done by Pearson chi-square test and a *P* value <0.05 was taken as significant.

RESULTS

Of the 100 children enrolled in the study with median (IQR) age of 6.5 years (3.5, 10), 68% were boys and 40% were between 5 and 10 years of age. Moderate pain was seen at presentation in 81 children and severe pain in 19. Among the 56 children with cancer, 66% (*n*=37) had acute lymphoblastic leukemia. Hemophilia (36.4%) and burns (31.8%) were the common non-malignant conditions. Nociceptive pain predominated in our study (*n*=96), while 4 children had additional neuropathic component, which included a child with leukemia with brain metastasis, and three hemophilia patients having nerve compression.

Codeine was prescribed for 81 children with moderate pain. At 48 hours, 93.6% (*n*=44) with malignancy (*n*=47) and 94.1% (*n*=32) with non-malignant conditions (*n*=34) responded. All children with moderate pain responded within 72 hours. There was no statistically significant difference in opioid response of moderate pain in malignant and non-malignant conditions. The dose requirement of

Table I Adverse Effects in Children Receiving Opioids for Pain in Malignant and Non-malignant Conditions

Adverse effects	*Severe pain (n=19)*		*Moderate pain (n=81)*	
	Malignant (n=9)	*Non malignant (n=10)*	*Malignant (n=47)*	*Non malignant (n=34)*
Constipation	2 (10.5)	4 (21.0)	10 (12.3)	10 (12.3)
Constipation with sedation	2 (10.5)	1 (5.3)	0	0
Constipation with nausea /vomiting	2 (10.5)	0	4 (4.9)	0

Constipation with nausea/vomiting and sedation in 1 child with severe malignant condition, and pruritus in one child with moderate pain in malignant condition were also noted. Only 2 children in malignant condition had only sedation as side effect.

codeine given 4-hourly was 0.5 mg/kg/dose for 96.3%, while 3.7% required 1mg/kg/dose.

Of the 19 children with severe pain started on morphine, none responded in 24 hours. At 48 hours, 80% (n=8) with non-malignant conditions responded compared to 11.1% (n=1) with malignancy. Severe pain took a statistically significant longer duration for response in both malignant and non-malignant cases. The dose requirement of morphine given 4 hourly was 0.3 mg/kg/dose for 57.9%, while the rest required 0.5 mg/kg/dose.

Of the children with moderate pain, 48.1% (n=39) had reduced severity at 24 hours, against 68.4% (n=13) with severe pain. Reduction in severity at 48 hours occurred in 93.8% (n=76) children with moderate pain against 94.7% (n=18) with severe pain. Thus, reduction in severity was faster in severe pain than moderate pain but this was not statistically significant.

Adverse effects occurred in 39 (39 children) and were increased in children with severe pain on morphine (73.7%, n=14), compared to moderate pain on codeine (30.9% n=25) (P=0.001) (**Table I**). The major adverse effect was constipation (36%). Adverse effects were more in malignancy, females (64.1%), under-five children (43.3%) and those with pain lasting beyond 2 weeks (50%).

All children were co-prescribed with bisacodyl anticipating constipation; 6% required cremaffin in addition. Those on morphine were co-prescribed with domperidone. Ketamine was given in a dose of 0.15 mg/kg sublingually to reduce incident pain in children with burns. Amitriptylline was given to reduce neuropathic pain in four children.

There were no misconceptions about opioids in 77% parents, whereas 20% were concerned about addiction and 3% considered that they were to be only used terminally.

DISCUSSION

Opioids are important in management of pain of both malignant and non-malignant causes in children. Although seldom used in non-malignant conditions, this study showed that they are equally efficacious. Children with acute lymphoblastic leukemia and hemophilia, accounted for the male preponderance [6]. Among children with moderate pain, all responded to codeine in 72 hours, with no significant difference between malignant and non-malignant conditions. Children with severe malignancy-related pain responded more slowly, possibly due to co-morbid conditions, therapeutic procedures and adverse effects of chemotherapy [7]. Severe pain treated with a strong opioid was more rapidly ameliorated than moderate pain, although it took longer for complete response. Although not statistically significant, this has immense clinical relevance.

Adverse effects were commoner in severe pain treated with morphine, than moderate pain treated with codeine similar to previous studies [8,9]. Increased adverse effects in younger children may be due to delayed clearance by immature hepatic enzyme systems. Parental misconceptions including fear of addiction and the belief that opioids were end stage drug, were overcome by timely counseling and guidance from physicians trained in pain management.

Limitations of the study include small sample size, lack of a control group and no follow-up beyond 72 hours. Besides, different age-appropriate tools were used to assess severity of pain, which may not be representative.

The World Health Organization has recently replaced the three-step analgesic ladder by two-step ladder since variable expressions of enzymes involved in biotransformation of codeine (CYP2D6) can lead to substantial differences in plasma concentration of the active metabolite, morphine [10]. However, in our study, codeine was found to be uniformly safe and efficacious in management of moderate pain. Hence, use of the three-step ladder in populations where it has been shown to work may be reconsidered, although this may require larger studies.

Contributors: MGG: conceptualized the study, supervised the study, contributed to review of literature, statistical analysis, critically analyzed and reviewed the manuscript; PG,VTA, AR: data analysis, critical review of manuscript: RVH: collection of

WHAT THIS STUDY ADDS?

- Opioids are efficacious in malignant and non-malignant pain in children, with frequent but non-serious adverse effects.

data, analysis, preparation of manuscript, review of literature. All authors were involved in the assessment and management of patients and approved the final version of manuscript.

Ethics clearance: Institutional Ethics Committee, GMC, Calicut dated Feb 14, 2012.

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CLIPPINGS

Vosoritide improves bone growth in children with achondroplasia (*Genet Med. 2021;23:2443-47*)

Vosoritide, a C-type natriuretic peptide analog, has been in development for the treatment of achondroplasia. A phase III study was conducted to determine the efficacy and safety of vosoritide in children (121 children, 5 to <18 years) with achondroplasia. Participants completed six months of a baseline growth study, followed by 52 weeks of a placebo- controlled study. Then they were eligible to participate in the phase 3 extension study, to receive vosoritide at a dose of 15.0 µg/kg/day (daily injections). Vosoritide group had annualized growth velocity 1.57 cm/ year (mean difference) more than that of the placebo group suggesting vosoritide to be a promising and persistent growth-promoting agent in children with achondroplasia. Vosoritide has now been approved by FDA for treatment of achondroplasia.

Improved detection of focal congenital hyperinsulinism with 68Ga-NODAGA-exendin-4 PET

(J Nucl Med. July 2021. Epub ahead of print)

Focal congenital hyperinsulinism (CHI) can be treated successfully, provided an accurate pre-surgical localization of the lesion is made. The present study compared 18F-DOPA positron emission tomography (DOPA PET) (the current standard imaging method for CHI) with 68Ga-NODAGA-exendin-4 (Exendin PET) for pre-surgical detection of focal CHI in 19 patients with CHI. Both the scans were done in all patients. The images were evaluated by an expert in hyperinsulinism along with a nuclear medicine physician. Surgery was performed in 14/19 patients having focal lesions. Based on expert readings, clinical sensitivity of exendin PET (100%) was higher than DOPA PET (71%). Inter-observer correlation was higher for exendin than for DOPA PET. Pediatric surgeons rated exendin PET superior to DOPA PET on a five point scale. Thus, exendin proves to be a superior technique with its better image quality and leads to precise intra-operative localization during surgeries.

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RESEARCH PAPER

Nutritional Status of Under-five Siblings of Severely Wasted Children in Bhopal

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Objective: To study the prevalence and associated factors of undernutrition in siblings of children with severe acute malnutrition (SAM). **Method:** It was a community-based cross-sectional study of under-five year siblings of children with SAM. **Results:** A total of 128 under-five years siblings were studied, 30% had SAM whereas 20% had moderate acute malnutrition (MAM). More than 7 members in a family (OR=4.23, CI 1.9-9.6, *P*<0.001), underweight mothers (OR=5.2, CI 2.08-13.0, *P*<0.001), children who received pre-lacteal feeds (OR=3.24, CI 1.33-7.87, *P*=0.007), and Muslim religion (OR=4.44, CI 1.78-11.1, *P*<0.001) were significantly associated with finding of another child with SAM in the family. **Conclusion:** There was high proportion of severe malnutrition in siblings of children with SAM. Consideration should be given to actively screen all under-5 children in the family of a newly diagnosed child with SAM for undernutrition.

Keywords: *Family, Nutritional status, Screening, Severe Acute malnutrition*.

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According to the National Family Health Survey-4 (NFHS 4, 2015-16), the prevalence of SAM (severe wasting) was 7.5% in children below 5 years of age [1]. In Madhya Pradesh, health indicators are among the lowest in the country with 42.8%, 42%, 25.8% and 9.2% children underweight, stunted, wasted, and with SAM, respectively [2,3]. We hypothesized that as children in the same family are exposed to the same genetic factors, similar nutritional exposure, and environmental factors, siblings of children with SAM are also at high risk of being undernourished. With this objective, we aimed to measure the nutritional status of siblings of children with SAM.

METHODS

This study was a community-based cross-sectional study done in the Bhopal district from June 2016 – September 2017. Out of five Nutritional Rehabilitation centers (NRCs) in Bhopal, two were selected purposively; one from urban area (Jay Prakash Hospital, Bhopal), and one from a nearby rural area (Berasia, Community health center) were selected.

The study was commenced after obtaining the ethical committee clearance from the institute. List of under-five children admitted with SAM from 1 January, 2016 to 31 December, 2016 was obtained from the NRC. Contact details of the children who were admitted at the above NRC were collected from the admission register. This was followed by home visits to the mentioned address. Visits were made in the evening time so that parents and children would be available at home and the maximum number of siblings could be enrolled.

Siblings were examined at home. The flow of recruitment of children is shown in **Fig. 1**. Documented SAM children with addresses and phone numbers available were included and traced to their home addresses. All siblings of these children were included by making multiple home visits. Children with SAM who belonged to the area outside municipal limits of the NRC in which they were admitted were excluded due to feasibility constraints, and children with SAM whose parents denied participating in the study were also excluded. Data regarding demographic and environmental parameters, anthropometry parameters for all children <5 years of age other than the index case of SAM were obtained. The mother's height and weight were also measured, and body mass index was calculated.

For calculating the *z*-score, WHO Anthro software version 3.2.2 (World Health Organization, available from *http://www.who.int/childgrowth/en*) was used. The *z*-score for weight for age, height for age, and weight for height were calculated using this application.

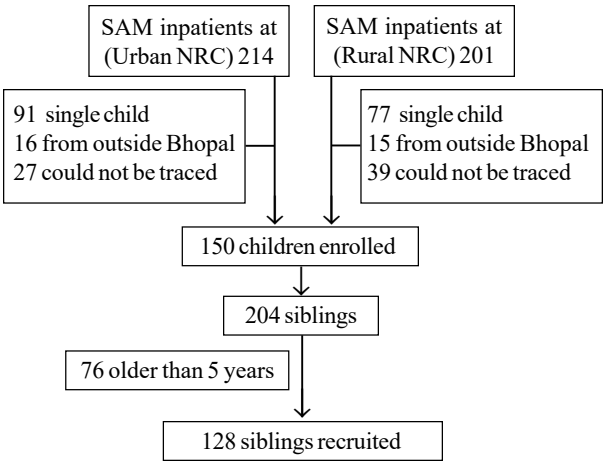

Fig. 1 Flow chart depicting enrollment of participants.

Statistical analysis: Data were entered in Microsoft Excel (Microsoft) and IBM SPSS version 23.0 (IBM Corp.). Comparison of different sociodemographic and other variables among families with more than one sibling having SAM and not having SAM was made by chi-square test. Logistic regression was done using significant parameters in univariate analysis. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Out of the 150 children with SAM that could be traced (**Fig. 1**), 128 siblings under five years were enrolled. The mean (SD) average age of children was 3 (1.5) years, and 60 (46%) were male (**Table I**). Sociodemographic characteristics showed that one-third of mothers were illiterate, and 13% were working (**Web Table I**).

Anthropometry of 128 under-five siblings showed that 62 (48%) children had wasting, 90 (70%) were underweight, and 80 (62.5%) children were stunted. Additionally, on categorizing severity, 32% of children were suffering from SAM, whereas 16% were having moderate acute malnutrition (MAM) based on weight for height criteria.

Univariate analysis of various sociodemographic factors showed that of more than seven family members (P<0.001), underweight mothers (P<0. 001), children who received pre-lacteal (P=0.007) and Muslim religion (P<0.001) were significantly associated with the probability of having another child with SAM in the family (**Web Table II**). On performing logistic regression, only religion was found to be an independent predictor (**Table II**).

DISCUSSION

In this descriptive study, we found that 50% of the siblings were suffering from malnutrition, one-third of them were severely malnourished, whereas 20% of them had moderate acute malnutrition, and only 20% of the children had received medical attention. NFHS-4 data reported 8% prevalence of SAM in Bhopal city, which was less as compared to the cohort of siblings of children with SAM (30%) in our study [3]. Olofin, et al. [5] analyzed the all-cause mortality in children with sub-optimal growth, and found that children with severe wasting have a mortality hazard ratio of more than 10% [5].

Under the ICDS program, Anganwadi workers (AWW) are supposed to do anthropometry of all children, but many children had remained underdiagnosed. The reasons could be due to the quality of training of AWW, as well as the burden of multiple responsibilities [6]. This could also be explained by the fact of non-availability of parents in the home during the daytime, as they leave home early in the morning for work and come late in the evening. AWW does refer the undernourished children to NRC, but due to fear of losing daily wages as the mother has to stay with the child till he/she meets the discharge criteria, parents do not prefer to go to NRC [7]. In a national survey, it was found that only 21% of children received supplementary food between the age of 6 -35 months [8].

To end undernutrition in children, the government must identify and intervene early at the community level. Few states (Bihar, Rajasthan, Maharashtra, Odisha) had initiated community-based management of acute mal-nutrition (CMAM), which was successful in reducing undernutrition in the community [9-11]. Unfortunately, due to the requirement of huge funds to sustain such a program, this could not be implemented at a larger scale. Nevertheless, India requires such a program to combat the undernutrition issue [11,12].

Our study has few limitations; being a cross-sectional study, it does not track the event history of a child's

Table I Undernutrition in Siblings of Children With Severe Acute Malnutrition (*N*=128)

Sibling age/sex	*Wasting n=62*	*Underweight n=90*	*Stunting n=80*
1 y			
Male	2 (1.6)	3 (2.3)	5 (3.9)
Female	2 (1.6)	9 (7.0)	9 (7.0)
1-2 y			
Male	8 (6.3)	9 (7.0)	6 (4.7)
Female	6 (4.7)	8 (6.3)	6 (4.7)
2-5 y			
Male	22 (17.2)	31 (24.2)	26 (20.3)
Female	22 (17.2)	30 (23.4)	28 (21.9)

Data presented as no. (%). Wasting – weight for height < –2 z-score; Underweight – weight for age <–2 z-score.

WHAT THIS STUDY ADDS?

- A high proportion (32%) of severe acute malnutrition (SAM) was seen in siblings of children with SAM.

Table II Logistic Regression Analysis for Factors Associated With Severe Acute Malnutrition in Siblings (*N*=150)

Factors	*Adjusted OR* (95% CI)	*P value*
Administration of pre-lacteal feeds	0.84 (0.36-1.95)	0.68
Religion	4.01 (1.11-14.47)	0.03
Family members >7	1.27 (0.53-3.06)	0.60
Underweight mother	0.50 (0.22-1.15)	0.10

malnutrition across their ages. Recall bias is also likely to be present among the respondents answering the questions relating to past events. We also did not measure the proportion of malnutrition in other children in the Bhopal city (study area) without a sibling of SAM for comparison. However, we were unable to find other similar studies mentioning about nutrition status of siblings of children with SAM.

Our study has shown a high proportion of SAM in siblings of children with SAM. All Pediatrician or health workers should consider actively screening other children in the family if they are encountering any child with SAM. It will be a window of opportunity to diagnose and treat them early. Further data from other regions will add more impetus to such a screening strategy.

Ethics clearance: IEC-GMC, Bhopal. No. 7658-60/MC/IEC/ 2016 dated March 22, 2016.
Contributors: BC,YC,DKP: conceptualize the manuscript; BC, YC, DKP, MD, HD: written the protocol for the project, helped in literature review, manuscript preparation, and critical revision. All authors have approved the final manuscript.
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Findings presented at IAPSMCON, Shimla in March, 2019.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Sociodemographic Characteristics of Families of Children with Severe Acute Malnutrition Enrolled in the Study (*N*=150)

Characteristics	*No (%)*
Education of mother	
Illiterate	49 (32.7)
Primary school	23 (15.3)
Middle school	46 (30.7)
High school	20 (13.3)
High secondary & above	12 (8)
Occupation of mother	
Housewife	131(87.3)
Laborer	14 (9.3)
Private job	5 (3.4)
Religion	
Hindu	119 (79.3)
Muslim	31 (20.7)
Total number of family members	
4-6	119 (79.3)
≥7	31 (20.7)
Socio –economic Status	
Upper middle class	1 (0.7)
Middle class	17 (11.3)
Lower middle class	80 (53.3)
Lower class	52 (34.7)
Water sanitation practices	
Boiling	56 (37.3)
Using water purifier	2 (1.3)
Direct consumption	92 (61.3)
Type of Family	
Joint	58 (38.7)
Nuclear	92 (61.3)
Defecation practices	
Sanitary Latrine	122 (81.3)
Open field defecation	28 (18.7)

Web Table II Association Between Various Sociodemographic Factors and SAM Status of Under Five-year Siblings

Factors		*SAM (N=41) n (%)*	*NO SAM (n=87) n (%)*	*P value*	*Odds Ratio*	*95% CI*
Religion	Muslim	15 (60)	10 (40)	<.001	4.44	1.78-11.1
	Hindu	26 (25.2)	77 (74.8)			
Type of family	Joint	16 (30.8)	36 (69.2)	0.8	0.91	0.42-1.93
	Nuclear	25 (32.9)	51 (67.1)			
Family members	≥7 members	20 (55.6)	16 (44.4)	<0.001	4.23	1.86-9.58
	<6 members	21 (22.8)	71 (77.2)			
Socio Economic status	Lower class	8 (21.1)	30 (78.9)	0.08	0.46	0.19-1.12
	Others	33 (36.7)	57 (63.3)			
Overcrowding	Present	28 (29.5)	67 (70.5)	0.29	0.64	0.28-1.46
	Absent	13 (39.4)	20 (60.6)			
Education of mother	Illiterate	17 (39.5)	26 (60.5)	0.56	1.66	0.77-3.59
	Literate	24 (28.2)	61 (71.2)			
Mother's BMI	Underweight	34 (44.7)	42 (55.2)	<0.001	5.20	2.08-13.0
	Normal	7 (13.4)	45 (86.5)			
Birth order	<2	39 (33.9)	76 (66.1)	0.22	2.82	0.59-13.3
	>2	2 (15.4)	11 (84.6)			
Administration of Pre-lacteals	Yes	14 (53.8)	12 (46.2)	0.007	3.24	1.33-7.87
	No	27 (26.5)	75 (73.5)			
Immunization status	Fully immunized	32 (32.3)	67 (67.7)	0.91	1.06	0.43-2.59
	Partially immunized	9 (31)	20 (69)			
Duration of exclusive breast feeding	< 6months	5 (26.3)	14 (73.7)	0.56	0.72	0.24-2.17
	≥ 6months	36 (33)	73 (67)			

RESEARCH PAPER

Factors Differentiating Multisystem Inflammatory Syndrome in Children (MIS-C) From Severe/Critical COVID-19 Infection in Children

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Objective: To differentiate severe/critical coronavirus disease 2019 (COVID-19) infection from multisystem inflammatory syndrome in children (MIS-C). **Methods:** Single-center chart review comparing characteristics of children with MIS-C and 'severe/critical' COVID-19 infection. Multivariate logistic regression was performed to create predictive models for predicting MIS-C. **Results:** Of 68 patients, 28 (41.2%) had MIS-C while 40 (58.8%) had severe/critical COVID-19 infection. MIS-C patients had a higher prevalence of fever, mucocutaneous, cardiac and gastrointestinal involvement and a lower prevalence of respiratory symptoms (P<0.05). Significantly lower hemoglobin, platelet count, serum electrolytes, and significantly elevated inflammatory and coagulation markers were observed in MIS-C cohort. Upon multivariate logistic regression, the best model included C-reactive protein (CRP), platelet count, gastrointestinal and mucocutaneus involvement and absence of respiratory involvement (performance of 0.94). CRP>40 mg/L with either platelet count <150x10^9 or mucocutaneous involvement had specificity of 97.5% to diagnose MIS-C. **Conclusion:** Elevated CRP, thrombocytopenia and mucocutaneous involvement at presentation are helpful in differentiating MIS-C from severe COVID-19.

Keywords: *C-reactive protein, Comorbidity, Platelet count*, SARS-CoV-2.

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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a spectrum of disease in children ranging from asymptomatic patients to critical coronavirus disease 2019 (COVID-19) requiring admission to the pediatric intensive care unit (PICU) [1]. It can also present with multisystem involvement including with circulatory shock and systemic inflammation, called as multisystem inflammatory syndrome in children (MIS-C) [2].

Patients with severe and critical COVID-19 infection (SC-COVID-19) and MIS-C present with non-specific symptoms, which often overlap, and differentiating these on presentation becomes difficult. Studies comparing the presenting symptoms and laboratory findings among these conditions are lacking. A recent systematic review showed that patients with MIS-C may have higher prevalence of gastrointestinal (GI), dermatologic and cardiovascular symptoms; however, this review included studies with significant heterogeneity in their inclusion criteria [4]. Similarly, hypoxemia, mechanical ventilation and use of inotropic drugs are more likely to occur in children with MIS-C [5]. Given the differences in treatment options, differentiating these two conditions at presentation is critical. In this study, we aimed to identify the clinical characteristics and laboratory markers at presentation that could help differentiate SC-COVID-19 in children from MIS-C.

METHODS

This is a retrospective chart review of children admitted to Oklahoma Children's Hospital from April 1- Dec 31, 2020 with diagnoses of MIS-C or SC-COVID-19. This study was approved by our institutional review board. We included data of patients aged 0-21 years with a diagnosis of SC-COVID-19 or MIS-C. Patients with no anthropometric data upon admission were excluded. Case definition of severe COVID-19 included individuals who had SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%, while critical COVID-19 included individuals who had respiratory failure, septic shock, and/or multiple organ dysfunction [6] . The case definition of MIS-C included an individual aged <21 years presenting with fever (≥38.0°C for ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen,

procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic or neurological); and no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms [3].

Data were collected by a review of electronic medical records. Demographics included age, gender and race. Clinical data included nutritional status, presence of comorbidities, symptoms at presentation, systems involved, presence of coinfections, need for PICU admission, oxygen requirement and maximum level of oxygen support required (none, nasal cannula, positive airway pressure (PAP), invasive mechanical ventilation), hospital length of stay (LOS), inotrope use and mortality. Nutritional status was classified based on current American Academy of Pediatrics guidelines into underweight (weight-for-length <2nd percentile or body mass index (BMI) <5th percentile), normal weight (weight for length 2nd-98th percentile or BMI 5th-85th percentile) and overweight/obese (weight for length ≥98th percentile or BMI ≥85th percentile) [7,8]. Laboratory markers obtained at presentation included white blood cell count, hemoglobin, platelet count, serum electrolytes (sodium, potassium, bicarbonate), renal function panel (blood urea nitrogen, creatinine and albumin level), liver function panel (aspartate and alanine transaminases and total bilirubin), markers of coagulation [international normalized ratio (INR) and D-dimer], markers of inflammation (CRP, ESR, procalcitonin and ferritin) and cardiac biomarkers [serum lactate, B-type natriuretic peptide (BNP) and troponin I].

