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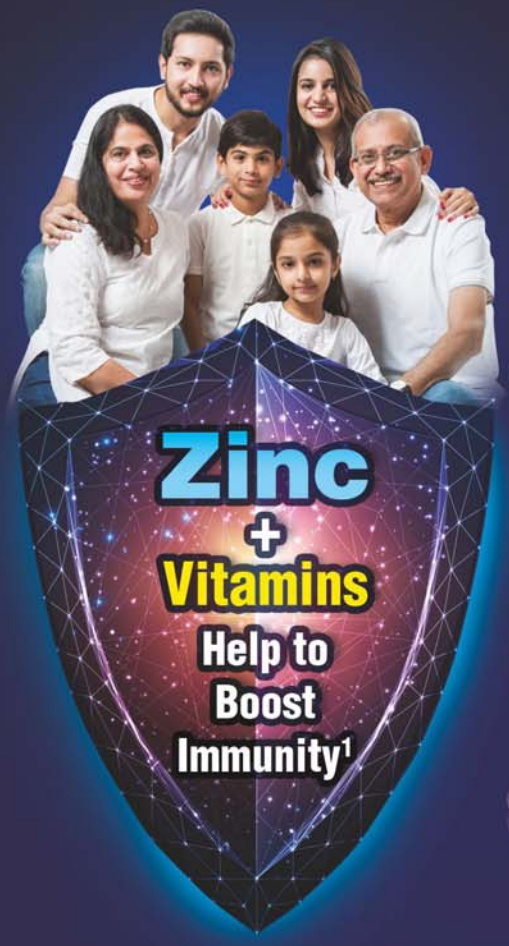

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Contents

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Aiding the Vision of an 'Anemia Mukt Bharat'

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The rhetoric of the 'lazy' child has been pervasive in the everyday narrative of many Indian households. Looking back, I can think of several instances – at home and in the school – where children are labeled as disinterested or unconcerned due to a general sluggishness in their movement that may be seen as reflective of their attitude towards school or physical activity. Although several unique factors affect each child's physiology, the alarming prevalence of anemia amongst children in India suggests that as parents and teachers, concerns about the child's attitude might be misplaced; and the same energy needs to be directed towards robust nutritional interventions for the children of this country. Evidence suggests that a poor nutritional status, especially in early childhood, can negatively impact a child's cognitive and behavioral development, reflecting directly in poor brain development and weak learning outcomes. This, in turn, can lead to prolonged absences from school, affecting their academic performance and overall development.

Despite the knowledge that our country can have palpable economic gains, better living conditions by expanding education and overall improvement in the health sector by overcoming nutritional anemia, we have not been able to address this challenge completely. The last two rounds of the National Family Health Survey documented an alarming rising trend of anemia pre-valence across the Indian population, most sharply in children who are 6-59 months old. The proportion of anemic children rose by almost 9%, from 58.6% in 2015-16 to 67.1% in 2020-21. The Comprehensive National Nutrition Survey conducted in 2016-2018, revealed that 41% of preschoolers (1-4 years), 24% school age children (5-9 years) and 28% of adolescents (10-19 years) in India have anemia.

Although, we have made some progress in early diagnosis of anemia and steady iron folic acid (IFA) supplementation for pregnant women, little has been achieved in terms of addressing anemia amongst children. The Anemia Mukt Bharat (AMB) program, launched in 2018, aimed to provide weekly iron folic acid supplementation to all children along with biannual deworming days. Under the program, mothers of under five children are supposed to receive a bottle of IFA syrup from their village ASHA. School-going children and adolescents receive IFA under the Weekly iron folic acid supplement (WIFS) program at their school or anganwadi. Under the Rashtriya Bal Swasthya Karyakram (RBSK), children are also to be screened for anemia at least once a year, using a digital hemoglobinometer. Those detected with moderate or severe anemia are referred to their closest health facility for treatment. Although well-intentioned and seemingly robust, the AMB has been wrought with implementational shortcomings. Most private schools opt-out of the program as they do not want to be liable for medicating students. The hesitancy is found in parents too, who may not trust the quality of government procured subsidized drugs. Thus, a majority of the cohort of private-school going children are missed out. The program has a tough time reaching out-of-school and migrant children as well, due to the lack of a regular and permanent platform. In the schools where it is operational, IFA supplementation is irregular and there are no independent monitoring frameworks to hold the schools accountable. Iron ingestion, especially on an empty stomach, can cause discomfort and nausea. A poor past experience is likely to make the child avoid future dosages, and so there is a need for detailed and convincing IEC/BCC in schools.

The AMB also encouraged states to procure digital hemoglobinometers for point of care screening, to eliminate the subjectivity of color scales and other older devices. While some states have rapidly procured these devices, their reach and usage are still negligible in rural and resource-poor regions. Further, there does not seem to be a follow-up mechanism to monitor the development of the children that do get diagnosed during these screenings. Although, they are encouraged to see a care provider, one cannot help but question how many of them actually end up receiving complete treatment for anemia. Lastly, while the strategy focuses on iron-deficiency and non-nutritional anemia in endemic pockets, little attention is given to other nutritional deficiencies such as vitamin A, zinc or B12, which are highly prevalent in school-age

children. That being said, we must laud the effort of the government to initiate such a large-scale, ambitious and purposeful effort towards addressing the public health issue of anemia in our country.

So how can each of us contribute towards a truly *anemia mukt bharat*? First, we can leverage our individual associations with the schools of our area to encourage participation in the weekly IFA supplementation. It is important to initiate a dialogue between the schools and health department officials to work through their concerns. For example, ensuring the time of supplementation is right after lunch is a small step that can go a long way in reducing discomfort for the child and negative feedback about the program in schools. Secondly, it is time to look at behavior change communication innovatively. The material needs to be designed with the unique sensibilities of parents, teachers, children and adolescents individually taken into account. The emphasis needs to be on diet diversification and increased intake of iron rich foods. In an earlier communication, I have already addressed the importance of infant's sixth month visit to the pediatrician. It can be a game changer if we spend quality time in detailed coun-seling of complementary feeding. The pediatrician can train at least one paramedic person in their clinic who then gives a detailed account of dietary diversity and minimum acceptable diet using the local resources. I am sure it will make a huge impact on reducing nutritional anemia in children. Children and adolescents can be picky eaters and a tricky audience to win over, especially with the multitude of food myths and diet fads they are exposed to. The message needs to come from a figure they look up to and trust, perhaps one of their own, more than authority figures like parents or teachers.

The strategy to address anemia in under 5 children can be integrated with the early childhood development (ECD) initiatives, such as including comprehensive nutritional counseling along with early and exclusive breastfeeding. Routine immunizations are a good touchpoint to opportunistically test children aged 6-59 month. Another two important interventions for helping AMB program are implementation of adequate water, sanitation and hygiene strategies and delayed cord clamping. While a pediatrician has a limited role in the former; each one of us attending a delivery can definitely ensure delayed cord clamping by at least three minutes and not earlier than one minute or until cord pulsations cease, especially for babies born to anemic mothers.

Efforts are required to make this practice a routine at all healthcare levels. There are new non-invasive hemoglobinometers entering the market, and emerging research on even app-based technologies. Even accounting for a slight loss of accuracy, these devices can be a great asset in detecting moderate or severe anemia, and can be kept handy for opportunistic screening. There are tremendous public health gains in securing the nutritional status of our future generations. The government is definitely doing its bit to improve the effectiveness and efficiency of programs like AMB. This will surely need to overcome the implementation challenges, making the technical capacity more robust and integrating it into parallel programs. We pediatricians must roll up our sleeves and do our bit to contribute to the vision of Anemia Mukt Bharat.

Jai Hind! Jai IAP!

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INVITED COMMENTARY

Bedside Severity Prediction Score for Predicting Severe Dengue in Children: A Shot in the Arm for Triaging Dengue Positive Children?

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Dengue has emerged as the most widespread and rapidly increasing vector-borne disease in the world [1]. About half of the world population is at risk of dengue with 100-400 million infections being reported each year [2]. India is one of the 30 most highly dengue endemic countries with outbreaks occurring in post monsoon season all over the country [3]. Though severe disease occurs only in a small proportion of dengue cases, delay in their recogni-tion can result in significant morbidity and even mortality [4]. Identifying these patients at risk of severe disease is helpful not only in reducing mortality, but also in reducing burden on the already strained healthcare systems by triaging such cases and directing more manpower and resources for their management.