Statistical analysis: Continuous data were compared using the Wilcoxon rank sum test. Categorical data were compared using the Chi-square or Fisher exact tests. Multivariate logistic regression was conducted to identify variables that would predict the diagnosis of MIS-C. Receiver operating characteristic curves were obtained using sensitivity analysis for individual variables to determine optimal cut-off values in predicting MIS-C. Statistical analysis was performed using JMP Pro 14.0 (SAS Institute). A P value <0.05 was considered statistically significant.

RESULTS

A total of 68 patients (42.7% male) were included in the study. 28 (41.2%) patients were diagnosed with MIS-C while 40 (58.8%) patients had SC-COVID-19. **Table I** provides demographics, clinical characteristics and outcomes of our cohort. Most patients were White (42.7%), and the median age was 10.6 (IQR 2.8-16.2) years and median weight was 42.3 (IQR 14.3-84.4 kg). MIS-C patients were more likely to be overweight/obese (P=0.02); 48 patients (70.6%) had at least one comorbidity. Comorbidities were significantly higher in SC-COVID-19 cohort (P=0.001). Indications for admission included respiratory failure, shock, seizures, pancreatitis, and diabetic ketoacidosis. Patients with respiratory failure requiring PAP or invasive ventilation, hemodynamic instability, diabetic ketoacidosis and Glasgow coma scale score ≤8 were admitted to PICU.

Higher prevalence of fever, rash and GI symptoms whereas a lower prevalence of cough and dyspnea were seen in MIS-C cohort (P<0.05). While higher proportion of patients with MIS-C required invasive mechanical ventilation (P<0.001) and inotropes (P=0.007), more patients with SC-COVID-19 required PICU admission (P=0.007). There was no difference in LOS and mortality among the two cohorts. MIS-C cohort had a significantly lower level of hemoglobin, platelet count, serum sodium, potassium, bicarbonate and albumin, and a significantly higher levels of total bilirubin, INR, D-dimer, CRP, procalcitonin, ESR and BNP (P<0.05) (**Table II**).

Upon multivariate logistic regression with outcome being MIS-C diagnosis, the best model was observed when CRP, platelet count, GI and mucocutaneus involvement and absence of respiratory involvement were incorporated in the model with performance of 0.94 (P<0.001) (**Web Table I**). On sensitivity analysis for individual variables, the optimal cut-offs to predict MIS-C were CRP ≥40 mg/L and platelet count <150 $\times 10^9$/L. Using these cut-offs, when both these criteria were fulfilled, the specificity to diagnose MIS-C was 97.5% whereas when neither of these criteria were fulfilled, the sensitivity was 96.4%. Similar specificity was observed when CRP ≥40 mg/L and mucocutaneous involvement were present. When both were absent, sensitivity to rule out MIS-C was 92.8%.

DISCUSSION

The results from this study suggest that elevated CRP, thrombocytopenia, GI and mucocutaneous involvement and absence of respiratory involvement at presentation can be helpful in differentiating MIS-C from SC-COVID-19 in children. A CRP value ≥40 mg/L with either platelet count <150 $\times 10^9$/L or mucocutaneous involvement had a high specificity of 97.5% to diagnose MIS-C.

A recent meta-analysis showed that presenting symptoms of SC-COVID-19 are non-specific and include fever, diarrhea, nausea, vomiting, malaise and fatigue [9].

Table I Demographics and Clinical Characteristics of Patients With MIS-C and Severe/Critical COVID-19

Parameters	*MIS-C (n=28)*	*Severe/critical COVID-19 (n=40)*	*P value*
Age (y)[a]	8.1 (3.1-12.9)	13.4 (2.7-16.9)	0.43
Male gender	10 (35.7)	19 (47.5)	0.33
Race			
White	13 (46.4)	16 (40)	0.82
Hispanic or Latino	7 (25)	9 (22.5)	
African American	4 (14.3)	9 (22.5)	
American Indian	2 (7.1)	3 (7.5)	
Asian	1 (3.6)	0 (0)	
Unknown	1 (3.6)	3 (7.5)	
Weight (kg)[a]	38 (14.9-63.9)	49.8 (13.2-96.9)	0.51
Underweight	0	10 (25)	0.02
Normal weight	15 (53.6)	26 (65)	
Overweight/obese	13 (46.4)	4 (10)	
Comorbidity			
Any	13 (46.4)	35 (87.5)	<0.001
≥2	4 (14.3)	23 (57.5)	<0.001
≥3	3 (10.7)	18 (45)	0.003
≥4	2 (7.1)	11 (27.5)	0.04
Comorbidities			
Asthma	4 (14.3)	9 (22.5)	0.40
Genetic/metabolic condition	2 (7.1)	5 (12.5)	0.47
Epilepsy	0 (0)	7 (17.5)	0.02
Cerebral palsy	0 (0)	6 (15)	0.03
Congenital heart disease	0 (0)	5 (12.5)	0.05
Symptoms at presentation			
Fever	28 (100)	25 (62.5)	<0.001
Cough	4 (14.3)	15 (37.5)	0.03
Dyspnea	5 (17.9)	22 (55)	0.002
Vomiting	18 (64.3)	9 (22.5)	<0.001
Diarrhea	13 (46.4)	3 (7.5)	<0.001
Abdominal pain	14 (50)	3 (7.5)	<0.001
Reduced oral intake	14 (50)	10 (25)	0.03
Lethargy	8 (28.6)	14 (35)	0.58
Rash	17 (60.7)	2 (5)	<0.001
Systems involved			
Respiratory	12 (26.7)	33 (73.3)	<0.001
Gastrointestinal	21 (75)	15 (37.5)	0.002
Mucocutaneous	16 (57.1)	3 (7.5)	<0.001
Neurologic	4 (14.3)	4 (10)	0.59
Cardiac	13 (46.4)	7 (17.5)	0.01
Coinfections	8 (28.6)	14 (35)	0.58
PICU admission	9 (32.1)	26 (65)	0.007
Oxygen support	11 (39.3)	39 (97.5)	<0.001
Maximum oxygen support			
Invasive ventilation	5 (17.9)	1 (2.5)	0.0006
PAP	0	18 (45)	
Nasal cannula	6 (21.4)	20 (50)	
None	17 (60.7)	1 (2.5)	
Length of stay (d)[a]	5 (3-7)	2 (2-8)	0.72
Inotrope use	8 (28.6)	2 (5)	0.007
Mortality	0	1 (2.5)	0.30

Values in no. (%) or [a]median (IQR).

Table II Laboratory Markers at Presentation in Patients With MIS-C and Severe/ Critical COVID-19

Parameters	*MIS-C (N=28)*	*Severe/critical COVID-19 (N=40)*	*P value*
Blood counts, n=68			
Leukocyte count (x10^9/L)	9.7 (6.1-15.1)	7.5 (5.6-11)	0.16
Hemoglobin (g/dL)	11.1 (10.1-12.3)	13.1 (11.6-15)	<0.001
Platelet count (x10^9/L)	158 (96-248)	222 (199-334)	0.001
Metabolic panel, n=68			
Sodium (mEq/L)	136 (131-139)	139 (137-141)	<0.001
Potassium (mEq/L)	3.9 (3.5-4.1)	4.4 (3.9-4.9)	<0.001
Bicarbonate (mEq/L)	22.5 (20-25)	25 (23-27)	0.01
Albumin (g/dL)	3.9 (3.5-4.3)	4.4 (3.9- 4.8)	0.02
Blood urea nitrogen (mg/dL)	12 (9-17)	12 (8-15)	0.66
Creatinine (mg/dL)	0.6 (0.4-0.8)	0.5 (0.4-0.9)	0.70
Aspartate aminotransferase (units/L)	51 (26-85)	48 (35-75)	0.98
Alcanine aminotransfercase (units/L)	48 (26-89)	31 (18-71)	0.07
Total bilirubin (mg/dL)	0.6 (0.4-1.1)	0.4 (0.2-0.7)	0.002
Coagulation markers			
International normalized ratio, *n*=50	1.3 (1.25-1.45)	1.2 (1.1-1.25)	<0.001
D-dimer (ng/mL), *n*=52	1130 (801-1971)	294 (222-1750)	0.003
Inflammatory markers			
Procalcitonin (ng/mL), *n*=50	2.3 (0.7-12.5)	0.1 (0.05-0.33)	<0.001
C-reactive protein (mg/L), *n*=68	142 (76-189)	14 (2.3-55)	<0.001
Erythrocyte sedimentation rate (mm/h), *n*=44	35 (24-76)	15 (6-62)	0.02
Ferritin (ng/mL), *n*=43	522 (163-1618)	256 (116-772)	0.20
Cardiac markers			
Lactate (mmol/L), *n*=35	1.6 (1.2-2.9)	1.5 (1-2.4)	0.70
Brain natriuretic peptide (pg/mL), *n*=58	101 (30-251)	25 (9-81)	0.007
Troponin (ng/mL), *n*=57	0.01 (0.01-0.04)	0.01 (0.01-0.02)	0.15

Value in median (IQR) MIS-C - multisystem inflammantory syndrome in children; COVID-19 - coronavirus disease 2019.

Similarly, MIS-C is also characterized by non-specific symptoms [10]. Moreover, both conditions can present with septic shock and multiorgan dysfunction [6,10].

The association of thrombocytopenia with MIS-C observed in this study is of particular importance. Thrombocytopenia has been associated with severity and poor outcomes in adults with active COVID-19 infection including ICU admission, progression to acute respiratory distress syndrome and death; however, such an association is not yet evident in children [11,12].

Cytokines like tumor necrosis factor-alpha and interleukin-10 have shown to distinguish between MIS-C and SC-COVID-19 [13]. However, cytokine profiling is time consuming and expensive. Our study used routinely obtained laboratory markers in combination to predict MIS-C. We believe that using such refined parameters will help in differentiating MIS-C from SC-COVID-19 infection in real time.

We also observed that a higher proportion of MIS-C patients were previously healthy. This is similar to previous reports [13]. A plausible explanation for this observation is a higher cytokine storm in previously healthy children leading to a severe immune response. Children with comorbidities are probably more likely to get severe infections and require more respiratory support as seen in SC-COVID-19 cohort [14]. Although, a higher proportion of MIS-C patients required inotropes and invasive ventilation, they were less likely to be admitted to PICU, as also previously reported [5]. This could be explained by higher proportion of SC-COVID-19 patients requiring oxygen therapy, especially PAP.

Our study has some limitations. Due to its retrospective nature, there is a possibility of potential unknown confounders being missed. As the sample size was limited, findings can only be considered as suggestive. Reference ranges for laboratory values are different at various institutions and the cut-off of CRP ≥40 mg/L might not be applicable.

In conclusion, elevated CRP in combination with either thrombocytopenia or mucocutaneous involvement is

WHAT THIS STUDY ADDS?

- Elevated CRP (≥40 mg/L) with either thrombocytopenia (platelet count <150x10^9/L) or mucocutaneous involvement is helpful in differentiating MIS-C from severe/critical SARS-CoV-2 infection.

supportive of MIS-C diagnosis. Thus, these routinely obtained markers may be useful in differentiating these two conditions and thus, aide in appropriate management of these patients. Since treatment options for these conditions differ, the findings from this study could be used for timely identification of patients with MIS-C, counsel families and plan appropriate treatment accordingly.

Ethics clearance: University of Oklahoma Institutional Review Board; No. 12928 dated December 31, 2020.
Contributors: NG: conceptualized and designed the study, did data collection, drafted the initial manuscript; ST: carried out the initial analyses, reviewed and revised the manuscript. Both authors approved the final manuscript as submitted.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Multivariate Regression Showing Performances of Various Models to Distinguish MIS-C from Severe/Critical COVID-19 Infection at Presentation

Parameters	*Adjusted OR (95% CI)*	*P value*
Whole model fit 0.94		<0.001
CRP (≥40 mg/L)	1.02 (1.01 – 1.04)	<0.001
Absence of respiratory involvement	7.6 (1.3 – 46.3)	0.018
Platelet count (<150 $x10^3/mm^3$)	0.99 (0.98 – 0.99)	0.04
Presence of mucocutaneous involvement	8.9 (1.5 – 54.3)	0.01
Presence of gastrointestinal involvement	2.1 (0.4 – 10.9)	0.36

Sensitivity analysis showing sensitivities and specificities of various models

Criteria	*Sensitivity (%)*	*Specificity (%)*
CRP <40 mg/L+Platelet count ≥150 $x10^3/mm^3$	96.4	57.5
CRP ≥40 mg/L+Platelet count <150 $x10^3/mm^3$	42.9	97.5
CRP <40 mg/L+ absence of mucocutaneous involvement	92.8	65
CRP ≥40 mg/L+presence of mucocutaneous involvement	57.1	97.5

CRP – C-reactive protein

RESEARCH PAPER

The Effect of Multi-source Feedback on Core Competencies of Pediatric Residents

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Objective: The study was conducted to evaluate impact of multisource feedback in pediatric residency training. **Methods**: A crossover study of pediatric residents at Wadia Children's Hospital was conducted with assessment of core competencies like knowledge, practice-based learning, system-based practice, professionalism, communication skills and interpersonal interaction. After randomization both groups (A and B) were given MSF and traditional feedback, respectively and later the groups were crossed over to other method of feedback. Control faculty assessed both groups at three points – Pre-intervention, after first and after second intervention. **Results**: There were 16 residents in each group (13,7,7 in first, second and third year of residency, respectively). Both groups had comparable scores in all six competencies at entry point. Group A after MSF showed significant improvement in all six competencies (all $P<0.01$). No significant improvement was observed in group B after traditional feedback. After cross-over to MSF, group B showed statistically significant improvement in all core competencies. Traditional feedback to group A after crossover showed statistically significant improvement only in knowledge, professionalism and system based practice. **Outcome**: MSF was beneficial in improving competency based performance scores in pediatric residents.

Keywords: *Feedback, Formative assessment, 360^0 evaluation.*

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Competency has been defined as "the ability to do something successfully and efficiently" [1]. In Miller framework of clinical competence, workplace-based methods of assessment target the highest level of the pyramid about performance in everyday work [2]. Thus, if learning objective is to develop professional identity of trainees, then we need an evaluation method which emphasizes on core competencies along with knowledge [3]. Formative assessments, like Multi-source feedback (MSF), are beneficial in checking and improving professional competency in residency training [4].

MSF, a questionnaire-based assessment, gathers perspectives from multiple stakeholders within a learner's sphere of influence, thus giving a vertical and horizontal collage of one's competencies. Feedback, an integral part of these assessments, helps in significant improvement in performance [5]. A systematic review [6] concluded that MSF is reliable, feasible and a valid way to assess competencies in pediatricians. Another study of anesthesiology residents [7] showed an improvement in performance in many core competencies with early exposure to MSF. Although popular in Western countries, studies of MSF in pediatric residency training from India are limited. We aimed to find out the effect of MSF on the performance of pediatric residents, when compared to traditional feedback.

METHODS

A prospective cross-over study was conducted in our pediatric super-speciality teaching institute in Mumbai, over a period of one year (2018-2019). Institutional ethics clearance was obtained prior to commencement of the study. Pediatric residents who were into at least three months of pediatric residency training were included, after an informed consent.

Six core competencies (patient care, knowledge and skills, communication skills, system-based practice, practice-based learning and professionalism) were pre-decided for assessment, in a focussed group discussion of faculty members. For MSF, questionnaires were prepared and validated for various raters. The questionnaires were simple, self-explanatory and permitted written comments in addition to the five-point Likert scale responses. Each resident was evaluated by eight raters (faculty - 1, peers - 2, nurses -2, parents-2, and self-assessment).

After giving unique identification numbers, pediatric residents were divided into two groups using EpiInfo randomization software. Group A received MSF and Group B was given traditional feedback first, and after cross over, group A got traditional feedback and group B-MSF. Three faculty members (control faculty) assessed the core competencies of the residents on a scale of 100 at three time intervals – pre (T0), after first intervention (T1) and after second intervention (T2) (**Fig. 1**). They were blinded to the group to which the residents belonged and assessed them at work without knowledge of the students.

MSF and traditional feedback were in structured format and were given by one faculty member each, separately. The feedback technique was a sandwich technique and was outcome oriented, one-on-one, confidential, descriptive, with clear learning objectives and plans for improvement [8]. One month was given to both groups to adapt to the feedback, and then they were subjected to intermediate assessment by control faculty (T1). After cross-over, Group B received MSF and Group A got traditional feedback followed by a month for assimilation and adaptation of respective feedbacks. This was followed by final assessment by control faculty (Time 2). The perception about MSF was obtained from students and faculty on a pre-designed feedback form and analyzed.

Statistical analysis: SPSS 21.0 was used for statistical analysis. For internal consistency of the instrument, Cronbach alpha was calculated for all the three time-points (Time 0, 1 and 2).The change in scores by the control faculty in both groups were calculated and compared. *P* values of ≥0.01 were considered significant. Comparison between pre, inter and post-intervention was done by Friedman test. Wilcoxon signed rank test was performed using different combinations of related groups.

RESULTS

Thirty two pediatric residents (20 males) spread over three years of training were enrolled. One student from group B dropped out of the study for medical reasons.

The control faculty evaluation form had a good inter-rater reliability with Cronbach alpha (95% CI) of 0.975 (0.96 - 0.986), 0.983 (0.978 - 0.991) and 0.985 (0.975-0.992) for the pre-intervention, intermediate intervention and post intervention phases, respectively. A Total of 249 (97.26%) questionnaires were collected which took 5 minutes for filling by each rater. The median scores for all six core competencies of both groups at T0 were comparable

Group A showed statistically significant change in all the six core competencies after MSF (all $P<0.01$); whereas, when they were crossed over to traditional feedback, only medical knowledge, system-based practice and professionalism had significant improvements (**Table I**). Group B did not show significant improvement in any core competency after traditional feedback, but when they were crossed over to MSF all the six core competencies

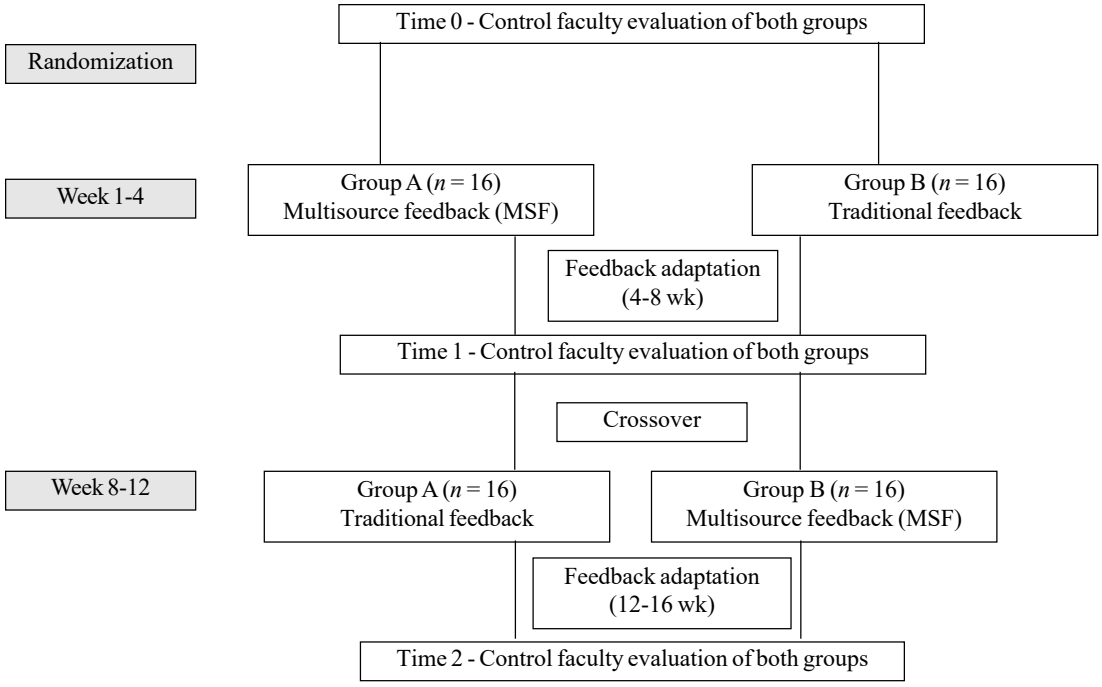

Fig. 1 Study flow chart.

exhibited significant change (**Table I**).

Second year residents among group A showed statistically significant change in their scores at T1, whereas among group B, year 1 and year 3 residents showed significant change at T1.

Perception about MSF was assessed from faculty members (n=8) and residents (n=31). All faculty members were satisfied by MSF, and a 6-monthly assessment was suggested by 62.5% of the faculty. MSF was considered very good by 96.7% (n=30) residents, and 6-monthly MSF was suggested by 58.1% (n=18). While 3-monthly evaluations were suggested by 22.6% (n=7) residents.

DISCUSSION

In this single-center study of pediatric residents, comparing MSF with traditional feedback, both groups showed significant improvement in all core competencies scores after MSF as against traditional feedback. Year-wise benefit could not be demonstrated uniformly.

Brinkman, et al. [9] showed that 360-degree feedback had a positive effect on communication skills and professional behavior among pediatric residents. MSF was found to be valid, feasible, reliable and useful method to evaluate pediatricians [6]. The best assessed competencies were communication, interpersonal skills, collegiality and medical expertise. The utility of MSF was also shown in few studies from other medical specialties [5,10]. Joshi, et al. [11] found 360-degree evaluation reliable and useful for assessment of residents' interpersonal and communication skills in field of obstetrics and gynecology. However, a non-comparative action based study by Archer, et al. [12] found that MSF in the form of Sheffield Peer Review Assessment Tool (SPRAT) did not provide enough data on trainees, and more assessments were suggested. Unlike our study, Tariq, et al. [13] showed improvement in communication and interpersonal skills in third year residents after MSF, but year-wise differences were not significant.

MSF has potential to be a useful tool, but current evidence suggests improvement in its administration [14]. Time constraint of busy clinical workload was possible reason of its under-utilization, as previously shown [15].

This can be overcome by preparing a competency based post graduate curriculum, year-wise segregation of the competencies and at-least one multisource feedback during residency training.

The brief study period for the residents to assimilate the feedback and show any kind of change in their competencies was the main limitation of the study. The crossover nature of our study design allowed residents to serve as their own control and thus minimized influence of confounding variables, but still there was a possibility of carry-over effects.

Significant improvement in core competencies after MSF depicted its usefulness in residency training thus suggesting its inclusion in the assessment modalities of Indian pediatric residency training programs.

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Table I Scores of Core Competencies in Pediatric Residents After Multi-source Feedback

Core competencies	*Pre-intervention*	*Intermediate intervention*	*Post- intervention*
Group A			
Patient care[a,e]	47.5 (36.3, 58.8)	60.0 (50, 68.8)	67.5 (56.3, 70)
Medical knowledge[a,c]	40.0 (40, 62.5)	56.5 (45, 73.8)	65.0 (51.3, 75)
Practice based learning and improvement[a]	42.5 (36.3, 63.8)	60.0 (45, 75)	65.0 (55.8, 75)
Interpersonal and communication skills[b,e]	50.0 (40, 60)	62.5 (51.3, 68.8)	63.5 (60, 73.8)
System based practice[b,d]	50.0 (40, 67.5)	62.5 (51.3, 73.8)	65.0 (56.3, 78.8)
Professionalism[a,d]	50.0 (40, 63.8)	65.0 (47.5, 78.8)	68.5 (56.3, 78.8)
Group B			
Patient care[c]	50.0 (40, 55)	55.0 (35, 62.5)	65.0 (52.5, 75)
Medical knowledge[c]	45.0 (40, 50)	55.0 (35, 60)	60.0 (52.5, 70)
Practice based learning and improvement[c]	45.0 (40, 50)	50.0 (35, 57.5)	65.0 (55,75)
Interpersonal and communication skills[d]	50.0 (40, 60)	60.0 (35, 67.5)	68.0 (55, 75)
System based practice[c]	45.0 (40, 50)	55.0 (40, 60)	65.0 (55, 70)
Professionalism[c]	45.0 (40, 57)	50.0 (40, 60)	65.0 (55, 75)

Data presented as median (IQR). For intermediate intervention - pre intervention, [a]P=0.001 and [b]P<0.01; For post intervention - intermediate intervention, [c]P=0.001, [d]P<0.01 and [e]P<0.05.