The work by Gayatri, et al. [5] published in this issue of *Indian Pediatrics*, provides a bedside severity score for predicting severe dengue in children. The authors have developed a model to predict the occurrence of severe dengue from a retrospective analysis of data from 125 children admitted with dengue in their hospital. They have then validated the model prospectively on 312 children with diagnosis of dengue. Children between 2 months and 12 years of age with confirmed dengue virus infection (NS1Ag and/or IgM ELISA positive) were enrolled in this study. Children co-infected with other tropical infections or having another proven focus of infection were excluded from the study. Fourteen risk factors as given in the National Dengue Guideline 2020 were taken to develop the risk score. Three characteristics, narrow pulse pressure (≤20 mm Hg in absence of shock), mucosal bleed and clinical or radiologic evidence of third space fluid loss were predictive of severe disease among the 125 children. Using canonical discriminant function for these three variables a scoring equation was calculated: A score nearer to 2.913 was associated with severe disease while scores closer to -1.056 was associated with non-severe disease. This score was then validated prospectively on 312 dengue positive children. The score was able to identify severe dengue with 86.7% sensitivity and 98.25% specificity and 95.2% overall predictive accuracy. Thirteen children were classified as non-severe dengue but were later observed to have severe disease, while four children were observed to have non-severe disease despite being predicted to have severe dengue. Case fatality rate was 2.5% among the prospectively enrolled children.

The score developed by Gayatri, et al. [5] is probably the only dengue severity prediction score for children that uses only bedside parameters [6,7]. Since laboratory investigations are not a part of this score, this tool will be useful in triaging children at point of contact for risk of severe disease. This can enable early referral in places where intensive monitoring and management are not feasible and also identify patients that require more intensive monitoring in places that can manage sick patients.

One important limitation of this scoring system, as acknowledged by the authors, is the need for a point of care ultrasound. Availability of ultrasound machines and trained personnel to use them may not be equally distri-buted in dengue endemic regions around the world. Also, the dynamic nature of dengue illness may require calcu-lating the score multiple times during the course of the disease. This may be a hindrance in adhering to a scoring system, especially in health care settings with high patient load and limited human resources. Further studies in different health care settings would help increase the generalisability of the score and bring to light the issues that one might face while using the score at these different settings and provide ideas to strengthen this dengue severity prediction score.

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INVITED COMMENTARY

Diagnosis of Shock in Neonates: Need for Multimodal Monitoring

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Shock is a state of cellular energy failure resulting from the lack of adequate oxygen delivery. Shock can result from multiple pathogenic pathways including hypovolemia, poor myocardial contractility, and failure of the regulation of vascular tone. Shock, especially due to sepsis, has a high case fatality rate. Careful monitoring of at-risk neonates, early detection, and rapid initiation and titration of therapy can improve the outcome of neonates with shock. A number of clinical (heart rate, pulse volume, blood pressure, capillary refill time, core-peripheral temperature difference, urine output), non-invasive bedside (perfusion index (PI), plethysmography variability index (PVI), functional echocardiography measurements), and laboratory (blood pH, lactate levels, mixed venous oxygen saturation) measurement are used for the detection and management of shock. However, no single measure has been found to be sensitive and specific for detection of shock. Following questions drive the choice of an appropriate measure for detection of shock and titration of therapy:

- In neonates at risk of shock, which measure is an early and sensitive marker of tissue hypoperfusion so that the state of shock can be detected before decompensation?
- Once treatment of shock is initiated, which measure can be used for titration of therapy?
- For the given measure, what are the normative values or therapeutic targets for neonates born at different gestations and of different postnatal ages?
- What is the reference standard against which the candidate measures for detection of shock must be tested?

The PI and PVI measured by pulse oximeter have been suggested as an objective assessment of the pulsatile flow of blood in peripheral arteries and the flow variability during breathing [1]. A large study in healthy term neo-nates reported a median (IQR) value of 1.7 (1.18 to 2.50) for PI [2]. Preterm neonates have lower values. Presence of patent ductus arteriosus (PDA) or measurement in a prone position are associated with higher PI. In this issue of the journal, Sharma, et al. [3] present the utility of PI, PVI, and serum lactate levels in diagnosis of hypotension (invasive mean blood pressure <5th percentile). Authors have used fixed values of 0.455, 23.5, and 4.65, respectively to label the test as 'positive.' Correlation between these measures and mean blood pressure was found to be weak to moderate and the diagnostic test characteristics of the individual tests were less than optimal with highest positive predictive value being 51.7% for serum lactate [3]. This is not unexpected. Hypotension in neonates can result from varied causes including asphyxia, sepsis, extreme prematurity, PDA, and fluid deficit. These causes have overlapping pathophysiogical pathways and neonates may present with illness at different stages of shock and compensatory response [4]. Therefore, a single measure is unlikely to be superior to multi-modal monitoring for detection of tissue hypoperfusion.