Ethics clearance: Institutional Ethics Committee, Bai Jerbai Wadia Hospital for Children; No. IEC- BJWHC/97/2018, dated August 30, 2018.
Contributors: SK: conceptualized the study, completed the data collection, analysed and drafted the paper; SP: feedback process and also did proof reading; TL: statistical analysis. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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CLIPPINGS

Potential marker for accurate prediction of pubertal onset in delayed puberty *(J Clin Endocrinol Metab. 2021;106:e3495-3505)*

A cutoff level of gonadotropins, whether basal or GnRH stimulated, which can differentiate constitutional delay of puberty from hypogonadotropic hypogonadism, has hitherto eluded investigators. This study was conducted to explore the potential role of FSH stimulated inhibin B (FSH-iB) for prediction of pubertal onset. FSH and GnRH analogue stimulation test were performed on exploratory cohorts (n=42, group 1-spontaneous puberty, group 2-hypogonadotropic hypogonadism [HH]) and a validation cohort (n=19, delayed puberty). Statistically significant increase in FSH-iB occurred in group 1 in both males and females, while the increment was not significant in group 2. Cutoffs of FSH-iB (males- 116.14 pg/mL and females- 116.50 pg/mL) had 100% sensitivity and specificity for marking pubertal onset. These cutoffs showed 100% positive predictive value, negative predictive value and diagnostic accuracy when applied to the validation cohort. Thus, FSH-iB can be considered as a novel and promising marker for prediction of pubertal onset, but requires further studies before labeling it as the gold standard.

Systematic cranial MRI in girls with central precocious puberty *(J Clin Endocrinol Metab. 2021;106:e2557-66)*

The necessity of performing magnetic resonance imaging (MRI) in girls with central precocious puberty (CPP), aged 6-8 years has always been considered debatable. This study was done on 770 Turkish girls with CPP to investigate the frequency of central nervous system (CNS) lesions and their potential predictors. In 654 out of 770 girls, pubertal onset occurred between 6 to 8 years; 104 (13.5%) girls had an abnormality on brain MRI. Out of these, only 2 (0.25%) girls had neoplastic lesions (1 low grade glioma and 1 meningioma), but they did not require any intervention on follow up. Pubertal onset age <6 years and leutinizing hormone/follicle-stimulating hormone (LH/FSH) ratio >0.6 were associated significantly with CNS lesions. However, both girls with neoplastic lesions were >6 years old, thus making the predictive power of age and LH/FSH ratio weak. The authors concluded that systematic MRI is an efficient approach to diagnose an occult CNS lesion in girls with CPP, but that the likelihood of finding a lesion requiring intervention remains low.

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RESEARCH PAPER

Prevalence and Determinants of Screen-Viewing in Children Under Two Years in Suva, Fiji

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Objective: To determine the prevalence of screen-viewing and factors affecting this behavior among children aged less than two years in Suva, Fiji. **Methods:** This cross-sectional study was conducted at three randomly selected maternal and child health (MCH) clinics among parents or accompanying guardians of 379 children. Data collection was carried out using a 20-item self-administrated questionnaire. **Results:** The prevalence of screen-viewing in children was 66.2%. Screen-viewing was more prevalent in children aged 12-24 months (89%) than in children below 12 months (57%). The risk of screen-viewing was high among those who had parents as daytime caregivers (RR (95% CI) = 0.93 (0.82 - 1.04), *P*=0.001), iTaukei (RR (95% CI) = 0.79 (0.71-0.87), *P*=0.001), and children younger than 12 months (RR (95% CI) = 0.64 (0.57-0.71), (*P*=0.001). Results show that availability of screen devices at home is significantly related to children's screen viewing (RR (95% CI) =1.03 (0.64-1.65), *P*=0.03). **Conclusion:** The study found early exposure and early adaptation to screen-viewing in children due to several determinants, and suggests the need for anticipatory guidance to parents.

Keywords: *Caregiver, Obesity, Screen time*.

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The screen device is a major part of the contemporary life for children [1]. Now, more than ever, children from a very young age are allowed unlimited access to a wide variety of screen devices, and the prevalence is increasing [1-4]. Excessive screen-viewing has been linked to several pediatric health determinants and outcomes [5-6], and various risk factors for this behavior [2-3,7,8]. It is important to be cautious about screen-viewing by children below two years as they are in a critical developmental period of their life.

In Fiji, there are 213 004 children aged younger than five years and of these 91 830 are from the Suva sub-division [9]. The aim of this study was to determine the prevalence of screen-viewing, and analyze the associated factors among children under two years in Suva.

METHODS

A cross-sectional study was conducted at three maternal and child health (MCH) clinics, randomly selected from the eight designated MCH clinics in the Suva subdivision. These included the Nuffield, Valelevu and Makoi MCH clinic. We enrolled caregivers who brought at least one child younger than two years to the clinics, and who were living in Suva for more than one year and attending the three MCH clinics during the study period.

The total population of children younger than two years was obtained from the Expanded Program on Immunization (EPI) monitoring registers of the three MCH clinics. The total population of registered children less than two years at the three clinics was found to be 5832. A proportional sampling method was then used to calculate the sample size using a 5% margin of error and 95%CI of parents or accompanying guardians of children aged less than two years at the three selected clinics. Considering a 5% non-response rate, the total sample size for this study was 379.

A 20-item questionnaire was administered directly by the researcher. The questionnaire included a set of standardized questions that included demographic characteristics (age, place of recruitment, childbirth order, number of children, ethnicity and daytime caregiver arrangement), and the screen viewing behaviors (watching/engaging with screens for some time) of the children. Pilot testing was done at the Makoi and Nuffield MCH clinics with a sample of eight volunteer participants who met the inclusion criteria of the study, ensuring that the questionnaire was readable and understandable by participants. It was also tested by the study supervisors to validate the content of the tool. Following the pre-test, minor changes were made to the questions and structure of the data collection tools.

The outcome variable for this study was infant/toddler screen time, which was defined as the time spent watching

screens such as television, DVDs, videos, smartphones, tablets or computers by children below the age of two years. Additional variables such as socio-demographic characteristics were studied as confounders to explore relationship with the main predictor (screen time). This included childbirth order, age of child (months), ethnicity, daytime caregiver arrangements, child's screen-time, fre-quency of screen-viewing and availability of screen devices.

Data collection was done from 1 March - 30 September, 2019. The researcher organized an initial meeting with the Sub-Divisional Medical Officer (SDMO) and sister-in-charge of the three MCH clinics. A week earlier than the actual data collection, an awareness meeting was also done with the medical officer, sister-in-charge and zone nurses of the MCH clinics to highlight the importance of this study and the support needed from the clinics.

During the data collection period, the participants at each MCH clinics were invited to respond to an anonymous, one-on-one questionnaire administered by the researcher, while waiting to see the healthcare providers at the clinics. With support of the MCH nurse on duty, an announcement about the study was done to all waiting participants in the three major languages, English, Hindi and *iTaukei*. In the announcement, information about the survey was shared and an open invitation made to potential participants to be part of the study. Recruitment of participants was done by the researcher. Participants who brought more than one eligible child to the clinic completed the questionnaire only for the youngest child. For those who volunteered to participate, a next round of one-on-one information was provided. Participants provided informed verbal and written consent prior to taking part in the study. Questionnaires were filled in by the researcher with each participant at a designated confidential space within the MCH clinic. Translation of the questionnaire was done in Hindi and *iTaukei* depending on the need of participants. In cases where both parents were present, both were included when filling the questionnaire and it was left to the parents to decide who took the lead in answering.

Data analysis: Data was entered in KoBo Toolbox for data cleaning and coding and then transferred to Microsoft Excel for analysis. Data was analyzed using descriptive statistics. Chi-square test was used for categorical variables to assess the relationship between risk factors and screen viewing. A *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 361 participants (88.9% response rate) answered the questionnaire completely and were included in the analysis. The study participants responding were predominantly female (82%). Majority (69.8%) of children were younger than 12 month, and were the youngest child (53.5%) in birth order (**Table I**).

Table I Demographic Characteristics of Participants (*N*=361)

Characteristic	*No. (%)*
Place of recruitment	
Makoi MCH clinic	136 (38)
Nuffield MCH clinic	124 (34)
Valelevu MCH clinic	101 (28)
Childbirth order (n=355)	
Youngest child	190 (53.5)
First born	154 (43.4)
Middle child	11 (3.1)
Daytime caregiver arrangement (*n*=355)	
Parents	252 (71.0)
Grandparents	72 (20.3)
Nannies	20 (5.6)
Home-based caregiver	11 (3.1)
No. of children at home (n=358)	
1	109 (30.4)
2	126 (35.2)
> 2	123 (34.4)
Ethnicity	
iTaukei	267 (74.0)
Fijian of Indian descent	76 (21.1)
Others	18 (5.0)

The prevalence of screen viewing in under two-year-olds was found to be 66.2%; higher in 12-24 months (89.9%) than in children below 12 months (57.1%). Most children (33.4%) used screens several times a week, regardless of age while 27.5% watched screens several times a day; 6.3% watched screens once a day. Most children (59%) spent less than 2 hours per day as screen time, while 41% spent two or more hours on screen per day. Television was the most popular form of screen-viewing, followed by smartphones. The main reasons given for children's screen time use were: used as a distraction tool (29.9%); to calm child or to prevent negative behavior (26%); and educational use (22%). Other reasons given for children's screen use were as part of family time, and used for the toddler to rest. Majority of children (98.1%) had screen devices at home, and it was significantly related to children's screen-viewing [RR (95% CI) = 1.03 (0.64-1.65); *P*=0.03]. The most common device used for screen viewing activity was either television (51%) or smartphones (45%).

Frequency of screen-viewing was high among first-borns (76.6%) (*P*=0.03), in children who had nannies as daytime caregivers (95%) (*P*=0.01) and in Fijians of Indian descent (80.3%) (*P*=0.002). The factors associated with screen-viewing are shown in **Table II**.

DISCUSSION

This study found that prevalence of screen-viewing is high

Table II Factors Associated With Screen-Viewing in Children (Aged<2 years) in Fiji

Factors	*Screen viewing*	*RR(95%CI)*
Parent as major caregiver	160 (63.5)	0.93 (0.82 - 1.04)
Ethnic group		
iTaukei[a,b]	167 (63.7)	0.79 (0.71 – 0.87)
Fijian of Indian descent	61 (80.3)	
Age <12 mo[a]	144 (57.1)	0.64 (0.57 - 0.71)

Values in no. (%). [a]P=0.001, [b]Compared to Fijian of Indian descent.

(66.2%) and that children are spending a substantial amount of time in front of screens. This was consistent with previous research [5,10,11,12], with around 40% of children under two years watching more than two hours of television per day [10,11]. This study also found that screen-viewing is more prevalent in children 12-24 months, similar to results of the study by Barber, et al. [13] that also showed that child TV time increased with age in a non-linear way. The findings are consistent with another study, which found that most children start using mobile devices in their first year of life [14].

The main screen devices, as highlighted by the study, included television and smartphones. These findings were consistent with the findings of a previous study in Philadelphia [14]. Children were more likely to view screens when under care of grandparents than with parents. An association was also found between the major ethnic groups and screen viewing, similar to a previous report in 2-3-year-olds [15]. This association with ethnicity implies that culturally specific interventions may be required to address the screen-viewing issue.

Results of this study cannot be generalized to all children in Fiji as the diversity of the study in terms of ethnicity was not fully proportional and representative, as *iTaukei* were over-represented. The baseline demo-graphical information did not show equal representation of sample in terms of age and ethnicity.

Prevalence of screen-viewing is high in children aged less than two years in Suva, Fiji. This high prevalence rate is a concern given the WHO recommendation of no screen time for children below two years. More research is necessary on the types of interventions that can mitigate the effects of screen exposure in children's development. Anticipatory guidance and alternatives to screen viewing activity that support positive development should be made available to families attending pediatric practices and MCH clinics in Fiji.

Ethics clearance: College Health Research Ethics Committee (CHREC) in Fiji National University, and the Ministry of Health and Medical Service's National Health and Research Ethics Committee.

Contributors: ND: designed the study, collected and analyzed the data. MM, AT: helped design reviewing, and supervise the research study. All authors contributed to writing and revising the manuscript in addition to reading and approving the final version.
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RESEARCH PAPER

Vaccination With Routine Childhood Vaccines and Severity of COVID-19 Among Children in Delhi

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Objective: To study the association between routine childhood vaccination and the severity of COVID-19 among children. **Methods:** A cross-sectional study was undertaken among 141 children (aged ≤15 years), tested positive for SARS-CoV-2 infection. **Results:** COVID-19 severity (combined moderate and severe) was significantly more in males (14.5%) than females (3.8%), and in those who did not receive first and second dose of MR vaccine (57.1%, and 40%, respectively) than who received (6.3%, and 6.1%, respectively). Disease severity was more in partially immunized children (16.7%) as compared to fully immunized children (7.0%). **Conclusions:** Children who did not receive both doses of MR vaccine had a severe infection when compared to those who were vaccinated.

Keywords: *Measles vaccine, SARS-CoV-2 infections*.

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SARS-CoV-2 infection among children manifests with mild to moderate disease [1]. The reasons why children have relatively low severity of COVID-19 remains unclear. Low infection rate and mild form of the disease in children are expected to be due to childhood vaccinations [2]. Measles containing vaccine has been suggested to reduce incidence of SARS-CoV-2 infection in children [3]. Measles-mumps-rubella (MMR) vaccine may provide strong protection from COVID-19 spread and mortality [4,5]. BCG vaccination may lessen the severity of COVID-19 among children [6]. This study was conducted to examine the association between routine childhood vaccinations and the severity of COVID-19.

METHODS

This observational study was conducted over six months among children of age group up to 15 years who tested positive for SARS-CoV-2 by rapid antigen test (RAT) or reverse transcriptase-polymerase chain reaction test (RT-PCR) in Central district, Delhi. Considering the prevalence of COVID-19 disease among children to be 2%, with a 95% confidence interval and with a permissible error of 2% (absolute), a minimum of 188 participants were required [7]. The final sample size was calculated to be 210 taking a non-response rate of 10%.

Out of 903 children up to 15 years with COVID-19, 210 were selected by simple computer generated random sampling. Auxiliary nurse midwives (ANMs) providing immunization services to the children were identified by the District Immunization Officer (DIO) and they were asked to provide data related to immunization and demographic characteristics of the study subjects on a semi-structured questionnaire. ANMs visited the concerned children and interviewed the mother or caregiver after obtaining informed written consent, and verbal assent where applicable. Among them, 141 (67.1%) completed responses were included in the final analysis. Children, who received one dose of BCG, three doses of OPV, three doses of Rotavirus, three doses of (Penta/DPT/HepB), two doses of fractional IPV, and one dose of MR vaccine, before completion of age of 1 year, were considered as fully immunized.

Data related to disease severity was obtained from the CDMO office, Central District, New Delhi. The disease status of the individual patients was maintained at the office of CDMO office and classified as per the guidelines of Government of India [8].

Statistical analysis: The analysis of data was done by SPSS Statistics for Windows, version 25 (IBM Corp.). Chi-square test and Fisher exact test were used for inferential purpose. A P value <0.05 was taken as statistically significant.

RESULT

Of the 141 children with SARS-COV-2 infection, 100 (70.9%) were symptomatic, with mild, moderate and severe disease in 88 (62.4%), 9 (6.4%) and 3 (2.1%), respectively. Among

those with moderate and severe disease, there was significantly higher proportion of boys (14.5%) (P<0.01). Age, religion, type of family, and socioeconomic status (SES) were comparable (**Table I**).

Among the participants, 114 (80.8%) were fully immunized, 24 (17.1%) partially immunized and 3 (2.1%) children were not immunized at all. Symptomatic infection was more in the case of partially immunized children as compared to the fully immunized children (75% vs 69.7%; P=0.60). In partially immunized children, combined moderate and severe disease was more (16.7%) as compared to fully immunized children (7.0%) (P=0.26). Among the recipients of the measles/MR (measles and rubella) vaccine (first dose as well as second dose), disease severity was significantly less as compared to those who did not receive [6.3% vs 57.1%; P=0.001] for first dose, and [6.1% vs 40%; P=0.005] for second dose. However, no such association was observed with other vaccines (**Web Table I**). The odds of having combined moderate and severe disease was 19.6 times higher (for the first dose) [OR (95% CI) 19.6 (3.74-103.4); P=0.001] and 10.2 times higher (for the second dose) [OR (95%CI) 10.2 (2.34-45.1); P=0.01] among those who did not receive measles/MR vaccine as compared to the recipient of the vaccine.

DISCUSSION

We found COVID-19 severity (moderate and severe) more among boys and those who did not receive measles/MR vaccine. A plausible explanation for the gender difference could be based on their immunological responses to foreign and self-antigens, and differences in innate and adaptive immune responses [9], or differences in their immunization status.

More symptomatic infections and higher disease severity in partially immunized might be due to the cross-reactivity of the components of the childhood vaccination to the SARS-CoV-2 virus. Contrary to this, in a mouse model, Kandeil, et al. [10], reported that none of the childhood vaccines provided antibodies capable of neutralizing SARS-CoV-2 up to seven weeks after vaccination. The low infection rate and mild form of disease presentations in children >1 year of age have been reported previously also, and suggested to be due to childhood vaccinations [2]. Salman, et al. [11] suggested that children were spared by COVID-19 disease owing to the low immunity in childhood that does not exaggerate the immune response against the virus as in an adult. In the present study, the severity of disease was significantly less in the recipients of the MR vaccine. This might be due to the cross-reactivity of measles or rubella components of the vaccine with the SARS-CoV-2 virus and the development of neutralizing antibodies towards the SARS-CoV-2 virus. MMR vaccine may provide strong protection from COVID-19 spread and mortality [4,5]. A significant negative correlation was observed between mumps virus titre and severity of COVID-19 disease [4]. More directly, there is also evidence that the rubella virus has a 29% sequence homology with a SARS-CoV-2 surface protein. Accordingly, the rubella component of the MMR vaccine may confer specific protection against COVID-19 [5,12].

MMR had previously been used to induce bystander immunity against other virus strains e.g., warts caused by human papillomavirus could be ameliorated using an intra-lesional MMR vaccine [11]. Sidiq, et al. [12] found that 30 amino acid residues homology between the Spike (S) glycoprotein of the SARS-CoV-2 virus including Fusion (F1) glycoprotein of measles virus (residues R389 to K419) as well as with the envelope (E1) glycoprotein of the rubella virus (residues A444 to K473). Thus, they believed that humoral immunity created through the MMR vaccination provides children with advantageous protection against COVID-19 as well. A recent case-control study in Sweden [14], on MMR vaccination in health care workers (adults) and COVID-19 did not support a substantial protective effect of the MMR vaccine in the whole study population. However, they concluded that there may be a protective effect of the MMR vaccine against SARS-CoV-2 in males but not in females [14]. Several researchers have reported that BCG vaccination may also lessen the severity of SARS-CoV-2 infection [6]. However, in the current study, such association could not be observed.

In conclusion, those who received the measles/MR

Table I Sociodemographic Profile of the Participants (N=141)

Characteristics	*Disease outcome* (*COVID-19*)		
	Asymptomatic	*Mild*	*Moderate and severe*
Males[a]	11 (17.7)	42 (67.8)	9 (14.5)
Hindu religion	35 (33.1)	61 (57.5)	10 (9.4)
Joint family	18 (27.7)	42 (64.6)	5 (7.7)
Age group (COVID-19)			
3-60 mo	15 (30.6)	29 (59.2)	5 (10.2)
6-10 y	8 (18.6)	33 (76.7)	2 (4.7)
11-15 y	18 (36.7)	26 (53.1)	5 (10.2)
Socioeconomic status[b,c]			
Class I	25 (32.5)	46 (59.7)	6 (7.8)
Class II	11 (20.4)	37 (68.5)	6 (11.1)
Class III	5 (50.0)	5 (50.0)	0

Values in no. (%). [a]P<0.01. [b]As per modified BG Prasad classification [15]. [c]None of the participants belonged to Class IV and V.

WHAT THIS STUDY ADDS?

- Children who did not receive measles/MR vaccine had a severe form of COVID-19 disease as compared to those who were vaccinated.

vaccine had a less severe form of COVID-19 disease as compared to those who were not vaccinated. Though this study is limited by small sample size, and non-estimation of antibody titters to corroborate the findings, this study suggests that the COVID-19 disease manifests in a less severe form among the recipient of measles/MR vaccine.

Ethics clearance: Institutional ethics committee, Maulana Azad Medical College, New Delhi; No. F.1/IEC/MAMC/80/08/2020/ No-246 dated October 01, 2020.

Contributors: MMM: data interpretation, data analysis, manuscript preparation; ALB: manuscript review, manuscript editing and definition of intellectual content; PL: concept, design, definition of intellectual content and manuscript review; MM: collection and assembling of data; KVR: facilitation of data collection and availability of data. All authors approved the final version of manuscript and are accountable for all aspects related to the study.

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

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Web Table I Disease Outcome and Vaccination Status of Study Participants (*N*=141)

Received vaccine	*Disease Outcome* (*COVID-19*)		
	Asymptomatic	*Mild*	*Moderate & Severe*
BCG (n=137)	41 (29.9)	84 (61.3)	12 (8.8)
OPV-0 (n=120)	37 (30.8)	74 (61.7)	09 (7.5)
HepB (n=106)	30 (28.3)	68 (64.2)	08 (7.5)
OPV-1 (n=137)	41 (29.9)	84 (61.3)	12 (8.8)
OPV-2 (n=135)	41 (30.4)	82 (60.7)	12 (8.9)
OPV- 3 (n=133)	40 (30.1)	81 (60.9)	12 (9.0)
f-IPV-1 (n=34)	10 (29.4)	22 (64.7)	02 (5.9)
f-IPV-2 (n=30)	09 (30.0)	19 (63.3)	02 (6.7)
ROTA-1 (n=32)	10 (31.2)	20 (62.5)	02 (6.3)
ROTA-2 (n=30)	10 (33.3)	18 (60.0)	02 (6.7)
ROTA-3 (n=29)	09 (31.0)	18 (62.1)	02 (6.9)
DPT-1 (n=70)	22 (31.4)	42 (60.0)	06 (8.6)
DPT-2 (n=69)	22 (31.9)	41 (59.4)	06 (8.7)
DPT-3 (n=66)	21 (31.8)	39 (59.1)	06 (9.1)
HepB-1 (n=70)	21 (30.0)	43 (61.4)	06 (8.6)
HepB-2 (n=69)	21 (30.4)	42 (60.9)	06 (8.7)
HepB-3 (n=64)	20 (31.2)	40 (62.5)	04 (6.3)
PENTA-1 (n=69)	19 (29.7)	39 (60.9)	06 (9.4)
PENTA-2 (n=63)	19 (30.2)	38 (60.3)	06 (9.5)
PENTA-3 (n=62)	18 (29.0)	38 (61.3)	06 (9.7)
Measles/MR-1 (n=126)[a]	38 (30.2)	80 (63.5)	08 (6.3)
Measles/MR-2 (n=115)[a]	34 (29.6)	74 (64.3)	07 (6.1)
OPV-Booster (n=118)	36 (30.5)	73 (61.9)	09 (7.6)
DPT-Booster-1 (n=109)	35 (32.1)	66 (60.6)	08 (7.3)
DPT-Booster-2 (n=77)	25 (32.5)	46 (59.7)	06 (7.8)
TT-1st dose (n=21)	07 (33.3)	10 (47.6)	04 (19.1)

Values in no. (%), [a]P<0.01, BCG- Bacillus Calmette Guerin, OPV- Oral polio vaccine, HepB-Hepatitis B vaccine, f-IPV- Fractional inactivated polio vaccine, ROTA- Rotavirus vaccine, DPT- Diphtheria pertussis tetanus, PENTA- Pentavalent vaccine, MR-Measles Rubella vaccine, TT-Tetanus toxoid vaccine.

COVID-19 in Children and Safety of SARS-CoV-2 Immunization in Children: Statement of the International Pediatric Association

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The global burden of coronavirus disease 2019 (COVID-19) exceeded 271 million cases worldwide, with over 5 million officially confirmed deaths due to COVID-19, with no country of the world spared [1]. According to the American Academy of Pediatrics, about 17.3% of all US cases through 12 December, 2021 were in children, while 0.1-1.8% of all child COVID-19 cases resulted in hospitalization [2].The global data compiled by the World Health Organization (WHO) in November, 2021, show that children and adolescents represent a small proportion of severe diseases, and of deaths from COVID-19 when compared to older age groups. However, the emerging evidence suggests that COVID-19 disease may not be uniform globally.

In addition to the direct effects of COVID-19, the COVID-19 mitigation measures have had a profound impact on the lives of children and adolescents, affecting their education, mental, emotional, and social health for the last two years, hindering normal child development. Experts suggest that the indirect effects of COVID-19 on children's education, mental and emotional health may be much more important in the long term than the direct effects.

The surge in COVID-19 cases driven by the greater circulation of transmissible variants (e.g., Delta) resulted in an increase in the COVID-19 associated hospitalization in children in many countries [3-5]. The Omicron variant, which has recently emerged, is highly transmissible. With its increased transmissibility, the number of cases, including severe cases, is likely to increase worldwide. Therefore, vaccination of children and adolescents assumes even greater importance given the substantial and increasing impact of COVID-19 and pandemic response on children and adolescents.

A number of vaccines have been developed and are approved for use in adults in various countries around the world for COVID-19 prevention. Available data suggest that vaccines are highly effective in prevention of serious illness and death. Several vaccines, including Covaxin, Moderna, Pfizer, Sinopharm, Sinovac, amd ZyCov-D have recently been authorized for emergency use in children in some countries. Limited published data exist for some of these vaccines, but available data suggest robust immunogenicity, efficacy, and safety in clinical trials [6,7]. Other data have been presented supporting pediatric immunizations to regulatory authorities and National Immunization Technical Advisory Groups (NITAGs). The International Pediatric Association encourages improved access of these data to the public, and peer review publication of these data. Thus far, in those 5 years of age or older, the benefits of COVID-19 vaccines in reducing hospitalizations and deaths due to COVID-19 appear to far outweigh any safety issues.

With several countries extending COVID-19 vaccinations to children, the International Pediatric Association, also supports and recommends vaccination of children, provided the vaccines are approved by regulatory authorities for children and recommended by NITAGs. Children should get the full benefit that COVID-19 vaccines can provide to improve their health and well-being.

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NEWS IN BRIEF

HOW SCHOOL START TIME AFFECTS SLEEP PATTERNS

In 2014, the American Academy of Pediatrics made a remarkable policy statement. They said that school start times for adolescents must be delayed and must not be before 8.30 AM. What was the science behind this important decision and what are the other fallouts of this?

Over the years there has been increasing data that adolescents are chronically sleep deprived. In 2013, a National Sleep Poll in the US found that 59% of sixth to eight graders had insufficient sleep and the number was as high as 87% in high school students. There are both biological and social reasons for the same.

The important biological reason is that with onset of puberty there is a 'phase delay' by 2 hours of the natural sleep onset. The reason is a delay in the release of melatonin in adolescents. Further the 'sleep drive' which accumulates over the day is delayed in teens. This means that the average teenager has great difficulty in falling asleep before 11 PM. However, their average sleep requirements of 8.5- 9.5 hours per day do not decrease compared to middle schoolers. This means they need to sleep till about 8 AM to be fully refreshed.

Schools; however, are oblivious to these biological circadian cycles. The chronic sleep deprivation due to early school timings in high school results in daytime somnolence, inattention, depression, mood swings and obesity. Risky behavior due to excessive caffeine consumption and recreational drug use may be linked to this phenomenon.

Recognizing the high cost of sleep loss several schools in the US started delaying school onset timings to suit adolescents.

There have been many studies to demonstrate the benefits of this policy. Academic performance has improved, children have performed better on computerised attention tests and math and reading scores have improved. Car crashes in counties which had changed school start times decreased by 16% as compared to a rise of 7.8% for the rest of the state which did not make that change.

In a recent study from Colorado, USA, called the 'The Changing Start Times: Longitudinal Effects Study (CaSTLES),' researchers have tried to provide a comprehensive evaluation of the impact of changing school start times. They found an interesting outfall of this policy decision. There was a significant improvement in sleep timings and daytime functioning of parents of high school students.

Chronic sleep loss in adolescents is rampant and national level policies may help to tackle this unrecognized problem. (*Sleep Health, Oct 2021*)

RISE IN PEDIATRIC CANNABIS TOXICITY IN CANADA

Canada became the second country to legalize recreational use of cannabis after Uruguay in October, 2018. It happened in a phased manner. In phase 1, between October, 2018 and January, 2020 cannabis flower products, seeds and oils were allowed. After January, 2020, till March, 2021 (Phase 2), the sale of commercial edibles like gummies and cookies became legal. This was done to take the profits out of the hands of criminals.

However, this has badly impacted pediatric health. A recent study in JAMA Network Open showed that pediatric emergency visits due to cannabis toxicity rose from 20 in the 2 years pre-legalisation to 29 in phase one of legalisation to 122 in phase two of legalisation. In fact, phase 2 of legalisation overlapped with the COVID pandemic where the cannabis related poisoning rose despite an overall decrease in all other pediatric poisonings. This has occurred despite several strict measures like child resistant packages, a maximum of 10 mg of tetrahydrocannabinol per eatable and market restrictions. Other countries who are advocating legalising marihuana must take note. (*JAMA Network Open. 2022*)

FIRST US PORCINE HEART TRANSPLANT

The University of Maryland was in the news after the transplant of a porcine heart into a 57-year-old man with heart failure who was not eligible for conventional transplants due to life threatening arrhythmias. The pig was genetically modified using CRISPR technology. One of the modifications is to remove certain glycans from porcine endothelial cell surfaces. Human beings have natural preformed antibodies against these glycans, which contribute to the hyperacute rejection. Six human genes were also introduced into the pigs to improve immune tolerance.

An Indian surgeon Dr Baruah was the first person to transplant a porcine heart and lung in a terminally ill patient in Assam in 1997. However, the patient died in 7 days of hyper acute rejection and Dr Baruah was imprisoned for 40 days under the Transplantation of Human Organs Act, 1994.

Xenotransplants using pig organs will be a game changer because pigs are easier to raise than primates, they achieve human heart size in 6 month, and pig heart valves have been used earlier with success. (*The New York Times 10 January 2022*)

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Indian Academy of Pediatrics (IAP) Task Force Recommendations for Incorporating Nurturing Care for Early Childhood Development (NC-ECD) in Medical Education in India

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Background: The World Health Organization (WHO) recommends promotion of nurturing care for early childhood development (NC-ECD) by focusing on five essential components viz., good health, adequate nutrition, promotion of early childhood learning, responsive caregiving, and safety and security. Indian medical graduates and pediatricians are the keys to successful delivery and propagation of NC-ECD in the community. Their training therefore needs to include skills and knowledge needed to promote and practice ECD. **Objective:** To evaluate the existing undergraduate (UG) and postgraduate (PG) curricula of pediatrics for components related to early childhood development, assess gaps in the training essential to practice and promote ECD, and suggest recommendations to incorporate NC-ECD in the UG and PG curricula. **Process:** Indian Academy of Pediatrics created a task force to review the UG/PG medical curricula, consisting of experts from pediatrics and medical education. The task force deliberated on 20 March, 2021 and identified the gaps in current curricula and provided suggestions to strengthen it. The recommendations of the task force are presented here. **Recommendations:** Taskforce identified that the UG/PG medical curricula are lacking training for propagating early childhood learning, responsive caregiving, caregiver support, and ensuring safety and security of children. The taskforce provided a list of competencies related to ECD that need to be included in both UG and PG curriculum. NC-ECD should also be included in topics for integrated teaching. Postgraduates also need to be exposed to hands-on-training at anganwadis, creches, and in domestic setting.

Keywords: *Competencies, Curriculum, Indian Medical Graduate, Postgraduate, Training.*

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Nurturing a child during the period of early childhood development (ECD) has an impact on future mental and physical health of the child. The World Health Organization (WHO) recommends promotion of five essential components viz., good health, adequate nutrition, promotion of early childhood learning, responsive care giving, and safety and security to achieve the optimal genetic potential of children into adulthood [1].

The Indian medical graduate (IMG) and pediatricians provide care before, during, and after birth, promote breastfeeding and good nutrition, monitor growth, and prevent and treat common childhood illnesses. Missing components of nurturing care most often are responsive caregiving, early learning, safety, security; and mental health of the caregivers. Updating the competency profile of the workforce and upgrading pre-service and in-service training are essential to create doctors that support nurturing care over the coming years, both for practice and mentor-ing and supervision to the paraprofessionals and frontline workers. Defining the competencies required for this aspect of care can make medical training more relevant [2].

In India, the Integrated Child Development Scheme (ICDS) and National Health Mission (NHM) are the major government initiatives that promote nurturing care for early childhood development [3,4]. The medical officers under the National Health Mission provide the healthcare benefits, oversee the administrative aspects of service delivery as well as oversee and coordinate the training of the healthcare workers. IMGs and pediatricians who join private sector provide health promotion and care for a large proportion of children needing domiciliary care in India, and hence can adopt interventions for nurturing care in their daily practice. It is thus crucial to train both the graduate students (undergraduates, UG) and the post-graduate (PG) trainees' in nurturing care for early childhood development (NC-ECD).

ECD in the Current UG Curriculum

The current competency based medical education (CBME) curriculum enlists competencies that the future IMG is expected to have achieved at the end of his/her training. Competencies addressing the subject of ECD are distri-buted across the subjects of pediatrics, community medicine and obstetrics and gynecology. Competencies of normal growth and development and factors affecting them, nutrition and related disorders, and immunization and national health programs are addressed in pediatrics. Those of normal pregnancy, antenatal care and lactation are addressed in obstetrics and gynecology, and competencies for nutrition, immunization and national health programs related to them are addressed in community medicine. The curriculum also has a suggestion for integration with basic sciences (anatomy, biochemistry, physiology) for the concepts of nutrition, immunization, embryology/brain development, pregnancy and lactation for each of the three subjects [5].

Though major concepts of early childhood development are addressed in more than 200 competencies on the topic, the IMG is not really being introduced to the term ECD and its concept. There is considerable overlap of competencies amongst various subjects and it is left to the discretion of the teachers to decide how to teach, integrated or otherwise. The NMC suggests integration for up to 20% of the curriculum and suggests a list of broad conditions like anemia, jaundice, diabetes etc. that may be taught in an integrated manner. As of now, ECD is not part of this list.

ECD in the Current PG Curriculum

The competency document for the post graduate pediatric course builds upon the competencies achieved in the undergraduate course. The current PG curriculum outlines the competencies in the cognitive, psychomotor, affective domains for pediatric training [6]. In the cognitive domain, the PG curriculum emphasizes on knowledge of the social, economic, biological and emotional determinants of child health. Besides, it also includes knowledge of normal and abnormal growth and development, nutrition, promotive-preventive care and rehabilitation and national health programs. In the psychomotor domain, PG training emphasizes on the skills of history taking, assessment of normal and abnormal growth and development, the ability to counsel regarding nutrition, breastfeeding and immunization. It also emphasizes on the need for a pediatric trainee to liaison with allied fields such as psychiatry and rehabilitation.

Like the UG curriculum, the PG curriculum also does not introduce the trainee to the concept of NC-ECD. Whereas it focuses on early detection and management of problems related to growth and development, it does not include concepts on nurturing normal growth and development. The current PG curriculum also does not prepare the future pediatrician to educate parents about responsive feeding practices, responsive parenting and early learning. While it includes detection and management of abuse, it does not cover the larger domain of child safety and security. Inter-departmental or inter-professional clinical exposure also does not get a mention in the PG curriculum.

OBJECTIVES

The taskforce was constituted to evaluate the existing UG/PG curricula for components related to early childhood development, assess gaps in the training essential to practice and promote ECD, and suggest recommendations to incorporate NC-ECD in the UG/PG curricula.

PROCESS

A task force was created by the Indian Academy of Pediatrics to review the UG/PG medical curricula and make recommendations on how the concepts and practice of NC-ECD can be incorporated in the current medical education. Experts from the fields of pediatrics and medical education were part of the task force. In a daylong meeting held on the 20 March, 2021, the members of the task force deliberated upon the gaps in the current UG/PG medical curricula and framed recommendations to strengthen this component.

RECOMMENDATIONS

The task force suggested a list of competencies related to ECD included in both UG and PG curriculum. NC-ECD should also be included in topics for integrated teaching. Emphasis needs to be on training for propagating early childhood learning, responsive caregiving, caregiver support, and ensuring safety and security of children. Postgraduates also need to be exposed to hands-on-training at anganwadis, creches, and in domiciliary settings.

Incorporating ECD in UG Curriculum

The task force observed that while NC-ECD related competencies are included in the current curriculum, certain crucial components are missing. **Table I** enlists the competencies needed to be included in the UG curriculum to address the five domains of NC-ECD. The task force also recommends that NC-ECD be included in the list of topics suggested for alignment and integration. It is also suggested that integration for the concepts of NC-ECD may be done using the correlation framework, and linker cases be used for the same. The task force advocated formation of sub teams at institutional level for developing modules for integration for case scenarios that include more than one department to cover different aspects of a competency.

Incorporating ECD in PG Curriculum

The task force observed that the current PG curriculum

Table I ECD-Related Competencies Needed to Be Included in Undergraduate Medical Curriculum

Knowledge	*Skills*	*Affective domain*
Nurturing good health		
• Normal growth, development monitoring • Immunization • Early signs of developmental delay • The concept of the 'mother and child health/protection card' for age appropriate development milestones tracking, positive parenting practices and early identification of warning signs. • Early detection of hearing and vision problems • Good quality preventive, promotive and curative care	• Assessment of normal growth parameters(anthropometry) • Use of growth charts	Counselling regarding general health care of infant and child
Nurturing adequate nutrition		
• Importance of breastfeeding • Age-appropriate diet and healthy food choices	• Growth monitoring and detection of growth faltering and malnutrition (WFA, HFA, Anemia)	• Counselling regarding breastfeeding promotion in antenatal clinics and community setting • Nutritional education for adolescents and women of reproductive age group • Nutritional education for infancy and early childhood
Nurturing early childhood learning opportunities		
• Introduction to the concept of age-appropriate play activities and use of age-appropriate toys to stimulate the brain		• Counselling about age appropriate activities (play and communication)
Nurturing responsive care giving		
• The concept of responsive care in early childhood • Caregiving practices to promote attachment and responsive care • Caregiving practices to promote positive behaviors • Factors affecting mental health of caregivers especially mothers		• Counselling to promote maternal mental health • Recognition of psychological and mental health problems in caregivers
Nurturing safety and security		
• Definitions of safety and security • Safe home environment-prevention of injuries, ingestion of harmful substances, exposure and drowning. Impact of environmental pollution.	• Recognition of signs of physical, emotional, sexual abuse and neglect • Arranging referral to child protection services for at risk and affected children and families	• Counselling about safe home environment, prevention of injuries, ingestions, exposure and drowning

does not train the future pediatricians about the holistic concept of ECD and NC-ECD. Specially the components of early childhood learning, responsive caregiving, caregiver support and nurturance, and safety and security, are not adequately covered. The task force recommends that the PG curriculum document, in addition to current components, must include the various components of NC-ECD under the various domains of postgraduate pediatric training, as listed in **Table II**.

The task force also recommends that the pediatric training should include an exposure to antenatal clinics and antenatal counselling, home visits and anganwadi center, and visits to crèches, social welfare to understand the implementation of national health programs; visits or posting at the District Early Intervention Centers (DEIC) and posting in psychiatry department for experience with caregiver anxiety and depression are also recommended.

Indian Academy of Pediatrics, in collaboration with National Neonatology Forum (NNF) and the Federation of

TABLE II ECD-Related Competencies Needed to be Included in Pediatric Postgraduate Curriculum

Knowledge	*Skills*	*Affective domain*
Nurturing good health		
• Clinical features, evaluation and management of language disorders in collaboration with allied specialists • Principles of developmentally supportive care • Basic principles of age appropriate developmental stimulation • Components of nurturing care • Critical periods of development • Recommendations for screen time and • physical activity • Referral pathways for children diagnosed with neurodevelopmental and/or behavioral disorders	• Developmental screening-milestones and assessment tools • Skills to provide developmentally supportive care, right from birth • Psychometry • Screening for hearing, vision and dental problems and neurodevelopmental disorders	• Communication skills to provide counselling and health education to patients, families and community
Nurturing adequate nutrition		
• Cultural beliefs and practices of breast feeding and complementary feeding • Age appropriate diet in health and illness • National health program • Principles and practice of IYCF • Feeding problems in children in general and in those with special needs and principles of its management • Antenatal breast care and preparation for lactation • Junk food and health food choices	• Positioning and handling infant during feeding	• Counselling of antenatal mothers regarding breast care, breastfeeding and age appropriate food choices, responsive feeding
Safety and security		
• Concepts of safety and security • Risk factors for child abuse and neglect • Identification and management of child abuse, maltreatment • POCSO Act • Timely referrals to concerned authorities/ departments • Principles of maintaining safe home and community environment • Importance of birth registration • Noninstitutional family care and early intervention for vulnerable children • Social and educational services for at-risk and affected children and families	• History and examination of suspected physical, emotional and sexual abuse in young children • Examination and provision of first aid to an injured child • How to arrange referral with social and educational services for at-risk and affected children and families	• Skills to coordinate with various departments including law • Counselling for injury prevention, safe home environment and use of a first aid kit
Nurturing responsive caregiving		
• Importance of responsive caregiving and responsive feeding • Common caregiving practices in the community • Caregiving routines for early childhood learning, social and emotional well being • Risk factors for disruption in responsive caregiving and management	• Identify at risk babies and families • Assess caregiver psychological and mental problems	• Counselling regarding responsive caregiving and feeing • Communication skills for advocacy
Nurturing early learning		
• Importance of stimulating home environment • Importance of non-formal education and continuity to primary school education • Age appropriate play and communication activities • Age appropriate books • Risk factors disrupting early learning		• Counselling regarding early learning opportunities

Obstetric and Gynaecological Societies of India (FOGSI); supported by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF), has committed to adopt all the components of the WHO/UNICEF Framework for Nurturing Care for Early Child Development (NC–ECD) in pediatric practice, as per Mumbai Call to Action [7]. This is in continuity and conformity with the IAP Consensus Statement on Early Childhood Development [8]. Action point 4a of Mumbai Call to Action calls for efforts to change perceptions and practices of medical students and allied professionals by pre-service capacity building by proposing modification in undergraduate and postgraduate training curriculum. The present recommendations mark a beginning in this direction.

The task force recommendations have kickstarted the process by outlining the topics to be included in pre-service education. A lot of work needs to be done such as defining the competencies for inclusion in the formal curriculum, converting competencies into learning objectives incorporating various levels of Miller pyramid, identifying teaching learning methods, and finally deciding the assessment tools. This will have to be conducted as a separate exercise. Guidelines also need to be prepared to integrate the ECD competencies with pre-clinical and para-clinical subjects.

The Way Forward

As of now, the recommendations of the task force need to be propagated and implemented at all levels in pre-service education. This would need a strong networking and advocacy, especially among the policymakers. It is heartening to note that NC-ECD is at the top of the global agenda of child health. Indian Academy of Pediatrics is committed to take all these steps as outlined above.

The need of the hour is to bring about a paradigm shift in our approach to pediatric practice that is focused on improving survival and decreasing morbidity, to 'Survive, Thrive and Transform' in alignment with the Global Strategy for Women's, Children's and Adolescents' Health, 2016-30 [9]. And this is doable only when we start early from inculcating these practices in the pre-service training years. Only then the health force can empower the parents for nurturing care to achieve the optimal develop-mental potential in their children.

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ANNEXURE

Members of the IAP-WHO Task Force

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Invited but could not attend: A Aggarwal, D Sareen, HB Mallikarjuna, JS Kaushik, M Kaur, OS Chaurasia, Sanjay KS, S Aneja, V Kalra.

Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets

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Justification: The emerging literature on prevalence of vitamin D deficiency in India, prevention and treatment strategies of rickets, and extra-skeletal benefits of vitamin D suggest the need for revising the existing guidelines for prevention and treatment of vitamin D deficiency in India. **Objectives:** To review the emerging literature on vitamin D prevalence and need for universal vitamin D supplementation. To suggest optimum vitamin D therapy for treatment of asymptomatic and symptomatic vitamin D deficiency, and rickets. To evaluate the extra-skeletal health benefits of vitamin D in children. **Process:** A National consultative committee was formed that comprised of clinicians, epidemiologists, endocrinologists, and nutritionists. The Committee conducted deliberations on different aspects of vitamin D deficiency and rickets through ten online meetings between March and September, 2021. A draft guideline was formulated, which was reviewed and approved by all Committee members. **Recommendations:** The group reiterates the serum 25-hydroxy vitamin D cutoffs proposed for vitamin D deficiency, insufficiency, and sufficiency as <12 ng/mL, 12-20 ng/mL and >20 ng/mL, respectively. Vitamin D toxicity is defined as serum 25OHD >100 ng/mL with hypercalcemia and/or hypercalciuria. Vitamin D supplementation in doses of 400 IU/day is recommended during infancy; however, the estimated average requirement in older children and adolescents (400-600 IU/day, respectively) should be met from diet and natural sources like sunlight. Rickets and vitamin D deficiency should be treated with oral cholecalciferol, preferably in a daily dosing schedule (2000 IU below 1 year of age and 3000 IU in older children) for 12 weeks. If compliance to daily dosing cannot be ensured, intermittent regimens may be prescribed for children above 6 months of age. Universal vitamin D supplementation is not recommended in childhood pneumonia, diarrhea, tuberculosis, HIV and non-infectious conditions like asthma, atopic dermatitis, and developmental disorders. Serum 25-hydroxy vitamin D level of >20 ng/mL should be maintained in children with conditions at high-risk for vitamin deficiency, like nephrotic syndrome, chronic liver disease, chronic renal failure, and intake of anticonvulsants or glucocorticoids.

Keywords: *Cholecalciferol, Infections, Recommendations, Sunlight, Vitamin D supplementation*.

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Vitamin D deficiency (VDD) has been reported as an emerging problem globally over the last decade. It remains a significant problem even in tropical countries, despite abundant sunlight [1]. The implications of VDD are believed by many to extend beyond skeletal manifestations to effects on infections, cancers, autoimmune diseases, and mental health conditions [2]. Global Consensus Guidelines for prevention and treatment of VDD and nutritional rickets in childhood were released in 2016 [3]. The Indian equinox with apparent abundant sun light in most parts of the country, darker skin color with high melanin content, different socio-cultural factors, and genetic variations [4], suggested the need for a guideline relevant to the Indian context; which were released by the Indian Academy of Pediatrics (IAP) in the year 2017 [5].