Of the various measures, low blood pressure or hypotension is one of the commonest indication of initiation of therapy for shock. Hence, many studies have used hypotension as a reference standard to evaluate the performance of other measures. However, blood pressure alone is an inadequate marker of tissue perfusion [5]. Although, normative values have been suggested, evidence lacks about the threshold below which treatment should be started or the blood pressure values that should be targeted while titrating the treatment. There is a lack of agreement on the blood pressure levels below which cerebral auto-regulation fails or reduced end-organ perfusion occurs. Various therapeutic thresholds suggested include mean blood pressure lower than gestation at birth plus postnatal age, mean blood pressure lower than 30 mm Hg, and mean blood pressure lower than 5th percentile [6]. Uncertainty also prevails regarding the association between treatment of low blood pressure (especially in the first 24-48 hours) and adverse outcome. Non-invasive blood pressure level is dependent on cuff length and width, and the infant's level of alertness, resulting in large inter- and intra-patient varia-tion. Relying only on blood pressure can lead to under-treatment or over treatment.

Other measures suggested to measure tissue perfusion include cardiac output, superior vena cava (SVC) flow and tissue oxygen saturation or oxygen extraction (e.g., cerebral) measured by near infra-red spectroscopy (NIRS) [5,7,8]. However, each of these have their own challenges. Cardiac output in first few days after birth is influenced by presence of PDA and left ventricular output can overestimate the systemic blood flow by upto 200%. SVC flow is not affected by presence of PDA and has been shown to be a better predictor of the development of intraventricular hemorrhage and adverse neurodevelopment outcome [5,9]. However, its routine bedside application is challenged by need of technical expertise and large inter-operator variability. Direct measurement of tissue oxygenation status is promising but targeting therapy to achieve 'normal' tissue oxygenation has not led to improvement in clinical outcomes [10].

Given the current status of evidence, neonates at risk of shock should continue to monitored using multiple complementary measures. Abnormal values of more than one measure and trend over time are more important than any single measure.

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INVITED COMMENTARY

Do We Have Enough Evidence to Lower the Urinary Bacterial Colony Counts for the Diagnosis of Urinary Tract Infection in Children?

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Urinary tract infection (UTI) is one of the commonest bacterial infections in childhood, affecting almost 2% boys and 7-8% girls in the first seven years of life [1]. Almost a third of these children would experience recurrence of UTI during childhood; hence, these patients require further imaging to identify underlying abnormality of urinary tract. UTIs may lead to post-infectious kidney scarring, subsequently causing proteinuria and hypertension. It is crucial to diagnose UTI quickly and appropriately to initiate prompt antibiotic therapy within 72 hours of onset of fever to reduce risk of kidney scarring [2]. However, it is also important to avoid over diagnosing UTI as it may increases antibiotic misuse. Overdiagnosis of UTI also exposes children to unnecessary investigations, increasing the cost and burden of healthcare.

Diagnosis of UTI in children, especially infants, can be problematic due to non-specific clinical features and difficulty in collecting urine. Many International guidelines recommend diagnosing UTI based on significant growth of bacteria in urine culture in the appropriate clinical context [4,5]. The threshold for positive urine culture is based on the assumption that it discriminates between true urine infection from false positive infection, and is chiefly extrapolated from studies performed in the adult population [6]. Since many uropathogens are also present in periurethral area and gut, collection of urine by clean catch and catheter is always fraught with risk of contamination.

While most recommendations agree on the cutoff for urine sample collected by suprapubic aspiration as 10^3 CFU/mL, the specific cutoff for defining positive culture by clean catch and catheter specimen remains controversial. Presently, the most commonly used threshold for positive bacterial colony count (>10^5 CFU/mL) was derived from studies by Kass and colleagues based on urine collected by non-invasive methods [6]. Even at that time, authors had stated that this specific cutoff would results in missing some patients with true UTI. Over the years, some studies have challenged this specific cutoff in identifying children with true UTI. Overall, review of these studies suggests that almost 10-25% of children with positive bacterial growth (CFU >10^3/mL) in urine sample collected by suprapubic aspiration had lower bacterial count (<10^5 CFU/mL) on simultaneously collected urine by mid-stream clean catch [7-9]. Most of these studies included children less than 2 years of age. Growth of bacteria in urine is affected by incubation period in bladder, transportation of sample, and type of culture media used in laboratory. Short incubation period in infants due to frequent voiding is one of the factors reported to contribute to lower bacterial CFUs.