The Comprehensive National Nutrition Survey (CNNS), by the Ministry of Health and Family Welfare, Government of India involving about 35,000 children aged between 1 to 19 years from all over India, was conducted in 2016-18 [6]. Prevalence of vitamin D deficiency defined as serum 25OHD <12 ng/mL was found to be 14% among children aged 1-4 years, 18% among school age children (5-9 years) and 24% among adolescents (10-19 years) [6], which was below the proportions reported in hospital and community-based studies from India. Gender disparity was observed to be most wide in adolescents with 34% of girls having deficiency as against 14% of boys. Thus, a need was felt to revisit the earlier recommendations.

OBJECTIVES

The present guidelines re-examine the role of vitamin D supplementation during infancy and childhood in the light of population data on prevalence of vitamin D deficiency. The present guidelines also summarize the recommendations on sunlight exposure for Indian children, and the optimum dosage, schedule, and duration of vitamin D therapy, relevant as per Indian literature. The present guideline is proposed to be used by general practitioners, pediatricians, and epidemiologists working in child health.

PROCESS

A group of experts were invited under the IAP Action Plan in March, 2020, which consisted of faculty from medical colleges, pediatric practitioners, office bearers of Indian Academy of Pediatrics, and external experts with experience in nutritional epidemiology and clinical research. Six sub-committees were constituted to conduct detailed narrative reviews on the following topics: *i*) Vitamin D deficiency-problem assessment; *ii*) Preventive strategy- maternal and infant supplementation; *iii*) Preventive strategy- natural dietary and sunlight; *iv*) Treatment of VDD and rickets; *v*) Role of vitamin D in extra skeletal health – infections; and *vi*) Role of vitamin D in extra-skeletal health – non-infective conditions.

Data were gathered through semi-structured search strategy with respect to the study question of each respective section. The search was performed on Pub Med and MEDLINE electronic databases.

The initial draft recommendations were discussed with supporting evidence as prepared by the writing committee through emails. The recommendations were then deliberated upon during 10 successive online meetings (March to September, 2021). Delphi technique was used to arrive at a consensus after discussions which helped formulate the final recommendations. An external peer-review was invited by an International expert who provided critical inputs for revising the manuscript.

The level of evidence of each recommendation was graded from 1-5 as per the Oxford Centre for Evidence-Based Medicine (OCEBM) classification [7]. The draft guidelines were circulated for approval to all the members of the Committee for suggestions, if any and final approval.

RECOMMENDATIONS

The Global Consensus Guidelines and earlier IAP Guidelines have classified vitamin D deficiency, insufficiency, and sufficiency as serum 25-hydroxy vitamin D levels as <12 ng/mL, ≥12-20 ng/mL and >20 ng/mL, respectively [3]. The Group observed that there is a dearth of robust scientific evidence to conclude if these cut-off levels of serum 25(OH)D are valid, especially for skeletal outcomes. Most available Indian studies had used variable cutoffs of 5-20 ng/mL for defining low serum 25(OH)D levels and adverse clinical outcomes [8-35]. Studies have demonstrated an inverse relation between serum parathyroid hormone (PTH) and vitamin D levels, but have not agreed on the inflection point of 25(OH)D level at which PTH begins to rise [36,37]. Most studies were observational and measured only association, thus lacked data on causality, on false positives for adverse skeletal outcomes, inflection point for increase in PTH levels, and correlation of 25(OH)D levels with bone markers and bone histomor-phometry. Other confounders like inflammation and adiposity have not been accounted during estimation of burden of VDD in CNNS survey. The Group agreed that in the absence of valid serum 25(OH)D cutoffs, a level of <12 ng/mL may be endorsed as the definition of VDD in concurrence with the earlier guidelines [3,5] and as per the cut off used in the CNNS survey [6]. Serum 25 (OH)D >20 ng/mL is considered as desirable/sufficient to provide a buffer for periods of stress, exigency, and seasonal patterns.

The burden of vitamin D deficiency in India shows a marked variation in prevalence across different studies. The prevalence is confounded by factors like age, concomitant calcium deficiency, study setting (community or hospital), study participants (healthy or diseased), geographical location (as per latitude of the area), and sociocultural factors (dressing pattern, dietary intake) [6,32,33,35].

Vitamin D Toxicity

As the therapeutic indications of vitamin D supplementation increased over the last decade, the possibility of vitamin D intoxication remained an area of concern. The Group felt the need to define urinary excretion cutoffs in addition to serum 25(OH)D levels alone for definition of vitamin D intoxication. The serum 25(OH)D cutoff of >100 ng/mL with associated hypercalcemia and/or hypercalciuria defines vitamin D toxicity. Serum levels between

50-100 ng/mL are unusual without supplementation and should alert the physician to avoid further vitamin D supplementation.

Estimation of Vitamin D

Automated immunoassay is the most common method utilized by the laboratories world-over [38]. It is simple to use, requires low sample volume and is relatively inexpensive. The major drawback is that it utilizes polyclonal antibodies which in turn get affected by changes in body protein concentrations. Immunoassays; however, cannot differentiate between the two forms of vitamin D, notably 25(OH)D2 and 25(OH)D3. The concentration of 25(OH)D2 is relatively more in infants and so the estimation of 25(OH)D levels by immunoassay may not be a reliable method during infancy [39]. Another inherent specificity issue with assays utilizing antibodies is cross-reactivity with other vitamin D metabolites; most notably vitamin 24,25(OH)2D3 which constitutes about 10-15% of the total 25(OH)D concentration [40]. These shortcomings can be overcome by utilizing the liquid chromatographic methods either LC-UV or LC-MS/MS [41].

Consensus statements and recommendations

1.1 *Definition and diagnosis*: Classification of Vitamin D status in children should be based on serum 25(OH)D levels and defined as deficiency <12 ng/mL, insufficiency: 12-20 ng/mL, and sufficiency >20 ng/mL [LOE 2].

1.2 *Hypervitaminosis and vitamin D toxicity*: Diagnosis of vitamin D toxicity can be made in the presence of serum 25(OH)D levels >100 ng/mL with hypercalcemia and/or, hypercalciuria; levels between 50-100 ng/mL should be viewed with caution. Serum PTH levels will be suppressed in cases with vitamin D toxicity [LOE 3].

The normal upper limit for serum calcium: birth to 12 month: 11.3 mg/dL; 1 to 3 year: 11.1 mg/dL; and, 4 to 18 year: 10.7 mg/dL. The normal limits for urine spot calcium: creatinine ratios by age: Up to 6 month: < 0.8; 6-12 month: < 0.6; ≥ 24 month: <0.2. Alternatively, 24-hour urinary calcium excretion >4 mg/kg/day.

1.3 Prevalence of vitamin D deficiency

1.3.1 Population-based studies measuring serum 25(OH)D remain the best method of estimation of the burden of vitamin D deficiency [LOE 2].

1.3.2 The prevalence of vitamin D deficiency is variable across different parts of India based on geographic location, age group and sociocultural and demographic factors [LOE 2]. National representative data on VDD are not available for infants under 1 year of age. Hospital and community-based studies (using cut offs of 10-20 ng/mL) have reported vitamin D deficiency in infancy to range from 22-92 % [LOE 3]. Prevalence in older children and adolescents range between 14-24% as per CNNS data.

1.4 *Estimatin of vitamin D levels*

1.4.1 Serum 25(OH)D level should be estimated for all clinical purpose where assessment of vitamin D status is required [LOE 5].

1.4.2 Vitamin D levels are best measured with liquid chromatography coupled to ultraviolet (LC- UV) or tandem-mass spectrometry (LC-MS/MS) [LOE 2]. Where LC-UV/ LC-MS/MS are unavailable, automated immuno-assay may be used [LOE 2]

Vitamin D Supplementation for VDD Prevention

The Group noted that the cutoff for vitamin D deficiency in pregnant women at less than 20 ng/mL is higher than that for children (<12 ng/mL) in view of physiological role of vitamin D in fertility and conception [42]; however, there is not enough evidence for 20 ng/mL to be used as a cutoff for the same. The pooled prevalence of low vitamin D levels (≤20 ng/mL) in pregnant women from India was reported as >30%, which seemed as a major public health concern [43]. However, the higher cutoff of defining VDD in pregnancy appears to be the reason for high prevalence.

The World Health Organization (WHO) has provided guidelines on the role of dietary interventions for improving pregnancy outcomes, which did not recommend routine vitamin D supplementation in pregnancy [44,45]. WHO also recommends that the required vitamin D needs should be met by sunlight exposure and dietary intake; the amount of time needed in the sun is; however, not known and depends on many variables [44]. An adequate dietary calcium intake should be encouraged during pregnancy. Calcium should be supplemented in dose of 1200 mg daily in all pregnant and lactating women [46] or in higher doses of 1.5 to 2 grams to improve outcomes for pre-eclampsia in those with low dietary intake [42,47].

The ethical dilemma of stigmatization during pregnancy with nutritional deficiency, unnecessary diagnostic testing and public health concerns like cost-effectiveness and equitable distribution; *vis-à-vis* significant clinical benefits of universal antenatal vitamin D supplementation need to be further explored.

The impact of vitamin D supplementation on other neonatal outcomes was investigated in another systematic review of studies from developing countries. A significant association of maternal VDD (≤20 ng/mL) was seen with low birth weight (LBW), small for gestational age and preterm birth (1 study). There was no association on NICU admission, head circumference or neonatal deaths/

stillbirth (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22) [48]. Similar conclusions were observed in other systematic reviews [49,50]. As per a recent Cochrane review, maternal vitamin D supplementation showed a reduction in incidence of LBW without any effect on preterm birth, whereas the combination of vitamin D and calcium, though reduced the risk of LBW but showed an increased risk for preterm birth [51].Similar positive effect of maternal vitamin D supplementation on birth length and birth weight without any reduction in incidence of SGA and preterm births was observed in another meta-analysis [52]. The recent WHO recommendations for nutritional interventions in pregnancy (2020) concluded little or no effect of vitamin D versus placebo on risk of preterm birth (eight trials, 2938 women; RR: 0.78, 95% CI: 0.48 to 1.27), little or no difference on risk of still birth (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22), unclear benefit on low birth weight and neonatal mortality. The administration of calcium with vitamin D or no vitamin D and calcium also did not conclude any significant effect on LBW, neonatal mortality and preterm birth [45].

The available data on prevalence of VDD in infancy mandating routine vitamin D supplementation were reviewed. As mentioned in section 1, the burden of deficiency was highly variable across different studies, with limited literature on impact of routine vitamin D supplementation. However, among different age-groups, infants were considered at higher propensity for VDD as breast milk is a poor source of vitamin D and options of complementary feeding are usually not fortified or rich in vitamin D [53]. The national vitamin D supplementation program providing 400 IU daily to children between 0-3 years showed a decline in prevalence of nutritional rickets in Turkey [54]. A dose of 400 IU daily was found beneficial to achieve serum 25(OH)D levels >20 ng/mL and for prevention of rickets in infants [55-58]. The administration of doses higher than 400 IU did not achieve any significant benefits in bone mineral content or bone markers, and a risk of hypervitaminosis was observed with doses of 1600 IU per day [57,58]. A few randomized controlled trials have shown inferior effect of dose of 400 IU than 800 IU in prevention of VDD in preterm babies [59-63].

Vitamin D supplementation in under-five age group of children was associated with mild improvement in linear growth [mean difference 0.66, 95% CI (-0.37 to 1.68); 3 studies, 240 participants], without any significant effect on length/ height *z*-scores [64]. Adolescence appears a vulnerable age for manifesting the effects of vitamin D and calcium deficiency as it is the period of maximum bone mass accrual. The prevalence of VDD was higher in adolescents (girls>boys) than other age-groups in the recent CNNS survey [6]. The Committee opined that the estimated average requirements (EAR) of vitamin D and calcium during adolescence should be met with sunshine and dietary intake without the need of universal vitamin D supplementation (see later). This further refutes the need to screen apparently healthy children for vitamin D deficiency.

A few children may remain at high-risk with their underlying disease states where routine requirements of vitamin D may not be met by natural sources. Such children should receive pharmacological supplementation (minimum 400 IU daily) for prevention of VDD. Routine supplementation with vitamin D was therefore considered as an effective strategy for prevention of vitamin D deficiency in infants and high-risk children.

Consensus statements and recommendations

2.1 *Maternal supplementation*

2.1.1. Maternal vitamin D status has no bearing on anthropometry outcomes and bone density of the offspring in infancy but may be associated with maternal and neonatal biochemical vitamin D deficiency and neonatal hypocalcemia if the deficiency is severe (LOE 1).

2.1.2 Maternal vitamin D supplementation may improve biochemical vitamin D deficiency in neonates and hypocalcemia in infancy, without any conclusive benefit for other fetal and neonatal outcomes, including neonatal infections, small for gestational age, preterm birth, congenital anomalies, large for gestational age, and fetal/ neonatal mortality (LOE 1).

2.1.3 Universal vitamin D supplementation is not recommended during pregnancy (LOE1).

2.1.4 Routine calcium supplementation should be ensured during pregnancy for optimizing maternal and neonatal health outcomes including skeletal health [LOE 1].

2.2 *Infant and childhood supplementation*

2.2.1We recommend routine vitamin D supplementation in infancy (0-1 years of age) in doses of 400 IU/day. Doses above 400 IU do not offer any additional skeletal benefit during childhood. Higher doses such as 1600 IU daily or above can result in toxicity (LOE2).

2.2.2 A dose of 400 IU/day is safe in preterm babies. Doses of 800 IU/day can achieve desired biochemical levels faster, but the level of evidence and safety data are not enough to make a separate dosing recommendation for preterm babies [LOE 3].

2.2.3 Routine vitamin D supplementation is not recommended during childhood and adolescence. Estimated average requirement (EAR) of vitamin D (400-600 IU/day) should be met from sunlight and dietary sources to prevent VDD in these age-groups.

2.2.4 We recommend routine vitamin D supplementation (minimum 400 IU daily) in children with underlying high-risk conditions (**Box I**). Routine screening of apparently healthy children for vitamin D deficiency is not recommended [LOE 5]. Asymptomatic children should be screened only if they are at risk for vitamin D deficiency (e.g., children receiving long term anticonvulsants or glucocorticoids; chronic kidney disease, malabsorption states, children with disabilities, chronic inflammatory diseases, etc) [LOE 5].

Sunlight and Diet for VDD Prevention

The primary source of vitamin D is endogenous conversion of 7-dehydrocholesterol into previtamin D3 with the help of ultraviolet-B rays (UV-B) of sunlight (wavelength: 290-315nm), which further undergoes isomerization into vitamin D3 (cholecalciferol) by sunlight. This conversion is linear in first 30 min after which there is a non-linear rate of conversion which peaks within 8 hours and is responsible for conversion of 80% of previtamin D3 into cholecalciferol [65]. However, usually only 10-15% of 7-dehydrocholesterol in the skin converts into previtamin D3. Cholecalciferol is converted to active vitamin D3 after successive hydroxylations occurring in liver and kidney, respectively. The previtamin D3 and cholecalciferol later get converted into inert metabolites like lumisterol and tachysterol with a ceiling effect after prolonged duration of sunlight exposure, which prevents development of vitamin D toxicity [66]. The increments in serum 25(OH)D are achieved with every increase in UV irradiance till peak of 55 nmol/L (22 ng/mL) after which the levels get saturated, possibly by the photoisomerization of previtamin D [66,67]. The rise in vitamin D production is higher in those with low baseline serum 25(OH)D levels, and plateaus with constant UVB dosing.

The amount of cutaneous biosynthesis of vitamin D depends on both host and environmental factors. Among the environmental factors, latitude, pollution, cloud cover and intensity of UV irradiance influence vitamin D production [65,68-70]. The UV irradiance should be received directly by skin and not filtered through surfaces like glass in window panes which can itself absorb UVR. The host factors which determine vitamin D synthesis are age, skin melanin content, single nucleotide polymorphisms in melanin gene, body surface area exposed (clothing), lifestyle and use of sun-barrier measures including topical creams and sunscreens [69,71]. Fitzpatrick skin type is used to classify skin types from I to VI based on their melanin content, where I is the lightest. Indian skin types have higher melanin content than Caucasians and are usually classified as IV or V [72].

Box I High-Risk Conditions Requiring Routine Vitamin D Supplementation in Children

- Non-ambulatory states like cerebral palsy, neuromuscular disorders
- Chronic kidney disease
- Chronic liver disease
- Malabsorption syndromes
- Long-term use of glucocorticoids, antiepileptic drugs, ketoconazole
- Endocrine disorders like hyperparathyroidism
- Disorders with extensive cutaneous involvement

VDD remains a significant public health concern even in tropical countries [73]. Studies have found a positive correlation between sunlight exposure and vitamin D production in skin, both from temperate countries as well as India [25,74]. Age is an important host factor which affects this association as the amount of 7-dehyro-cholesterol is constant till old age when it begins to decline [75]. The body surface area (BSA) is also greater for similar exposed body parts in infants and younger children than adolescents or adults. Therefore, young adults demonstrate higher vitamin D levels than older subjects after exposure to the same amount of solar radiation [76]. A rough estimation of BSA for children approximates face, forearms, hands, lower legs and feet to 7-10%, 8%, 4%, 8-12% and 8% BSA, respectively making a cumulative score of approximately 40% in young children (<5 year). The same area in an adolescent or adult would be approximately 30% [77,78].

Sunlight doses have been measured as 'minimal erythema dose (MED)' which is defined as dose of UVR required to produce barely perceptible erythema. UV-B MED in skin type IV and V varies from 40-60 to 60-90 mJ/cm^2 (= 400-600 J/m2) which is almost three times the lighter skin type (type I and II) [72]. However, as MED would vary significantly with skin pigmentation, a unit of standard erythemal dose (SED) is commonly used. It is the erythemally weighted radiant UVR equivalent to 100 J/m^2 solar UV index. SED does not rely on erythema and is independent of skin type. One SED is equal to 0.5 times the MED for type I skin [66]. Doses equivalent to MED induce skin damage and may be harmful, instead sub-erythemal doses have shown to be more effective in cutaneous vitamin D production [66]. Also, frequent small UVB dosing were found more efficacious in increasing serum 25(OH)D levels than single large exposures. This could be explored as a feasible option in Indian settings to utilize natural sunlight exposure.

Studies conducted in different ethnic and geographical locations suggest variable duration of sunlight exposure to achieve sufficient serum 25(OH)D levels. The increase in serum 25(OH)D is higher in summer than winter months

[16,31,79-82].A review suggested 30-45 min of daily sunlight exposure over 12-18% of BSA as sufficient to maintain vitamin D levels in the Indian population [83]. Data available from few other Indian studies in infants, children and adults have been extrapolated to suggest an optimal duration of sunlight exposure, though the rise in serum 25(OH)D may be unpredictable with the underlying host and environmental factors [28,84-86]. This guideline does not endorse artificial UV sources for vitamin D production in children. At present safety data for skin cancers with sunlight exposure in Indian children is unknown [87,88].

Systematic reviews based on adult studies have also shown that serum vitamin D level increases after both, sunlight and vitamin D supplementation; however, the rise is higher and more predictable with vitamin D supplementation than sunlight [89-92]. The rise in serum 25(OH)D was less after long-term sunlight exposure and artificial UVB source than natural sunlight [89]. Compliance to supplementation and sunlight remains a major confounder in estimating the efficacy in natural settings.

Among the dietary sources, vitamin D3 (cholecalciferol) is mainly obtained from animal source like fish, liver, cod liver oil and eggs while vitamin D2 (ergocalciferol) is found in plants, especially mushrooms [93]. The content of vitamin D in Indian foodstuffs can be approximately estimated according to the Indian food composition tables (IFCT), 2017 [94]. There is minimal amount of natural vitamin D in milk (5-40 IU/L) and milk products like cheese and butter (30 IU/100g), which contribute minimally to the RDA [95]. The consumption of skimmed or low-fat milk with reduced fat content of 0.1% and 1% further reduces the amount of vitamin D. Unfortified whole milk, toned milk and full cream milk have higher fat content (>3%) with vitamin D levels between 0.2 –0.6 µg/L (8-24 IU/L) [96]. Egg yolk contains variable amount of vitamin D (27-40 IU/egg) and may not be a rich source of the vitamin. Cooking of animal products like boiling eggs, pasteurization of milk, baking and heating meat does not cause significant vitamin D loss. Among fishes, fatty fish like salmon, tuna, mackerel have higher vitamin D content with maximum content in fish liver (1200 µg/kg) than non-fatty fish [96].

Data from CNNS report showed that most (54-56%) children in India consumed vegetarian diets without eggs with higher prevalence of vitamin D deficiency in vegetarians than non-vegetarians [6]. Among the non-vegetarian sources, oily fish, or cod liver oil are unlikely to meet the RDA of vitamin D in amounts likely consumed by children. Data from other developed countries showed low median intake of vitamin D at less than 10 µg/day (400 IU/day) in children and adults [97-101].

Both, vitamin D and calcium intake are crucial for optimal bone health. In the absence of calcium, bone mineralization may remain poor even with replete vitamin D intakes. The major sources for calcium intake in Indian diets are dairy, coarse cereals like ragi, whole legumes like chickpea and green vegetables [13,102]. The nutritional trend in India by National Nutrition Monitoring Bureau (NNMB) from 1975 to 2017 showed that only 37% households in India had daily consumption of >70% RDA of calcium with 44% households having <50% RDA consumption [103]. Likewise, guidelines for Indian children recommend increase in RDA of calcium to 500 mg/day in infancy, 600 mg/day in 1-9 yr old and 800 mg/day in adolescents [46]. However, the dietary insufficiency was substantially overestimated in these publications because: *i*) NNMB primarily sampled the underprivileged, resulting in a bias for national projections; and *ii*) the estimates used the dated Nutritional Requirements for Indians with the Recommended Dietary Allowance (RDA) metric for comparison, which is intended to meet the requirements of 97.5% of the individuals. The updated Nutritional Requirements for Indians, recently published by the Indian Council of Medical Research, use the appropriate metric for comparison, namely the Estimated Average Requirements (EAR), reflecting the average intakes of the populations (needs of half of the population), which are substantially lower than the RDA. The EAR was calculated to meet serum 25(OH)D levels of 40 nmol/L (midpoint between 30-50 nmol/L). The Writing Committee did not have access to the NNMB raw data to provide dietary estimates. Statistical analysis reported an EAR of approximately 400 IU/day in children and 600 IU/day in adolescents (as obtained from natural resources) as sufficient to meet the desired serum vitamin D level [104]. Similar data were not sufficiently available for infancy, suggesting continuing with a recommendation of 400 IU/day as EAR (*details in section 2*).

Consensus statements and recommendations

3.1 *Sunlight*

3.1.1 Sunlight exposure increases serum 25(OH)D levels and is recommended for children and adolescents across all regions of India to prevent vitamin D deficiency (serum 25(OH) D <12 ng/mL) (LOE 2).

3.1.2 A daily sunlight exposure of 17-30 min in infants and 30-45 min in older children over 15-40% body surface area is recommended at least five times a week during noon (11AM-3PM) for preventing vitamin D deficiency across different regions and seasons (LOE 3.)

3.1.3 Daily application of sunscreens decreases serum vitamin D levels and are not recommended for routine use in children (LOE 3)

3.1.4 The rise in serum 25(OH)D is marginally higher with

vitamin D supplementation than sunlight in adults (LOE 1). Evidence is not enough to recommend superiority or inferiority of vitamin D supplementation over sunlight exposure in preventing vitamin D deficiency in children (LOE5)

3.1.5 The risk of skin cancers with prolonged sunlight exposure in Indian pediatric population is unknown (LOE 3)

3.2 *Diet*

3.2.1 An adequate intake of calcium should be ensured during childhood to meet the dietary requirements. The calcium demand can be met from both dairy and non-dairy (cereal, vegetables etc.) sources (LOE 5).

3.2.2 Foods rich in vitamin D may not contribute sufficiently to meet the vitamin D requirements; however, their intake should be encouraged for consumption as part of a balanced diet within the usual dietary practices (vegetarian or non-vegetarian) (LOE 5).

Treatment of Rickets and VDD

Symptoms of vitamin D deficiency in children include nutritional rickets, hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy, bony deformities and osteomalacia [3]. There is evidence that all children with nutritional rickets be treated for vitamin D deficiency, irrespective of serum 25(OH)D levels, since they are at increased risk of deformities, muscle weakness and fractures [3,105].

Asymptomatic individuals may be screened if they are at risk for vitamin D deficiency (e.g., children receiving long term anticonvulsants or glucocorticoids; chronic kidney disease, malabsorption states, children with disabilities, chronic inflammatory diseases, etc) [42]. Currently, there is not enough evidence to recommend screening for vitamin D deficiency in healthy population and asymptomatic individuals who are not at risk [106]. The treatment of isolated biochemical derangements in serum vitamin D levels (that do not correlate clinically) is unclear. However, incidentally detected serum 25(OH)D level of less than 12 ng/mL in healthy children should be treated to prevent development of clinical features related to vitamin D deficiency. There is also evidence that children with symptomatic vitamin D deficiency (serum 25(OH)D $\leq$ 20 ng/mL) without rickets, but with clinical features e.g., hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy, should be treated as for vitamin D deficiency [42].

Both, daily as well as intermittent regimes are efficacious in the management of nutritional rickets [107-115]. Daily doses are more physiological than bolus doses. Lower doses of vitamin D (up to 2000 IU/day) have been shown to heal rickets in infancy [107,108,116]. However, there is not enough evidence to suggest that intermittent bolus doses of vitamin D are safe in infancy and childhood [110,111]. In some situations, therapy with large cumulative doses spread over a few weeks or months may be more feasible if it is felt that there might be issues with compliance with daily vitamin D therapy. Thus, although daily regimens are preferred, vitamin D dose recommendations for both treatment options, daily as well as bolus regimens is a practical and feasible approach [3]. Bolus doses may be administered at interval of 2-4 weeks comparable to the equivalent daily dose to decrease the risk of hypervitaminosis.

Based on the available evidence [3,107-115], we recommend daily treatment as the first line of management. The issue of safety of bolus regimens in doses equivalent to those used in daily regimes need to be established in well-powered randomized controlled trials in the future, especially in infants.

Oral treatment is the preferred form of vitamin D administration, which more rapidly restores serum 25(OH)D levels than intramuscular (IM) treatment [117,118]. Parenteral administration of mega doses of vitamin D (> 300,000 IU) is not recommended. When single large doses are used, vitamin D3 appears to be preferable compared to D2 because the former has a longer half-life [119]. Vitamin D3 is reported to be better than vitamin D2 to raise serum 25(OH)D levels (mean difference 15.69, 95%CI: 9.46 to 21.93 nmol/L) with average dose per day being a significant predictor, irrespective of the participant demographics, baseline vitamin D levels, total dose, and vehicle of supplementation [120].

Vitamin D oral doses are packaged in India in maximum of 60,000 IU per unit, unlike other developed countries which package as 50,000 IU per unit. Studies have shown comparable efficacy of lower doses of vitamin D, suggesting a feasible dosing regimen of five doses of 60,000 IU for cumulative 300,000 IU. There are no randomized controlled trials on the optimal duration of daily treatment for nutritional rickets in children. Most studies and expert opinion, recommend optimal healing in nutritional rickets after 12 weeks of daily therapy [107,108, 121-125].

Healthcare providers should be aware of the various vitamin D preparations available in India and counsel patients regarding both desirable doses and variability among formulations. Most preparations available in the Indian market contain vitamin D3 [126]. Unsupervised intake of alfacalcidiol and calcitriol, which are not recommended for vitamin D deficiency and nutritional rickets, could result in adverse effects including toxicity. Calcitriol has been used in children with hypocalcemic

seizures, along with intravenous calcium gluconate administration in initial treatment to augment clinical improvement.

Oral calcium supplementation (dose 50-75 mg per kg per day to maximum of 500 mg) should be routinely prescribed in combination with vitamin D while treating vitamin D deficiency [121,127,128]. Oral calcium is supplemented frequently as calcium carbonate in children. Preparations with calcium phosphate should be used in younger children and infants who have low phosphate levels to prevent phosphate sequestration with calcium carbonate.

Monitoring during therapy

There is insufficient literature to guide the frequency of testing in children receiving vitamin D therapy. There are no randomized trials specifically regarding this issue. In this situation, one may infer that to assess response to therapy as well as to detect toxicity, serum calcium, phosphate, alkaline phosphatase, serum 25 (OH)D levels should be performed at 12 weeks after vitamin D therapy [110,111,114]. Some children may require longer treatment duration for normalization of alkaline phosphatase [129].

We suggest that in a child with rickets, radiographs should be performed at 4 weeks and 12 weeks after vitamin D therapy to look for evidence of healing. The earliest sign of healing would be evident on a radiograph by 4 weeks, an absence of radiological line of healing should alert towards an underlying non-nutritional cause of rickets. If complete radiological healing and normalization of biochemical parameters is not attained in rickets by 12 weeks, therapeutic doses of vitamin D and calcium should be continued. At the same time, the child should be assessed for refractory rickets as per flowchart shown in **Fig. 1**. Maintenance dose of vitamin D should be started once complete healing has been achieved. Urine calcium: creatinine ratio and renal ultrasonogram should be done when there is hypercalcemia or hypervitaminosis D.

Recommendations

4.1 Indications for treatment (**Fig. 1**)

4.1.1 Children with nutritional rickets should be treated for vitamin D deficiency and monitored for therapeutic response (LOE 2) (**Fig. 1** and **Table I**).

4.1.2 Children with clinical pointers towards non-nutritional rickets, should undergo evaluation for etiology of rickets including assessment of serum 25(OH)D levels and parathyroid hormone (**Fig. 1**) (LOE 5).

4.1.3 Children with other symptoms attributable to vitamin D deficiency (e.g., hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy) AND having serum 25(OH)D level $\leq$ 20 ng/mL should also be treated for vitamin D deficiency (LOE 2).

4.1.4 Incidentally detected low serum 25(OH)D level < 12 ng/mL in healthy children or $\leq$20 ng/mL in those at high-risk should be treated (LOE 5), as per protocol for nutritional rickets.

4.2 *Dose, regimes, and duration of vitamin D therapy*

4.2.1 We recommend daily treatment as the first line of management (LOE 2). The safety of intermittent bolus doses of vitamin D is not established, especially in infancy. The issue of safety of regimens involving administration of bolus intermittent doses need to be established in well-powered randomized controlled trials in the future, especially for infants (LOE 5).

4.2.2 Vitamin D (2000 IU/day) is recommended for treatment of nutritional rickets and symptomatic vitamin D deficiency in infants, 3000 IU/day or its equivalent in weekly/monthly bolus doses may be given in children older than 1 year (LOE 2) (**Table I**).

4.2.3 We recommend that the above therapy be given for a minimum of 12 weeks (LOE 2). Some children may require a longer treatment duration for normalization of alkaline phosphatase and serum 25(OH)D levels (LOE5)

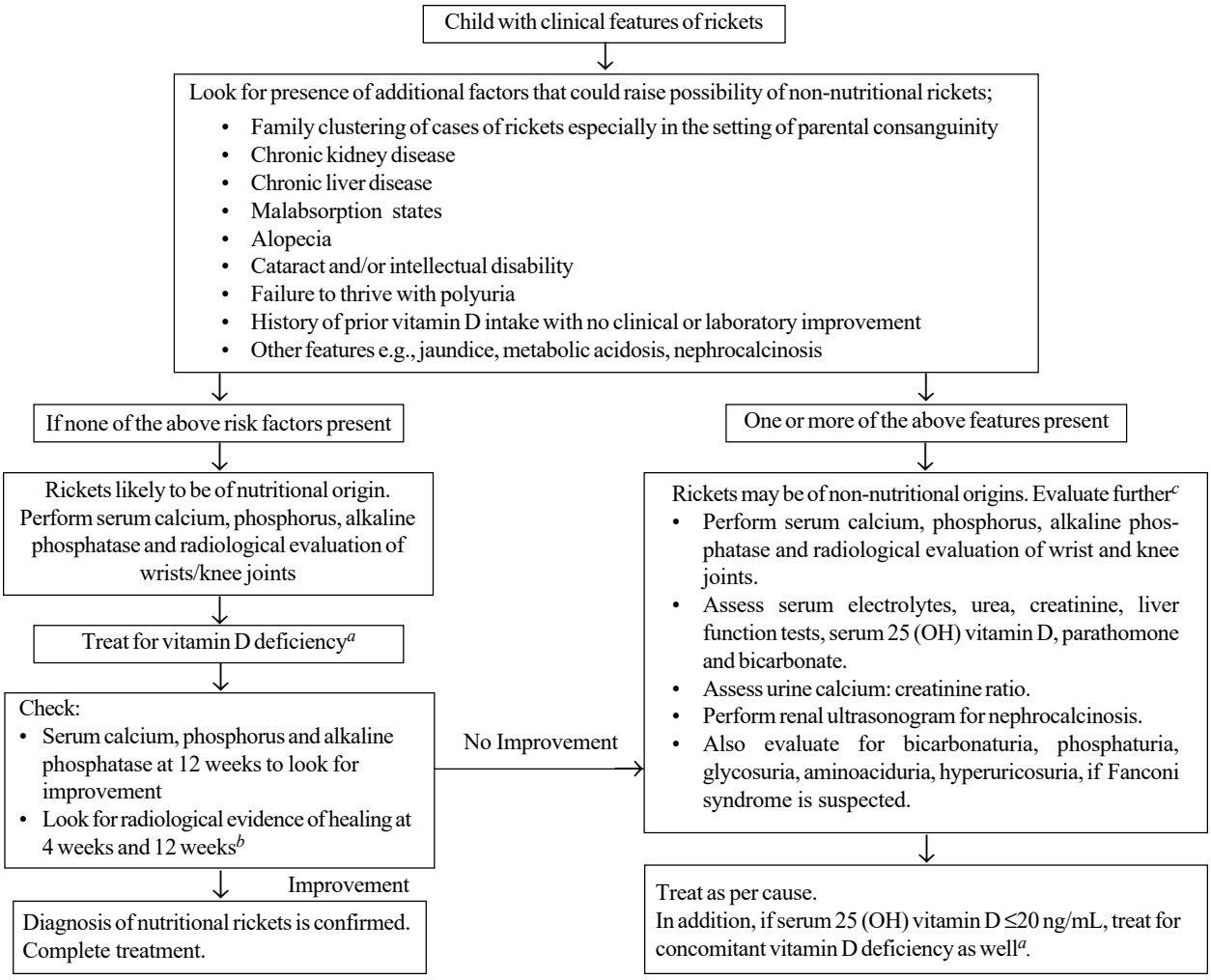
4.2.4 There is paucity of information regarding the role of lower dose of vitamin D (less than 2000 IU/day) for treatment of rickets (LOE 3)

4.2.5 Calcium intake of 50-75 mg/kg/day (not exceeding 500 mg/day) must be ensured either through diet or supplementation in combination with vitamin D (LOE 1).

Table I Doses for Management of Vitamin D Deficiency or Nutritional Rickets in Children

Age	*Daily dose for 12 wk*[a]	*Alternative intermittent dose regimen*[b]	*Maintenance dose (daily)*[c]
<6 mo	2000	NA	400
6-12 mo	2000	Equivalent of 2000 IU/day may be given on a monthly or weekly basis	400
>12 mo	3000	60000 IU fortnightly (after every 2 weeks) x 5 doses	600

[a]Reassess response after 12 weeks. Ensure daily calcium intake of 50-75 mg/kg/day, not exceeding 500 mg/day. [b]In certain situations, if compliance is not good, intermittent regimens may be prescribed (in children above 6 months of age only). [c]Ensure daily intake of recommended dose through supplementation or dietary sources. Optimum duration of maintenance vitamin D therapy is not known at present



[a]Treatment of vitamin D deficiency includes calcium supplements along with vitamin D. [b]Monitoring of therapy is discussed in section 4.1. [c]Other investigations as clinically indicated.

Fig. 1 Algorithim for evaluation of rickets.

4.3 *Different formulations of vitamin D*

4.3.1 Oral treatment with vitamin D is recommended, which more rapidly restores serum 25(OH)D levels and is safer than intramuscular (IM) treatment (LOE 1). We suggest that intramuscular route is to be used only when absorption of oral dose is doubtful e.g., in malabsorption states (LOE 5)

4.3.2 When intermittent bolus doses are used, vitamin D3 is more efficacious than vitamin D2 in improving vitamin D status. For daily treatment, vitamin D3 is only marginally better than vitamin D2 in improving vitamin D status (LOE 1).

4.3.3 Healthcare providers should be aware of the various vitamin D preparations available in India and counsel patients regarding both desirable doses and variability among formulations (LOE 5).

4.3.4 Alfa-calcidiol (1-hydroxycholecalciferol) and calcitriol are not recommended for management of nutritional rickets and vitamin D deficiency (LOE 5).

4.4 *Monitoring during treatment with vitamin D for nutritional rickets*

4.4.1 Radiographs should be obtained at 4 weeks and 12 weeks after vitamin D therapy in rickets to look for evidence of healing (LOE 3).

4.4.2 Serum calcium, phosphate, alkaline phosphatase, serum 25 (OH)D levels should be performed at 12 weeks after vitamin D therapy to measure response and toxicity (LOE 3).

4.4.3 If complete radiological healing and normalization of biochemical parameters (serum 25(OH)D >20-50 ng/mL) is not attained in rickets by 12 weeks, therapeutic doses of vitamin D and calcium should be continued. Maintenance dose of vitamin D should be started once complete healing has been achieved (LOE 5).

4.4.4 Urine calcium:creatinine ratio and renal ultrasonogram should be done when there is hypercalcemia or hypervitaminosis D (as mentioned in section 1) (LOE 5).

Extra-skeletal Health – Infections

5.1 *Vitamin D and pneumonia*

There is mounting evidence that vitamin D has an immune-modulating effect and helps in intensifying innate immunity [130]. Many observational studies and systematic reviews have suggested an association between vitamin D deficiency and acute lower respiratory tract infection (ALRTI); however, the same biological effect of vitamin D has not been well documented by experimental studies and systematic reviews of RCTs [131-137].

5.2 *Vitamin D and tuberculosis*

Growing evidence suggests the immunomodulatory effect of vitamin D in tuberculosis (TB). The exact mechanism of action of vitamin D as an immune regulator is not fully understood [138]. The possible mechanism through which vitamin D helps in preventing *Mycobacterium tuberculosis* (MTB) infection is through the binding of the active form of vitamin D (1,25[OH]2D3) to VDR. There are many observational studies on the association of vitamin D deficiency and TB in adults, with limited literature in children. A meta-analysis of five clinical trials in which one study addressed the pediatric population, found no evidence of a beneficial effect of vitamin D in the treatment of TB [139]. A systematic review and meta-analysis of eight clinical trials with 1787 patients with active pulmonary TB reported that vitamin D has beneficial effects in improving sputum smear and culture conversion. However, the authors did not present results for the subgroup of children [140].

5.3 *Vitamin D and HIV infection*

Vitamin D deficiency in HIV leads to decreased innate and adaptive immune response, increase inflammation, and increases the susceptibility of infection due to alteration of monocyte and T cell function [141]. Observational studies in adults and children have reported a low level of vitamin D in HIV-infected children [142-144]. A systematic review, which included thirty studies out of which two were undertaken in children, concluded significant hetero-geneity in included studies and the need for further controlled studies to establish a relationship between vitamin D and HIV infection [145]. There is a paucity of literature on the therapeutic effect of vitamin D on HIV infection in children [146,147].

5.4 *Vitamin D and diarrhea*

Early studies in infants and children have shown lower levels of vitamin D in children hospitalized with diarrhea than healthy controls, suggesting the role of vitamin D in childhood diarrhea. Lower levels of serum 25 (OH)D were also associated with higher risk of diarrhea with bacteria producing enterotoxins (ETEC) unlike those which had invasive or cytotoxic properties [148]. Most observational and interventional studies have shown association of vitamin D status with number of episodes and severity of diarrhea. However, no causality with VDD or therapeutic efficacy of vitamin D could be established in acute diarrhea in normal-weight or underweight children [26, 31, 149-151]. A recent meta-analysis [135] did not show benefit of vitamin D supplementation in childhood diarrhea with data from two trials.

Consensus statements and recommendations

5.1.1 Vitamin D levels are lower in children with pneumonia, and a lower level of vitamin D may be associated with higher incidence and severity of pneumonia (LOE 1).

5.1.2 There is no beneficial role of routine vitamin D supplementation in the treatment of pneumonia in children (LOE 1).

5.2 Vitamin D levels are significantly lower in children with tuberculosis (LOE 1). There is no advantage of routine vitamin D supplementation in childhood tuberculosis (LOE 1).

5.3 An association has been demonstrated between vitamin D deficiency and HIV infection in children (LOE 3). The therapeutic effect of vitamin D supplementation in pediatric HIV is not established. (LOE 2)

5.4.1 Vitamin D levels show poor correlation with incidence and severity of acute diarrhea (LOE2)

5.4.2 Vitamin D supplementation is not beneficial in acute childhood diarrhea (LOE 1)

Extra-Skeletal Health–Non-Infectious Conditions

Vitamin D and asthma: Numerous observational studies had suggested that a low level of vitamin D is associated with an increased risk of asthma in children [152-154]. A systematic review and meta-analysis of twenty-seven studies, out of which eighteen studies included children, indicated a positive correlation of vitamin D and lung functions in both adults and children with asthma [155]. Although epidemiological studies showed a low level of

vitamin D in children with asthma, several meta-analyses on vitamin D supple-mentation in asthma in children reveal conflicting or limited evidence for protection against exacerbations [156-159].

Vitamin D and obesity: Various hypotheses have been proposed to explain possible link of vitamin D level with obesity and metabolic syndrome. Most reviews indicate marginal and insignificant effect, if at all, on few parameters like abdominal obesity, arterial stiffness, and insulin secretion [160-164]. Systematic reviews of intervention studies with vitamin D supplementation in obese adolescents have failed to demonstrate any utility over insulin action [165-167].

Vitamin D, atopy, and skin conditions: Vitamin D shows effects on keratinocyte proliferation and differentiation, suppression of inflammatory responses, expression of antibacterial peptides, maintenance of integrity of the permeability barrier, production of cathelicidin and suppression of IgE mediated cutaneous reactions [168]. Incidence of AD was higher among specific vitamin D receptor polymorphism type [169]. However, reasonable number of studies either refuting any such association or even indicating reverse association make it difficult to draw clear conclusions. [170-173].

Vitamin D and nephrotic syndrome: Vitamin D deficiency has been established at different types and stages of various form of nephrotic syndromes, further compounded by the ongoing disturbances in the biochemical *milieu* where there is a loss of vitamin D binding globulin with proteinuria. Patients also exhibit osteoblast suppression and osteoclast induction which further compromise the bone health in these patients. Metabolic bone health may be further compromised with the frequent use of high dose corticosteroids [174-175]. Supplementation of vitamin D is indicated primarily for restoration of the bone health in these patients, which is documented in various studies as improvement in biochemical and radiological parameters of bone health [176,177] and is recommended by international and national guidelines [178,179].

Vitamin D and childhood developmental disorders: Maternal vitamin D level and supplementation may affect the fetal brain development as well as the neurodevelop-mental outcomes of the offspring [180]. The neuro-protective effect of vitamin D is believed to be secondary to its influences on neuronal calcium homeostasis, release of neuromediators, production of neurotrophins and protection from oxidative damage [181]. Among the various neurodevelopmental disorders affected by vitamin D status, attention deficit hyperactivity disorders (ADHD) and autistic spectrum disorders (ASD) have been studied among children. Several studies indicate higher incidence of vitamin D deficiency among children affected with ADHD or ASD [182,183]. There is some evidence that optimal vitamin D status is associated with better symptomatology in these children and is advised to be maintained with supplementation [184,185].

Consensus statements and recommendations

6.1 Vitamin D levels are lower in children with asthma, which may be associated with reduced lung function and asthma exacerbation in children. (LOE 1). Despite that,vitamin D supplementation in children with asthma has not proven to be beneficial (LOE 1).

6.2.1 Vitamin D status is associated with obesity and parameters indicating glycemic handling (LOE 2).

6.2.2 Routine vitamin D supplementation is not recommended in obese children and adolescents for weight and metabolic outcomes (LOE 1).

6.2.3 Vitamin D levels should be maintained in sufficiency range (>20 ng/mL) in children with obesity and metabolic syndrome. The precise dosing amount and frequency cannot be generalized for these patients (LOE 3).

6.3.1 An association between vitamin D status and pathophysiology and clinical presentation in atopic dermatitis is known (LOE 3).

6.3.2 Routine supplementation of vitamin D in children with atopic dermatitis is not recommended as supplementation showing improvement in atopic dermatits is not proven (LOE 2).

6.4.1 Routine vitamin D and calcium supplementation is recommended in children with nephrotic syndrome to maintain serum 25(OH)D levels above 20 ng/mL (LOE 3).

6.4.2 Serum 25(OH)D concentrations may be monitored annually in children with nephrotic syndrome (LOE 4).

6.5.1 Literature indicates higher incidence of vitamin D deficiency among children with ADHD and ASD (LOE 2).

6.5.2 The direct therapeutic role of vitamin D in ADHD and ASD is not supported by literature. It is advisable to maintain optimal vitamin D status in these disorders (LOE 2).

CONCLUSIONS

The present guidelines endorse the earlier classification for vitamin D deficiency, insufficiency, and sufficiency as serum 25-hydroxy vitamin D levels as <12 ng/mL, ≥12-20 ng/mL and >20 ng/mL, respectively. Oral vitamin D supplementation in dosage of 400 IU/day should be continued during infancy. The estimated average requirement of vitamin D of 400 IU/day in childhood and 600 IU/day in adolescents should be met from dietary sources and sunlight. Sunlight exposure is recommended for all

Box II Areas for Future Research

- Representative survey to estimate prevalence of VDD in infants.
- Population-based studies to explore association of vitamin D deficiency and sufficiency with parathyroid hormone, skeletal and non-skeletal outcomes.
- Predicting response to controlled sunlight exposure in different ages.
- Role of sunlight versus routine vitamin D supplementation.
- Safety of bolus regimens needs to be established in well-powered randomized controlled trials for treatment of nutritional rickets, especially for infants.
- Efficacy of doses of vitamin D lower than 2000 IU/day for treatment of nutritional rickets.
- The optimal time points for monitoring treatment during treatment for nutritional rickets
- The functional benefit of treatment of isolated biochemical derangements in serum vitamin D levels (that do not correlate clinically).

ages, the exact duration and body surface area; however, will differ on host and environmental factors. Oral cholecalciferol with calcium carbonate should be used for treating vitamin D deficiency and rickets in a dose not exceeding 300,000 units across different ages. Daily vitamin D therapy is more physiological than bolus doses, though the Indian experience with daily vitamin D therapy is limited. The Committee suggest treatment of incidentally detected low serum 25(OH)D level <12 ng/mL in healthy children or ≤20 ng/mL in those at high-risk. Vitamin D supplementation only shows an association with common childhood infections and extra-skeletal diseases, not sufficient to mandate routine vitamin D supplementation in children with these conditions.