In this issue of the Journal, Nyayadhish and colleagues [10] compared the characteristic of patients between two group of children with low counts (10^{4-5} CFU/mL) and those with counts >10^5 CFU/mL. Authors observed that 9 (4.2%) children had low bacterial CFUs and there was no significant difference in parameters between two groups except the antibiotic treatment rates and *E.coli* growth in urine [10]. The follow-up findings of the children in lower bacterial CFUs groups who did not receive antibiotics would be of interest. As these observations will provide us the clue whether culture in these children becomes sterile without antibiotic therapy. The authors [10] have done a commendable job in carrying out this prospective study and reporting that using conventional cutoff for clean catch and catheter urine sample may result in missing few children with true UTI. Based on conclusion from present study, we may be missing one in nine children with underlying abnormality of urinary tract.

While the authors conclude that nine (4.2%) children were diagnosed to have UTI if lower bacterial CFUs is considered but we do not have gold standard test to say with conviction that all of these children have true UTI. Previous studies have used >10^3 CFU/mL in urine sample collected by suprapubic aspiration as a surrogate for gold standard test. While lower CFUs did identify one patient

with abnormal tract but it would also increase the use of antibiotics in children who may not have true UTI. However, in the present study [10], authors left the decision of antibiotic therapy to the primary physician; hence, four out of nine patients with lower bacterial CFUs received antibiotics. Going forward, the ideal study design to answer this question would be to randomize children with lower CFUs in urine culture into treatment with antibiotics or placebo groups and compare the resolution of symptoms, repeat urine culture and kidney scarring on late-phase DMSA.

To conclude, a lower cutoff of bacterial CFUs to diagnose UTI can be considered in children, especially the infants, where shorter incubation period may not allow enough CFU in urine culture. However, one should not rely on a specific precise cutoff of bacterial growth alone in urine; rather, clinicians should use their wisdom keeping the clinical context in mind to make a diagnosis of UTI even with lower bacterial CFUs than that used conventionally.

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INVITED COMMENTARY

Pediatric COVID-19 and MIS-C – Lessons Learnt and the Way Forward

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread worldwide leading to innumerable deaths [1,2]. Children are just as likely as adults to get infected and the most common source of infection in children is through close contact [3]. Epidemiology of pediatric COVID-19 has been variable in the literature but overall children account only for approximately 10% of patients diagnosed with COVID-19 infection [3].Of these, approximately one-third were estimated to have occurred in South Asia (including India). Most children are; however, asymptomatic or have mild symptoms [4]. Severe disease may be seen in infants or children who have other comorbidities or underlying conditions [4,5]. There is a knowledge gap concerning this low sensitivity to COVID-19 in children and its mild presentation in the pediatric population. Many hypotheses have been put forward ranging from the possibility of children having an immune response to the virus lesser than the adults to viral interference in the respiratory tract of young children, leading to a lower SARS-CoV-2 viral load [4]. The different expression of the angiotensin converting enzyme 2 receptor (the receptor for SARS-CoV-2) in the respiratory tracts of children and adults has also been attributed to the less severe disease in children [4]. The other possibilities include pre-existing cross-reactive antibody, a protective off-target effect of live vaccines, developmental differences in adaptive immune responses in children, and age-related differences in the nasopharyngeal microbiome.

Fever, cough, nausea, vomiting, diarrhea, skin rashes, fatigue, headaches, and nasal congestion are the common clinical features [5]. Whilst primary infection with SARS-CoV-2 has been relatively benign in children, a small proportion develop multisystem inflammatory syndrome in children (MIS-C) [6].

MIS-C shares the clinical and laboratory features with Kawasaki disease (KD) as both diseases are characterized by systemic inflammation and vascular injury, possibly leading to coronary artery lesions [6]. Therefore as in KD, prompt recognition in MIS-C is important to halt the inflammation and organ damage, especially cardiac failure, hypotension and/or shock. Cardiovascular abnormalities (e.g., heart failure, arrhythmias, myocarditis, pericarditis, cardiogenic shock, pulmonary embolism, ST elevation myocardial infarction, coronary artery aneurysms) have been reported in various case reposts and series [7]. In this issue of this journal, Tomar, et al. [7] have reported various cardiovascular findings in children with MIS-C that included coronary vasculopathy, pericardial effusion, valvular regurgitation, ventricular dysfunction, diastolic flow reversal in aorta, pulmonary hypertension, bradycardia and intracardiac thrombus. They also report a survival rate of 99%, which is in contrast to the 11.7% mortality reported by Poovalhagi, et al. [8] from another tertiary care pediatric center in India,which is also one of the research papers in this issue. However, Poovalhagi, et al. [8] reported acute kidney injury, HLH, need for ventilation and mitral regurgitation as the significant risk factors for mortality in their cohort of children with MIS-C and no mortality was encountered among children without Kawasaki or shock phenotype. The differences in mortality in two different centers in India due to MIS-C might have been due to the differences in the demographic profile and time frame of the study periods.