The committee noted the lack of robust scientific evidence to objectively conclude few aspects of prevention and management of vitamin D deficiency in childhood, and further proposed areas for future research (**Box II**).

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Annexure 1: List of Participants

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Study Designs: Diagnostic Studies

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Diagnostic tests are evolving with betterment of technology, quest for patient safety with less invasive medicine, and evolution of new diseases. It is important to assess diagnostic accuracy of a new test, and clinical impact of introduction of new test on outcomes and cost. A diagnostic study is planned for the index test based on place of new test in diagnostic pathway (screening, triage, diagnostic or add-on test) and established information of the test. A reference standard is used to classify population into diseased and healthy, and the discriminating ability of index test is measured. A sample size is calculated for expected sensitivity/specificity, margin of error and prevalence of disease in population. For dichotomous outcomes, sensitivity, specificity, predictive values and likelihood ratio are used to describe diagnostic accuracy. Efforts should be made to avoid common forms of bias including spectrum bias and partial verification bias, and blinding of observers should preferably be done.

Keywords: *Diagnostic accuracy, Index test, PPV, ROC, Sensitivity, Specificity.*

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Diagnostic tests evolve with development of newer medical technologies and refinements of older technologies. With focus on patient safety, there is a trend towards increasing use of non-invasive tests (doppler monitoring cardiac output *vs.* conventional invasive catheterization) and radiation free imaging modalities like ultrasound and magnetic resonance imaging (MRI) of chest vs. chest *X*-ray and computed tomography (CT). There has been a recent interest in various biomarkers for diagnosis and prognosis. Though these new diagnostic tests appear attractive for clinicians, it is equally important to ascertain that diagnostic accuracy is not significantly compromised over conventional reference standard tests. Studies evaluating diagnostic tests utilize unique methodology and statistical methods. We, hereby, review the methodology, statistics and pitfalls while performing clinical studies to evaluate diagnostic tests.

Indications of Diagnostic Studies

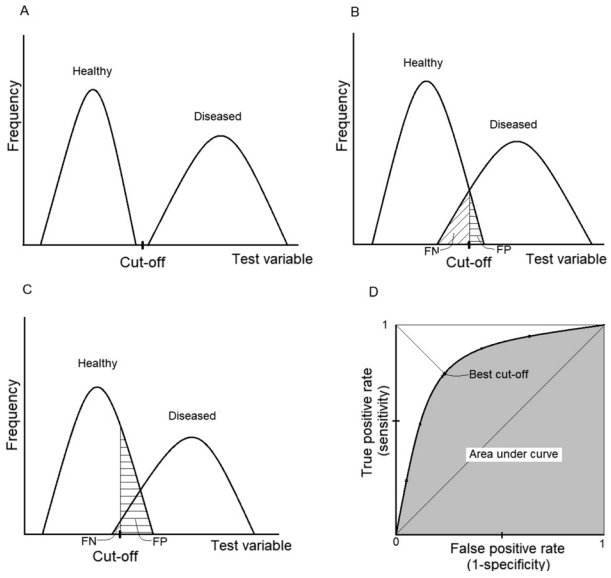
A diagnostic test is based on differential expression of certain characteristic among diseased, affected at-risk and healthy population. It could be a molecule of metabolic pathways (e.g. lactate for shock, creatinine for renal failure), or as a combination with clinical features (e.g. eschar for scrub typhus, PICADAR score for primary ciliary dyskinesia). An ideal diagnostic feature should not overlap between diseased and general population (**Fig. 1A**). However, for a continuous variable (e.g. lactate), a cut off is decided to differentiate diseased and healthy population with minimum overlap (**Fig. 1B**).

An algorithmic approach in the diagnostic pathway guides the characteristics of the test (**Fig. 2**). The various types of tests are:

a. Screening test: A screening test is used to identify individuals who are diseased/at high risk among asymptomatic population. Screening test should be highly sensitive to identify most of the diseased population, while they might also be positive in healthy individuals (lower specificity, often a trade-off for high sensitivity); e.g. immunoreactive trypsinogen (IRT) for cystic fibrosis (CF) in neonates [1]. Patients positive on screening test should undergo confirmatory test to corroborate the diagnosis.

b. Triage test: Triage test are utilized for screening positive population to further decrease number of individuals requiring confirmatory diagnostic test. This approach is useful when confirmatory test is expensive, inaccessible or invasive. For example women with positive screening on pap-smear are traditionally subjected to invasive tests including colposcopy. Introduction of triage test (human papilloma virus (HPV) test) reduces the number of patients needing colposcopy without additional risk of missing cervical malignancy [2]. Triage test should be highly sensitive and reasonably specific.

c. Diagnostic test: Diagnostic test confirms presence of a disease in screen positive population or individuals coming to clinics with symptomatic diseases. Diagnostic tests are desired to have high sensitivity as



FN: false negative, FP: false positive.

Fig. 1 A. Ideal diagnostic test with no overlap of measurements between diseased and healthy population. **B.** Diagnostic test demonstrating overlap of measurements with cutoff for best diagnostic accuracy. **C.** A screening test with lower diagnostic cutoff. **D.** Receiver operating characteristic curve for a diagnostic curve. Cut-off for best diagnostic accuracy corresponds to the point nearest to left upper corner of the graph.

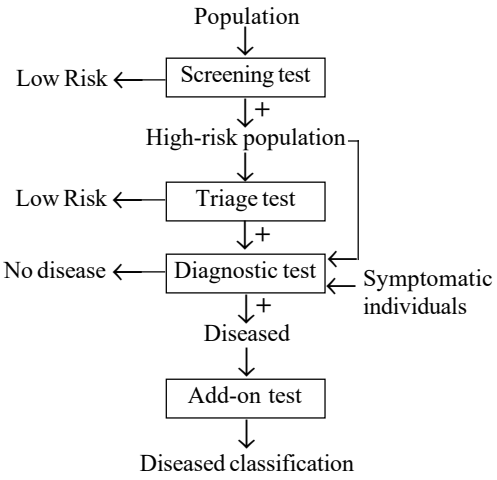


Fig. 2 Diagnostic pathway demonstrating place for various tests.

well as high specificity, e.g. sweat chloride assay for confirming diagnosis of CF in symptomatic neonates with elevated IRT or in a child with recurrent pneumonia.

d. Add-on diagnostic test: Add-on tests are used to increase sensitivity or specificity of current established diagnostic tests. These tests can be used with established test as either positive (to decrease false negative) or both positive (to decrease false positive) approach for starting treatment. These tests are usually costly, or invasive, but might be useful in subset of population where diagnostic test have limitations. For example, the use of positron emission tomography for distant metastasis where conventional imaging (CT or MRI) is inconclusive [3].

The diagnostic accuracy of a new test or new indication of an old test may be evaluated in any of these situations [3]:

1. *Replacement*: New screening or diagnostic test may have superior diagnostic accuracy over conventional diagnostic algorithms. For example, *c*omparison of GeneXpert with sputum smear for diagnosis of tuberculosis. It may instead have similar efficacy but can be less-expensive, faster, non-invasive, less radiation exposure. For example, MRI chest instead of CT for follow-up of mediastinal pathologies.
2. *Triage*: Addition of new test in diagnostic pathway like HPV test in cervical cancer screening in population with positive pap smear, decreases need for invasive testing without additional risk of missing malignancy.
3. *Add-on*: To test benefit of an add-on test on existing diagnostic pathways.

Study Designs for Evaluation of Diagnostic Tests

Similar to clinical trials for new interventions, diagnostic studies can also be classified as four phases [4]. *Phase 1* studies focus on establishing a normal range for the new test. It involves cross-sectional observational studies with random sampling of healthy subjects from the population.

Phase 2 studies focus on establishing diagnostic accuracy of the new test. These include case control, or cohort studies with healthy subjects and diseased patients, aimed at establishing cut-offs, sensitivity, specificity, predictive values, and likelihood ratios for the new test. These studies also include comparison of diagnostic accuracy of a new test with a reference test, like comparison of sweat chloride estimation and sweat conductivity for diagnosis of CF [5], or diagnostic accuracy of QuantiFERON-TB gold test and tuberculin skin test for diagnosis of tuberculosis [6]. These studies are paired and have advantage of smaller sample size, and less bias due to heterogeneity of population. Randomized trial study design is preferred in situations where paired study cannot be performed because of interference of one test with another or invasive nature of tests. It is desirable to evaluate a diagnostic test in a diseased population similar to the final population where it is likely to be used.

For example, a rapid diagnostic test for enteric fever should be tested in children with fever, all of whom would undergo testing for enteric fever with blood culture. This approach will be preferable to a study recruiting patients with culture confirmed enteric fever and healthy individuals.

Phase 3 studies establish clinical impact of new diagnostic test in diagnostic pathway with respect to patient benefit and harm. These involve randomized trials where individuals undergo new test or comparator test, and outcomes and further treatment depends on the results of these tests. Outcome parameters include change in diagnosis, change in treatment choices, patient outcomes, and cost-effectiveness. A non-inferiority randomized trial of procalcitonin guided antibiotic administration to adults with acute respiratory infection is an example of addition of a triage test [7]. The potential benefits of procalcitonin guided regimen are decrease in antibiotics administration while concerns/potential harm are adverse clinical outcome such as treatment failure, or increased hospital stay.

Phase 4 studies are follow-up studies to determine clinical impact in different settings. These studies are aimed at establishing diagnostic accuracy of a new test and clinical impact of introduction of new test (triage/add-on) in clinical pathway, like efficacy of clinical scores in predicting mortality or guiding hospitalization.

Measurement of Diagnostic Accuracy

The aim of diagnostic studies is estimation of ability of the test to discriminate diseased from healthy individuals. The discriminative ability of index test (test being evaluated) is compared with a reference standard test. For tests with dichotomous outcome (positive or negative), a 2 X 2 contingency table can be prepared (**Table I**). Parameters assessed include sensitivity, specificity, predictive values, and likelihood ratio.

Sensitivity and Specificity

Sensitivity is the ability of the test to detect individuals who have disease (or a condition), while specificity is the ability to detect individuals who do not have disease (or a condition). These can be calculated as below:

$$Sensitivity = \frac{True\ positive}{All\ with\ disease} = \frac{a}{a+c}$$

Table I Contingency Table for Tests with Dichotomous Outcomes

		Reference standard	
		Diseased	*Healthy*
Index test	Positive	a (true positive)	b (false positive)
	Negative	c (false negative)	d (true negative)

$$Specificity = \frac{True\ negative}{All\ without\ disease} = \frac{d}{b+d}$$

Sensitivity and specificity depend on distribution of measurement parameter between diseased and healthy individuals and ability (accuracy and precision) of the index test to measure the parameter. These do not depend on prevalence of the disease. However, they are mutually dependent according to the cut-off of the test. As in **Fig.1B** (best diagnostic accuracy) and **Fig. 1C** (lower cut-off), more diseased patients are detected if a lower cut-off is used (sensitivity increases) but simultaneously more healthy individuals are classified as diseased (specificity decreases).

Predictive Values

While sensitivity and specificity describe discriminating characteristics of the test, it is hard for a clinician to understand the significance of an individual positive or negative test based on these parameters. Positive predictive value (PPV) is the proportion of a true positive tests among all positive tests. Similarly, negative predictive value (NPV) is the proportion of true negative tests among all negative tests.

$$PPV = \frac{True\ positive}{All\ positive} = \frac{a}{a+b}$$

$$NPV = \frac{True\ negative}{All\ negative} = \frac{d}{c+d}$$

PPV and NPV depend on test characteristics (sensitivity and specificity) as well as prevalence of the disease. For example, a test kit for dengue IgM with known sensitivity (0.9) and specificity (0.9) disease may be used for 1000 febrile patients in region A (50% of febrile patients have dengue) and B (10% febrile patients have dengue) each (**Table II**). In region A, PPV = 450/(450+50) = 0.9 while in region B, PPV = 90/(90+90) = 0.5. In region A, NPV = 450/

Table II Contingency Table for IgM Dengue Tests for Two Regions With Different Prevalence (Hypothetical Data)

IgM dengue	*Region A n=1000*		*Region B n=1000*	
	Dengue	*other febrile illnesses*	*Dengue*	*other febrile illnesses*
Positive	450	50	90	90
Negative	50	450	10	810
Total	500	500	100	900

(50+450) = 0.9 while in region B, NPV = 810/(810+10) = 0.99. PPV for a test increases with increase in prevalence/ pre-test probability while NPV decreases with increase in prevalence/ pre-test probability.

Likelihood Ratios

Likelihood ratio (LR) represents the ratio of post-test odds to pre-test odds.

Post - test odds = Likelihood ratio X Pre-test odds

Positive LR (LR+) is ratio of likelihood of positive result in a diseased individual to likelihood of positive result in healthy individual. Negative LR (LR-) is the ratio of likelihood of negative test result in a diseased individual to likelihood of negative result in healthy individual. Higher LR+ and lower LR- are desired. LR+ of 10, 6, 2, and 1, and LR- of 0.1, 0.2, 0.5 and 1 are classified as excellent, very good, fair and useless test. LR can be calculated as:

$$LR+ = \frac{a/(a+c)}{b/(b+d)} = \frac{sensitivity}{1 - specificity}$$

$$LR- = \frac{c/(a+c)}{d/(b+d)} = \frac{1 - sensitivity}{specificity}$$

LR is the ratio of post-test and pre-test odds and not probability. For using LR for estimation of post-test probability, odds can be converted into probability by the following equations:

Probability = odds / (odds + 1)

Or,

$$P_1 = P_0 \text{ X } LR/(1 - P_0 + P_0 \text{ X } LR)$$

where P_1 is post-test probability and P_0 is pre-test probability.

More commonly, Fagan nomogram is used for post-test probability estimation from pre-test probability and LR [8].

Diagnostic accuracy of a test can be calculated as proportion of true positive and true negative results among all tests:

$$Accuracy = \frac{a+d}{a+b+c+d}$$

Diagnostic accuracy/discriminatory power for tests measuring continuous variable (for *e.g.* creatinine, blood glucose) with dichotomous outcomes (*e.g.* acute kidney injury: yes/no, diabetes: yes/no), can also be represented as area under (AU) receiver operating characteristic (ROC) curve. ROC curve is plotted with true positive rate (sensitivity) on y-axis and false positive rate (1-specificity) on x-axis for different cut-offs of the test (**Fig. 1D**). AUC of 0.5 to 0.6 is almost useless, 0.6 to 0.7 is poor, 0.7 to 0.8 is fair, 0.8 to 0.9 is very good and >0.9 is excellent.

Designing Diagnostic Studies

First step in any diagnostic study is identification of existing clinical pathway which will include the index test. Role of index test as screening, triage, diagnostic or add-on test has to be clearly defined. Expected proportion of patients with target disease among the general population is estimated based on prevalence studies or meta-analysis. Most diagnostic studies are conducted on population cohort where a proportion of individuals have a target condition but are not diagnosed. Case-control approach is more appropriate in conditions with low prevalence. Impact of the index test on the study population is ascertained, and minimally acceptable criteria (MAC) for sensitivity and specificity are decided and study hypothesis is established [9].

Sample Size Estimation

Sample size of the study is related to expected sensitivity and specificity, maximum margin of error (usually set as 0.05 or 0.02, lower limit of confidence interval should not cross MAC), α- and β-error [9]. Sample size is estimated separately for sensitivity and specificity for required individuals with target condition and without target condition respectively (true for case-control studies). In cohort studies, where diagnosis is not established in beginning, sample size is adjusted for prevalence of the target condition in population. Formula for calculating sample size for diagnostic studies is given in **Table III** [10]. Similarly, sample size can also be calculated for studies for estimating diagnostic accuracy of new test or comparison between tests on basis of predicted AU-ROC.

Statistical Analysis: A reference standard is required which could be a diagnostic test, or combined classification based on clinical tests and diagnostic test, to identify individuals with target condition/ disease amongst the enrolled population. The index test is applied to the same sample and the ability to correctly categorise into patients with or without target condition is compared with the reference standard.

Testing diagnostic accuracy of a new test: Minimally acceptable criteria (MAC) for the index test are pre-defined based on place of diagnostic test in clinical pathway. For a screening test, MAC for sensitivity will be kept at high level of greater than 0.85-0.9 while for a diagnostic test, specificity is equally important. The diagnostic accuracy parameters such as sensitivity and specificity are described with 95% confidence interval (CI), lower limit of which should not cross MAC. For example, the diagnostic accuracy of chest X-ray to differentiate bacterial and viral

pneumonia in children was based on combination of tests including viral culture and antigen testing from nasopharyngeal aspirate, and IgM and paired IgG serology for acute and convalescent samples for bacterial and viral antigens (reference standard). Sensitivity and specificity of alveolar infiltrates on chest *X*-ray for identification of bacterial pneumonia was 0.72 and 0.51, respectively. No pre-determined MAC were reported in this study [11].

Establishing cut-off: A diagnostic cut-off needs to be established for a new diagnostic test measuring a continuous variable. A lower cut-off (targeting high sensitivity) will be advised for a screening test or test identifying highly infectious and lethal illness requiring isolation. If there is no preference for sensitivity or specificity, cut-off for best diagnostic accuracy can be identified by various methods like Youden's index, point of minimal distance from top left corner of ROC curve (**Fig. 1D**), using Bayesian approach or analytical methods (numbers needed to misdiagnose) [12]. Cut-off with maximum Youden's index (sensitivity + specificity -1) is chosen.

Comparing Diagnostic Accuracy of Two Tests: For a new test aimed at replacing older test, diagnostic accuracy of both the tests is compared by AU-ROC for of both tests [13].

Comparison when there is no gold standard: There may be no accurate reference test or it may not have been performed on all individuals included in study because it is expensive or invasive. Alternatives for this situation such as imputation and bias correction methods, and differential verification (when reference standard is missing), correction methods, and use of multiple imperfect reference standard (when reference standard is imperfect are described). Other methods are study of agreement, true positivity rate or analytical validation for new test and imperfect reference standard instead of usual diagnostic accuracy tests [14].

Pitfalls

Inadequate sample size: Sample size estimation is frequently omitted in diagnostic studies. In a survey of diagnostic studies, only 2 out of 40 (5%) reported sample size calculation [15]. Inadequate sample size leads to loss of power of study while large sample size adds to cost and complexity of diagnostic studies. *A priori* sample size calculation should be done in all diagnostic studies.

Intra- and Inter-observer variability: Tests involving complex procedures, multiple steps, and subjective parameters can have significant variability when performed repeated by same observer (intra-observer variability) and different observers (inter-observer variability). For dichotomous outcomes, agreement between two observers can be simply calculated as proportions of test results agreed by both the observers (positive as well as negative). This method doesn't account for inter-observer agreement due to knowledge of prevalence of disease, which is adjusted while estimating a better parameter as kappa statistics. Kappa ranges from -1 (perfect disagreement) to 1 (perfect agreement) and values above 0.8 are considered very good and 0.6-0.8 are considered good [16]. For continuous outcomes, inter-observer variability can be expressed as coefficient of variation (=standard deviation/mean). Mean difference between paired measurements by two observers can also be assessed by Bland-Altman analysis [17].

New test is more sensitive than gold standard: Newer test especially molecular tests such as polymerase chain reaction (PCR) for detection of infectious agents are at-times more sensitive than existing gold standard/ reference test. When diagnostic accuracy is calculated for such test, both sensitivity and specificity are underestimated. For example, in a study comparing efficacy of different tests for tuberculosis, culture identified 50/125 (40%) samples as positive, while GeneXpert ultra was positive in 73/120

Table III Sample Size Estimation for Various Diagnostic Studies [10]

Study design	*Sample size*	
Diagnostic accuracy of a new test with dichotomous outcome		
a. Case-control	$cases = Z_{\frac{\alpha}{2}}{}^2 \frac{Se\ (1-Se)}{d^2}$	$controls = Z_{\frac{\alpha}{2}}{}^2 \frac{Sp\ (1-Sp)}{d^2}$
b. Cohort study (Use larger of the samples derived from sensitivity and specificity formulas)	$n = Z_{\frac{\alpha}{2}}{}^2 \frac{Se\ (1-Se)}{prevalence \times d^2}$	$n = Z_{\frac{\alpha}{2}}{}^2 \frac{Sp\ (1-Sp)}{(1-prevalence) \times d^2}$
Sample size for comparing the sensitivity (or specificity) of two diagnostic tests	$n = \frac{[Z_{\frac{\alpha}{2}}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}]}{(P_1-P_2)^2}$	

P_1: Sensitivity or specificity of test 1; P_2: Sensitivity or specificity of test 2, P: average of P_1 and P_2; n: sample size; Se: Sensitivity; Sp: Specificity; $Z_{\frac{\alpha}{2}} = 1.96$; $Z_{\beta} = 0.84$.

Key messages

- Study design of a diagnostic study should be planned based on place of new diagnostic test in diagnostic pathway.
- *A priori* sample size estimation should be conducted in all diagnostic studies.
- Reference standard should be carefully chosen especially in cases where new diagnostic test could potentially have better diagnostic accuracy than established gold-standard.
- Blinding of assessors should be performed to avoid bias.

(60.8%) samples [18]. The reported sensitivity and specificity of GeneXpert ultra was 88% and 58.6%. Large number of patients who were detected on GeneXpert ultra were labelled as false positive which led to significant underestimation of sensitivity and specificity. In these situations, it is better to consider alternative method of reference (clinico-radiological diagnosis of tuberculosis as reference standard in above example) and compare diagnostic accuracy of new test and established gold standard.

Bias

Source of bias in a diagnostic study can arise from patient selection, index test method, reference test or study flow and outcomes. QUADAS-2 tool is used for assessing risk of bias in diagnostic studied included in systematic review and meta-analysis [19]. Common sources of bias are described below [20]:

Patient selection: It is easier for a diagnostic test to differentiate a severely ill patient from healthy individual. Studies which include only severely ill patients are prone to overestimate diagnostic accuracy of the index test. This is called spectrum bias. Spectrum bias is also likely to be higher in case-control study design where cases are typical disease phenotypes. If possible, cohort study design should be utilized for diagnostic accuracy studies. The severity of illness of the study population should be reported.

Similarly, if the center conducting the study is a referral center, patients who clearly have the target condition or do not have the target condition, get diagnosed at the referring center. So, the referral center gets mostly patients with overlapping features and applying index test in such situation is likely to underestimate the diagnostic accuracy of the test.

Index test: Methodological differences can make significant differences in performance of the test. Difference in yield of a fine needle aspirate (FNA) could vary between studies due to differences in staining methods, use of rapid on-site evaluation, experience of physician performing aspirate, use of small or larger needle or use of ultrasound guidance. Hence, it is very important to describe methodology of index test in great detail and use same method for all procedures during the study.

Reference test: An imperfect reference test can lead to misclassification of the population. This is likely to underestimate sensitivity and specificity of index test.

Patient flow: If only a fraction of patients is undergoing reference test (if too invasive or costly), it is possible that patients negative in index test receive more intensive reference standard testing. Or if reference test is performed more frequently in patients positive on index test (*e.g.* invasive biopsy following a positive FNA). These could introduce partial verification bias.

If index test and reference test are done in sequence and the observer is aware of index test results, his interpretation of reference test can be biased. For example, the interpretation of a CXR or CT of patients with interstitial lung disease may be biased if biopsy results are known before. Similarly, assessment could be biased if observer assessing clinical outcomes knows about of diagnostic algorithm used. Observers estimating index test should be blinded from result of reference test and vice-versa, and observer assessing clinical outcomes and adverse effects should be blinded from both index and reference test results.

Reporting

Standard reporting guidelines for diagnostic studies are standards for reporting of diagnostic accuracy update 2015 (STARD-2015) and transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) [21,22].