Neurologic manifestations have been described in children hospitalized with acute COVID-19 and includes febrile and non-febrile seizures, stroke, central nervous system infection/demyelination, Guillain-Barré syndrome/ variants, acute fulminant cerebral edema, headache, weakness, anosmia, ageusia, and delirium. Seizures in febrile children with COVID-19 appear to be more common with the Omicron variant than with earlier variants [9]. Neurological symptoms in children with MIS-C are elaborately described by Herini, et al. [10]

from Indonesia, where the authors report 24% of children with MIS-C having acute neurologic symptoms, thus suggesting the need to consider MIS-C as a diagnostic possibility in any child with acute neurological presentation and fever in this post pandemic era.

There is currently no standardized treatment regimen for MIS-C and supportive treatment is the mainstay. The management of MIS-C is very similar to KD. Various treatment strategies have been used by different centers, but mostly the treatment includes intravenous immunoglobulins, various immune modulators, steroids, aspirin, and anticoagulant therapies [6]. Although previous studies have shown that children with MIS-C receiving both IVIG and steroids had better course than IVIG alone, the clinical evidence of benefit is yet to be established. In a recently published study, Welzel, et al. [11] concluded that recovery rates, including occurrence and resolution of coronary artery aneurysms, were similar for primary treatment with intravenous immunoglobulin when compared to glucocorticoids or intravenous immunoglobulin plus glucocorticoids. Therefore, initial treatment with glucocorticoids appears to be a safe alternative to immunoglobulin or combined therapy, and might be advantageous in view of the cost and limited availability of intravenous immunoglobulin in many countries [12].

India has been significantly impacted by the COVID-19 epidemic, and children are not exempt from its impacts. Around 80 million COVID-19 cases have been reported in India as of March, 2023. Although, adults have been the majority of the cases, children have also been affected [13]. However, it is not possible to determine the extent of infection among children, due to lack of available data. The risk of COVID-19 in children is influenced by a number of factors, including population density, poverty, and access to healthcare [13,14]. Children living in crowded urban areas or in poverty may have been at higher risk of contracting the virus due to difficulties in social distancing and access to proper hygiene facilities. Many asymptomatic children were unlikely to be tested and therefore may not have been reported. Furthermore, co-infection with other microorganisms, such as virus, bacteria and fungi, act as significant challenge in diagnosis, treatment and prognosis of COVID-19 children in tropical country like India. Likewise, the epidemiology of MIS-C in India is still not fully understood, as the condition is relatively rare and cases may be underreported due to limited testing and healthcare access in some areas. Nevertheless, the incidence and severity of MIS-C has declined during the Omicron wave of the COVID-19 pandemic as compared with earlier waves; although, the precise reason for this remains obscure. However, there has been a sudden surge in cases of hand foot mouth disease in both children and adults, as reported by Mohta et al. [15] during the ongoing COVID-19 pandemic. Similar reports have emerged from others places in India during the last three months that describe a sudden surge of H3N2 and adenoviral infections; although, the relationship between COVID-19 and these viral infections is unclear and not clearly understood [16].

There is still uncertainty regarding the future course of COVID-19 and MIS-C in children, and much will rely on how the pandemic develops over time. There have been advancements in both vaccine and therapy, but there are still numerous questions about the long-term consequences of the virus and how it affects children [14].The availability and efficacy of COVID vaccines in children as well as the ongoing clinical trials exploring the safety and efficacy of additional vaccine candidates may influence COVID-19 and MIS-C in this population, with a possibility that these conditions will be reduced. Vaccines have been shown to be effective in reducing the risk of illness, hospitalization, and death from COVID-19 in children. However, the virus' ability to evolve into new forms may be a cause for concern. Even while the present vaccines are effective against the current variants, it is likely that other variants that are more contagious or severe may emerge, which may put children at higher risk of developing COVID-19 and MIS-C, necessitating the development of new prevention and treatment methods. Research on the causes and remedies of MIS-C may also be ongoing. Even while the illness is still not fully understood, future research could provide additional details on its underlying mechanisms and point to potential treatments.