CONCLUSION

With evolution of technology and trend towards medical safety, increasing number of new and safer tests are being available. Appropriate study design based on place of test in diagnostic pathway and calculated sample size will help in developing reliable evidence for their use.

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RESEARCH LETTER

Adherence to Home Treatment Guidelines Among Pediatric Home Treated COVID-19 Patients in Puducherry

We studied the adherence to Government of India guidelines for home treatment of asymptomatic/mild covid-positive children, whereby a family member is designated as caretaker for the patient. Proportion of caretakers adhering to guidelines was 68%. Persistence in adherence was 6 (1.4) days. 14 children (16.5%) developed symptoms while in home isolation. The most reported commonly barrier was it was that time consuming.

Key words: *Coronavirus, Covid-19, Guideline adherence, Pandemic, Patient isolation, SARS CoV 2.*

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To tackle the growing number of COVID-19 cases during the peak, the Government of India instituted home isolation and treatment of asymptomatic and mildly symptomatic patients including children without co-morbidities, and formulat specific guidelines for the same [1]. Instructions on the guidelines were given to the patients' caretaker, which included care and monitoring of the patient, use of mask, gloves, hand hygine, disposal of waste and environmental sanitation at the time of initiation of home isolation [1,2]. As much depended on caretaker compliance and it being a novel approach, the present study was undertaken to evaluate the caretakers' adherence to home treatment guidelines, the outcome of these home-treated patients and the barriers/difficulties faced by the caretakers, if any.

A sample size of convenience of 85 was planned. Inclusion criteria were caretakers of eligible home treated COVID-positive children aged 8 to ≤12 years willing to participate in the study. After getting ethics clearance, a total of 350 patients, phone numbers were retrieved from register for those home treated between August and December, 2020. Systematic randomized sampling technique was followed whereby every third caretaker of these home-treated patients was enrolled during the study period from July to September, 2021. Caretakers whose numbers were not reachable, switched off, who did not answer two calls, were not willing to participate, and those with incomplete responses were excluded (n=65). After getting informed verbal consent, details were obtained by telephonic interview by a single trained research assistant and data entered into a pre-tested validated semi-structured questionnaire. The items in the questionnaire were adapted from the MOHFW guidelines on home isolation and biomedical waste disposal [1,2,4]. There were five broad indicators viz use of mask with five items under it; use of gloves along with mask having four items under it; hand hygiene with nine items; environmental sanitation with six items; and, general isolation guidelines with six items under it. Adherence was scored as one for each item and non-adherence as zero. Adherence was assessed as proportion of caretakers following recommended guidelines for each of the indicators, and persistence in adherence as the mean number of days the guidelines were followed out of the 10 days of home isolation. Adherence score was classified based on the mean total score for all the subjects, and sociodemographic variables were compared. Perceived barriers were assessed by open-ended questions, and analyzed for multiple responses.

Descriptive statistics was used to calculate adherence proportion, outcome and perceived barriers, and adherence persistence. Chi-square test was used to compare low and high adherence groups based on their adherence score (below and above 20). A P value of <0.05 was taken as statistically significant.

Of the 85 children included, 59 (69.4%) were asymptomatic (mean (SD) age, 6.5 (3.6) years). The overall proportion of caretakers who adhered to the guidelines was 68% with mean (SD) persistence in adherence of 6 (1.4) days. The minimum total adherence score was 13/30 and maximum was 28/30. The highest mean adherence was in the area of hand hygiene (87%) followed by general measures on isolation (76%), environmental sanitation (65%) and use of mask (60%). The least adherence was in the use of gloves cum mask for cleansing and sanitation (43%). This was in contrast to a previous study [6], where the compliance was <30% for both mask and hand hygiene. Li, et al. [7], in their study among adults, observed full compliance to use of mask in 93.5% and to hand hygiene in 75%. The combined use of mask and hand hygiene has already been demonstrated to be efficacious [8].

With respect to individual guidelines, highest full adherence was seen in refraining children from social gatherings (94.2%) followed by practice of hand hygiene before eating, after use of restroom, and whenever hands looked dirty (90.6%). Similarly, reasonable proportion of participants used soap with water or alcohol based solution as recommended for hand hygiene (83.4%) and refrained from sharing child's personal items (81.2%) and disallowed visitors to the child (88.2%).The least adherence to individual guidelines was to disposing biomedical waste in yellow bag (3.5%) , use of 1% sodium hypochlorite solution to disinfect mask before discarding (10.6%), and in the use of both mask gloves for cleaning surfaces, for handling the child and soiled linen (11-18%).

Except for the socioeconomic class, there were no significant differences between the low-and-high adherence groups (**Table I**). This may be attributed to the wide dissemination of information, education and communication materials made available to the general public through media. However, this is in contrast to the findings reported by Lou, et al. where age and gender of both the child and the caretaker influenced compliance.

Table I Baseline Characteristics of the Participants

Variable	*Low adherence group, n=48*	*High adherence group, n=37*
Child's age[a]	6.4 (3.6)	6.6 (3.7)
Male gender	26 (54.2)	22 (59.5)
Clinical status		
Asymptomatic	28 (58.3)	17 (45.9)
Mildly symptomatic	14 (29.2)	12 (32.4)
Pre-symptomatic	6 (12.5)	8 (21.6)
Caretaker – mother	34 (70.8)	32 (86.5)
Caretaker's age, y[a]	17.8 (1.9)	23.3 (2.1)
Caretaker's educational status		
Illiterate	2 (4.2)	1 (2.7)
School	17 (35.4)	18 (48.6)
College	29 (60.4)	18 (48.6)
Socio-economic class[b]		
1	15 (31.2)	16 (43.2)
2	23 (47.9)	7 (18.9)
3	5 (10.4)	7 (18.9)
4	3 (6.2)	7 (18.9)
5	2 (4.2)	0
Nuclear family	30 (62.5)	23 (62.2)

All values in no. (%) except [a]mean (SD). [b]P=0.02.

Of the 85 children, 14 children (16.5%), who were asymptomatic at the time of home isolation, developed symptoms later while in home isolation. However, all of them improved on home isolation treatment and none required hospitalization. Self-reported perceived barriers to following the guidelines were, it was time consuming (*n*=50, 49.5%), and busy schedule (*n*=27, 26.7%) (**Fig. 1**).

Limitations of the study were small sample size and single center study. Data on secondary attack rate in the household would have provided further insights about the effectiveness of the compliant behavior.

In conclusion, most caretakers (68%) were able to follow the guidelines and individual compliance was good for 4 of the 5 indicators.

Ethics clearance: Institute ethics committee; No.3/315/IEC/32/PP3/2021, dated Feb 19, 2021.
Contributors: CB: concept, design, data acquisition, analysis, interpretation, drafting, reviewing for intellectual content. Devikittu: design, data analysis, interpretation; SB: data interpretation, drafting, reviewing for intellectual content; SP: reviewing for intellectual content; RC: data acquisition, drafting. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

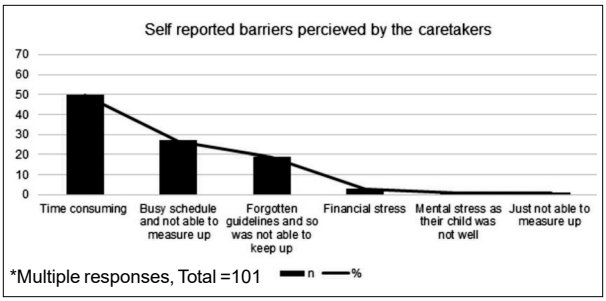

Fig. 1 Caretaker perceptions regarding barriers to following home treatment guidelines.

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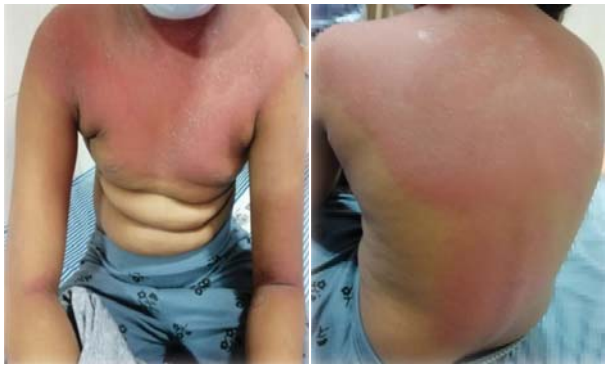
SDRIFE-Like Rash With COVID - 19

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously termed drug-related Baboon syndrome, is described as type IV hypersensitivity to a systemic drug [1]. SDRIFE has been commonly associated with beta-lactams, antihypertensives, radiocontrast media, chemotherapeutic agents and biologics, though its occurrence has also been described in the absence of previous drug exposure [2,3]. There are reports of SDRIFE- like rashes associated with infections including parvovirus infections and of late, in coronavirus disease 19 (COVID-19) patients [1,4,5].

A 9-year-old girl presented with a history of fever and a peculiar SDRIFE-like rash with reactive sever acute respiratory syndrome (SARS-CoV-2) coronavirus 2 antibody. The rash started as an erythematous maculopapular eruption on the upper arm which slowly progressed. A similar erythematous rash involving the flexural aspect of the knee and elbow joints was noted on the second day (**Fig. 1 a** and **1 b**). On the third day, the rash progressed further to form a large plaque involving the upper chest and posterior trunk, with a clear line of demarcation from the normal skin. The child also had a low-grade fever and sore throat. By the 7th day of onset of the rash, erythema of skin resolved with desquamation followed by normalization of the involved areas, with complete resolution by the next day. Her blood counts, liver function tests, renal function tests and urine examination were within normal limits. Her SARS-CoV-2 rapid antigen test and RT- PCR were reported negative; however, SARS-CoV-2 IgG antibody was reactive. On reviewing the history, the child as well as four other family members had history of fever with upper respiratory tract infection two months back. In view of fever with rash in a post- Covid-19 state, a possibility of multisystem inflammatory syndrome in children (MIS-C) was considered. However, the clinical diagnostic criteria were not satisfied, and the inflammatory markers were within the normal range, and MIS-C was ruled out. A diagnosis of SDRIFE was made considering the typical morphology and distribution of the rash, as well as the rapid and complete resolution of the lesions. Treatment given were antibiotics, antihistamines and calamine lotion.



(*a*) (*b*)

Fig. 1 (*a*) Erythematous rash with clear demarcation from normal skin involving the flexures on day-2; (*b*) Rash spreads to form plaques on day-3.

SDRIFE has been defined by inclusion of the following criteria: (*i*) exposure of a systemically administered drug at the time of first or repeated doses (contact allergens excluded); (*ii*) sharply demarcated erythema of the gluteal/perianal area and/V shaped erythema of the inguinal/perigenital area; (*iii*) involvement of at least one other intertriginous/flexural fold; (*iv*) symmetry of affected areas; and (*v*) absence of systemic symptoms and signs. The clinical scenario which we encountered was consistent with the above mentioned clinical features [2,3].

SDRIFE usually arises within a few hours to days following administration of the so-called offending agents, though it is also known to be triggered by infections [1,4,5]. Most cases spontaneously resolve via desquamation within 1 to 2 weeks which was the case with our patient also. The typical morphology of the rash helps to make the diagnosis. Interestingly, there was no history of drug intake prior to onset of rash in our patient. The patient had a positive SARS-CoV-2 IgG antibody and a history suggestive of Covid infection in the family two months back. Though SDRIFE-like rash has been reported in association with SARS-CoV-2 infection earlier also, the presence of SARS-CoV-2 IgG antibody in this patient could be a mere coincidence. At this stage, we need more data to assess if there is a true correlation between COVID-19 and SDRIFE-like rash.

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Infantile Immune Thrombocytopenic Purpura Secondary to Perinatal Transfer of SARS-CoV-2 Antibody

Immune thrombocytopenia (ITP) has been described following several viral infections [1], and since the onset of the coronavirus disease (COVID-19) pandemic, several reports of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-associated ITP in adults have emerged [2]. In children, more than the acute infection, multi-system inflammatory syndrome (MIS-C) presenting with thrombocytopenia has been reported [3].

A 6-week-old girl, born full term with uneventful antenatal and postnatal period, was brought with multiple purplish skin lesions all over the body since one day, followed by a right sided focal seizure lasting for 40 minutes. She looked pale with multiple ecchymotic patches all over the body. She required multiple anti-epileptic drugs along with mechanical ventilation. Her computed tomography brain showed sub-arachnoid and intra-parenchymal hemorrhage in the left parieto-temporal region while laboratory investigations revealed severe thrombocytopenia (platelet count $<100\times10^9$/L) with anemia (hemoglobin, 6.7 g/dL). Coagulation profile, dengue serology, HIV serology, hepatitis B antigen, inflammatory markers (C-reactive protein, serum ferritin), liver and renal function tests were normal. Peripheral blood smear showed no evidence of hemolysis, with a negative direct Coomb test. Nasopharyngeal swab for COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) was negative.

A packed red blood cell transfusion was given for the anemia. She was also transfused random donor platelets but thrombocytopenia persisted. Further evaluation showed high immature platelet fraction and increased megakaryocytes in bone marrow suggesting peripheral destruction of platelet. Considering diagnosis of severe infantile ITP, she was given intravenous (IV) pulse methylprednisolone (MPS) at 30 mg/kg/day for 3 days followed by oral prednisolone. On probing the parents further, mother revealed having upper respiratory tract infection symptoms during the last trimester of pregnancy, with loss of smell and taste in father at the same time. Both mother and the infant tested positive for IgG antibody to the nucleocapsid spike protein of SARS-CoV-2. As thrombocytopenia was persistent ($<10\times10^9$/L), the infant was given 2 g/kg of intravenous immunoglobulin (IVIG), following which the platelet count increased to 44×10^9/L at 72 hours. Child was extubated on day 5 of stay. Post-extubation, she showed no neurological deficits while subsequent platelet counts normalized within one week. She was discharged after 10 days of stay on tapering dose of prednisolone. The serial platelet count on subsequent follow-ups showed a rising trend.

ITP is often a retrospective diagnosis based on exclusion of other causes of thrombocytopenia and assessment of the response to treatment. Diagnosing ITP secondary to SARS-CoV-2 remains a challenge considering the various coexistent conditions associated with COVID-19 including a systemic hyper-inflammatory state, a distinct coagulopathy and therapeutic anticoagulation using hepari. Mild thrombocytopenia has been detected in 58-95% of severe cases of COVID-19 with the mechanisms for the same likely being multifactorial [4]. The combination of viral infection and mechanical ventilation leads to endothelial damage triggering platelet activation, aggregation and thrombosis in the lung, causing vast platelet consumption. Direct infection of bone marrow by coronaviruses results in an auto-immune trigger against the blood cells with low grade disseminated intravascular coagulation [4]. The expression of ACE2 surface receptor, the receptor used by SARS-CoV-2 to invade host cells, in hematopoietic and lymphoid tissues and resultant autoimmune antibody production and CD34+ mediated specific cell death and thrombocytopenia has been suggested [5].

In our patient, the diagnosis of COVID-19 antibody associated ITP is supported by an isolated thrombocytopenia, a low post-transfusion platelet increment, the exclusion of other causes, good response to treatment with MPS plus IVIG and historical evidence of parents having COVID-19 like illness in final trimester of pregnancy with demonstration of SARS-CoV-2 IgG antibodies in both the infant and the mother. The above represents a newer perspective on possible presentation of infantile ITP post maternal COVID-19 infection. The mechanisms of thrombocytopenia in ITP have been attributed to the development of platelet autoantibodies directed toward the different platelet antigens including platelet surface glycoproteins [6]. Similar mechanisms secondary to SARS-CoV-2 IgG antibodies may be postulated. The emergency treatment of ITP with severe bleeding such as in our infant warrants the use of combination therapy with pulse MPS and IVIG [7]. Our infant received the combination therapy in a similar chronology and had an incremental rise in platelet count within a week. Recent data in neonates born to COVID-19 positive mothers have demonstrated the transfer of maternal SARS-CoV-2 IgG antibodies across the placenta after asymptomatic as well as symptomatic infection during pregnancy [8].

In the current epidemiological scenario, in neonates and young infants presenting with isolated thrombocytopenia, a possibility of SARS-CoV-2 antibody mediated immune thrombocytopenia should be kept in mind. It will help pediatricians to recognize early and provide prompt immunomodulation. Similar experience, if reported, would need to be taken into consideration before concluding on the possible pathophysiology involved and standard therapy.

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

Sd/ Dr Devendra Mishra
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Reusable, Low-Cost Alternative for Standard Personal Protective Equipment for Use in Non-COVID-19 Healthcare Service Areas

Personal protective equipment (PPE) consist of gown, goggles, face-shield, mask, gloves, head cover and shoe cover [1]. The health ministry has laid down guidelines on the type of PPEs to be used in different outpatient (OPD) and inpatient setting [2]. In non-COVID treatment areas of the hospital, the recommendation is to assess patient profile and to use PPE judiciously as per hospital infection control practices [1]. The rapid rise in cases has resulted in huge demand for PPEs due to high demand-to-supply ratio [3]. The standard, hospital grade, disposable PPE kits cost anywhere from 250 to 2000 INR per unit and can incur significant expenditure on hospitals, thereby indirectly raising the overall healthcare costs. All these factors underscore the need for a low-cost, reusable alternative for PPE, which can be used during this pandemic.

We propose a cheaper and reusable alternative to PPE gowns that can be used in non-COVID OPD and inpatient areas of hospital in resource-limited setups. This includes using a synthetic, high quality, breathable, micro-polyester, waterproof raincoat with hood that wraps the entire body from head to feet. The hood covers the head and neck and hair is tucked inside the head cover. The raincoat should be taped at the seams to prevent fluid/droplets/aerosol entry. This can be combined with gloves, goggles, face shield and masks to provide overall protection against contact with infectious material/agents. It can be reused multiple times after surface cleaning with 1% sodium hypochlorite solution. Ease of performing clinical examination and auscultation using stethoscope will be better than standard PPE [1,4]. This cheaper alternative can help to overcome the shortage of PPE kits, especially in non COVID-19 areas of the hospital, where healthcare workers have contact with patients who might be asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carriers thereby increasing the risk of contracting COVID-19 infection.

Authors admit that there are obvious limitations with the overall efficacy of this model when compared to a standard PPE kit in terms of protection against SARS-CoV-2 transmission and this model should not be used in COVID-19 patient care areas. Other limitations include inability to achieve airtight seal like in standard PPE, the need for surface cleaning which carries infection risk, and difficulty in standardizing the quality and specifications of raincoat. Nevertheless, considering the risk versus benefit, increased demand and cost factor, this proposed alternative may be worth exploring in resource-limited settings, in non-COVID areas of the hospital, where the risk of acquiring infection is still high from asymptomatic COVID-19 patients. However, widespread use of this model can be recommended only after testing its efficacy and validity from studies in different settings.

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The Link of Maternal Mental Health With Early Childhood Development

I read with interest the compilation on Early Childhood Development (ECD) in the recent supplement issue of *Indian Pediatrics* [1]. The various articles have addressed the role of active parental involvement as an enabler for ECD, but the issue of maternal mental health has not been addressed.

ECD has been linked to status of maternal mental health for quite some time now [2]. Family environment is the sole source of providing experiences for their young children especially through the critical first 1000 days of life. Good mental health and strong motivation among caregivers, especially mothers, is essential for them to perceive their child's experiences and needs.

The period of motherhood from conception through early childhood coincides with the period that is critical for optimal ECD. Incidentally pregnancy and post-natal period is also the time that is frequently associated with maternal mental health problems like anxiety and depression. Stress through pregnancy is known to disrupt maternal programming [3]. Disrupted maternal programming is associated with maternal mental disorders and her ability to appropriately respond to her infant. These negatively affect fetal development resulting in insecure mother–infant attachment and subsequent difficulties with their emotional behavior. Secure attachment can form only with a caregiver who herself enjoys good mental health and can provide security, safety, affection, and comfort to her child.

In case a mother gives birth to a preterm, small or sick newborn, parenting challenges are compounded by separation anxiety with limited opportunities for early bonding, while she is already dealing with her own frail health amidst lack of respectful amenities in a facility setting and responsibilities towards care of her sick one.

A mother who herself is struggling with these challengeswhen her child needs a nurturing environment, creates possibility adverse outcome in such children such as difficulties with learning, memory, attention, and executive functions.

Firstly we need to take cognizance that nurturing care can crumble under conditions of maternal, family and societal stress that substantially raise risks for poor ECD. ECD will foster if we provide family assistance to enable nurturing care, social protection, financial stability, knowledge, time, skill and psychological support [5]. Strategies addressing maternal anxiety and depression should be integrated into early child development programs to improve both maternal mental health and child development outcome [6].

Policies and programs need to align to provide equitable, affordable and accessible maternal and child health services especially focusing on maternal mental health and opportunities. Policies supporting paid parental leave, child care leave through pregnancy and early years, time off for breast feeding at work, free pre-pregnancy education etc. can enable fostering ECD. With help from civil society and social enterprises, we can work towards local solutions to mitigate adversities on ECD due to poor maternal mental health.

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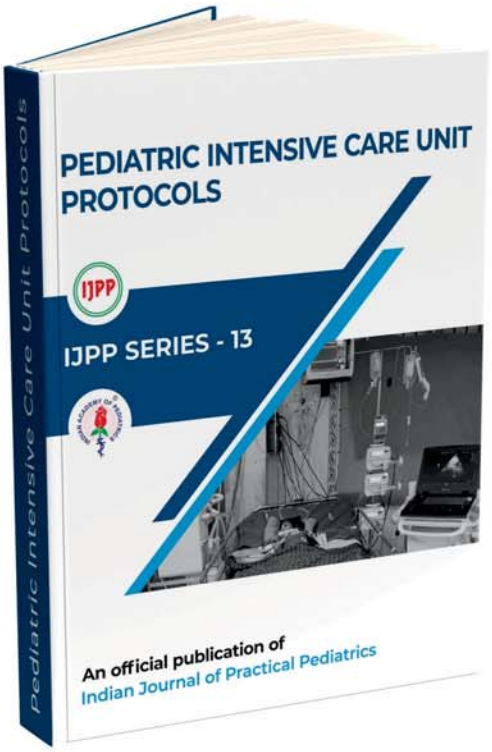

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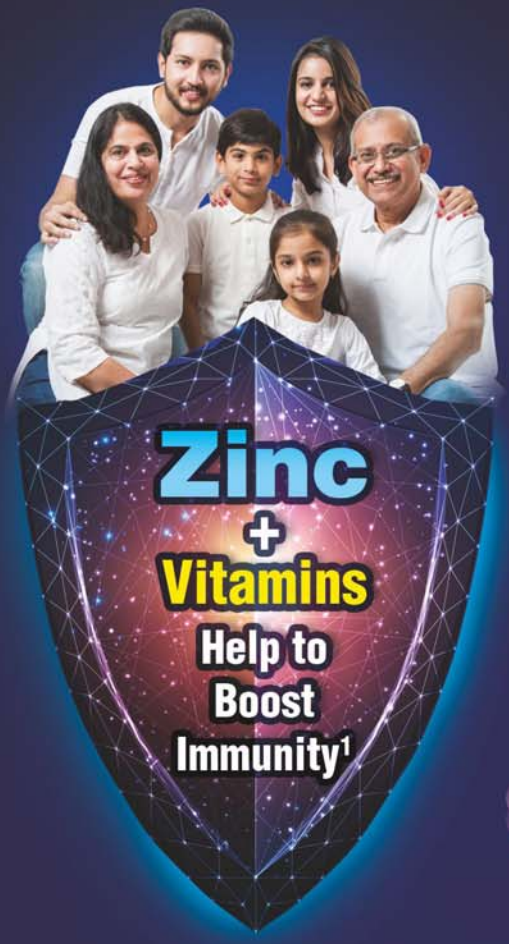

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