In conclusion, there are important lessons learned from pediatric COVID-19, which include the pattern of infections; importance of timely and accurate diagnosis; the need for more pediatric-specific research into the epidemiology, diagnosis and treatment, and understanding the longterm effects of COVID-19 and MIS-C in children. In addition, there is a definite need for good clinical trials for appropriate use of steroids in viral infections such as dengue, based on the proven benefits of steroids in severe COVID and MIS-C.

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PERSPECTIVE

Point-of-Care Ultrasound in Neonatology in India: The Way Forward

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The clinician-performed point-of-care ultrasound (POCUS) is a useful tool, and its scope includes bedside assessment of pulmonary (e.g., pneumothorax, pleural effusion), cardiac (e.g., pulmonary hypertension, ductus arteriosus), gastrointestinal (e.g., necrotising enterocolitis), and intracranial (e.g., intraventricular hemorrhage, cerebral blood flow velocities) pathologies, procedural guidance and rapid assessment of etiologies of acute clinical deterioration (e.g., pneumothorax, poor cardiac contractility, intraventricular hemorrhage). Despite its potential to improve patient care, a curriculum and a structured program for POCUS training is lacking in India. Homogenous approach to training and ongoing quality assurance is essential to optimize benefits of POCUS as an effective tool in clinical practice. The training needs, the legal and infrastructural barriers to successful implementation of POCUS, and strategies to implement the program at the national level are discussed.

Keywords: *Assessment, Intraventicular hemorrhage, Management, Pneumothorax.*

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Point-of-care ultrasound (POCUS) has been extensively used in adult medicine but is now gaining acceptance and recognition in neonatology. While neonatologist-performed echocardiography has been at the forefront of the POCUS in neonatology, evidence has demonstrated its utility far beyond the cardiac ultrasonography (USG). POCUS augments clinical decision making, and aids in the diagnosis by providing rapid and real time information, and also improves procedural success [1]. Critically ill premature infants often cannot be safely transported out of the neonatal intensive care unit (NICU) for external radiology studies. POCUS is performed at the infant's bedside, it is radiation free, and typically can be done faster, facilitating prompt diagnosis and intervention. Experts around the world are convinced about its bedside utility, and international evidence-based guidelines are now available for use in neonatology [2,3].

Traditionally, USG is interpreted by radiologists and cardiologists whereas POCUS is clinician-performed and interpreted, thereby playing an important role in timely management of many conditions. The aim of POCUS is not to replace cardiology/radiology services but to complement it. Low- and middle-income countries (LMICs) like India have a shortage of specialized workforce, especially in tier II and tier III cities, where a major share of sick neonates are cared for. The World Health Organization (WHO) recommends that "task shifting" may be a useful tool in this context, whereby specific tasks are moved, where appropriate, from specialized health workers to health workers with shorter training and fewer qualifications, in order to make more efficient use of the available human resources for health [4]. Task shifting might mitigate medical inequity to some extent in LMICs. It is important to note that it does not mean disconnecting from speciality services. POCUS-trained clinicians will still have the backup from these experts at any given point of time. However, to make task shifting successful, efforts should be made to increase the number of health workers trained in POCUS. While there has been a rapid pace of adoption of each of the individual components of POCUS in India through workshops and modules, held at regional and national levels, it is also important to determine the adequacy of the training imparted and skill gained, so that patient care is not adversely affected by its injudicious or inadequate application. Creating a POCUS curriculum and a training program at a national level, which assures quality, and includes a certifying process, would be the pragmatic way forward.

UTILITY OF POCUS

POCUS encompasses the widespread use of bedside ultrasound as a diagnostic, therapeutic, and procedural tool (**Table I**). Role of cardiac POCUS in diagnosis and treatment of patent ductus arteriosus and pulmonary hypertension is well known. However, diagnostic echocardio-

Table I Point-of-Care Ultrasound in Neonatology: Scope of Practice

Site/procedure	*Utility for the neonatologist*	*Benefits/advantages of ultrasound*	*Comment*
Utility as a diagnostic tool			
Cardiac ultrasound	Preload assessment, fluid responsiveness. Qualitative and semi-quantitative cardiac function assessment. Diagnosis of pericardial effusion PDA assessment and treatment monitoring Pulmonary hypertension assessment and management monitoring. Recognition of abnormal cardiac anatomy, particularly duct dependant lesions.	Rapid determination of hemodynamics with serial functional assessments. Role in PDA, acute/chronic pulmonary hypertension assessment, ventricular function.	'Difficult to acquire' POCUS skill. Supplements, cannot replace clinical assessment, hemodynamic monitoring. Need for improved standardization and quality assurance. Early referral to pediatric cardiologist for structural evaluation of cardiac anatomy is warranted.
Cranial ultrasound	Estimation of cerebral blood flow velocities GMH/IVH Cerebral midline shift Hydrocephalus	Calculation of RI and PI Diagnosis of IVH useful in a 'crashing neonate' in the NICU, and may aid in the redirection of care Multiple indices are in use to monitor the size of hydrocephalus	RI and PI are useful measurements for non-invasive monitoring of ICP and prognostication in HIE Calcifications, ischemic changes, hydrocephalus and periventricular leukomalacia may be assessed by the clinician, but requires confirmation by the radiologist
Lung ultrasound	Respiratory distress syndrome TTN Pneumonias Air leaks Pleural effusion Lung edema	Can guide decision making for administration of surfactant In a 'crashing neonate': early detection of pneumothorax/ pleural effusion Aids in thoracocentesis	Rapid learning curve Reduces the number of *X*-rays and associated ionizing radiation
Abdominal ultrasound	Bowel viability assessment Bladder assessment for anuria or urinary retention	NEC: assessment of bowel peristalsis, vascular perfusion, pneumatosis intestinalis, portal venous gas, bowel-wall thickness, free fluid. May predict surgical intervention May guide peritoneal fluid aspiration	Prominent artefact may be produced by ventilators mimicking NEC and unstable infants may not tolerate the manipulation. Advantages of US over *X*-ray in NEC include real-time assessment of the bowel, earlier diagnosis and earlier identification of ominous findings. If anuric, assessment can suggest if there is urine in the bladder, requiring a urinary catheter placement.
Utility as a tool to aid in procedures			
Central line tip placement and localization	Placement of umbilical lines, PICC catheters, including lines through internal jugular, subclavian, femoral veins	Catheter tip localization can be tracked, as catheters can migrate after placement	Decreases incidence of tip malposition Time to confirm PICC line position by US is lesser compared to radiography
ETT localization	US shown to be useful in ascertaining ETT tip position	US appears comparable to *X*-rays when determining ETT position in this population.	POCUS more easily available than *X*-rays and is without radiation. A useful tool during transport.
Lumbar puncture	Reduction in number of traumatic lumbar punctures	Good resolution of image, lack of ionizing radiation and poten-	In neonates, incompletely ossified spinous processes and minimal fat

contd....

Table I *contd. from pre-page*

Site/procedure	*Utility for the neonatologist*	*Benefits/advantages of ultrasound*	*Comment*
		tial for real time guidance	aids in locating the space more easily, compared to older children/ adults.
Suprapubic tap	Aids bladder visualization for suprapubic urine collection for cultures	Improved acquisition of urine. Number of needle insertions decreased; increased amount of urine obtained	Suprapubic urine collection through bladder aspiration ideal
Pericardiocentesis and thoracocentesis	May be useful in delivery room for neonates with hydrops or congenital pleural effusion	Useful tool in a crashing neonate with pericardial effusion.	Improves success and decreases complications associated with the procedures.

GMH/IVH:germinal matrix hemorrhage/intra ventricular hemorrhage; ICP:intracranial pressure; TTN:transient tachypnea of newborn; US:ultrasound; NEC:necrotizing enterocolitis; PICC:peripherally inserted central catheter; ETT: endotracheal tube; RI:resistive index; PI:pulsatility index; ICP:intracranial pressure; HIE:hypoxic ischemic encephalopathy; POCUS:point of care ultrasound.

graphy must be differentiated from 'cardiac POCUS,' wherein, the former is cardiologist-performed to assess the structural anatomy of the heart. Conversely, cardiac POCUS is clinician driven, to assess the cardiac function [5]. In the Indian scenario, there is a staggering shortfall of pediatric cardiology services [6,7], potentially impacting neonatal cardiac care, particularly in tier II and III cities, and we endorse training of clinicians, not only in cardiac POCUS, but also in early recognition of structural heart disease so that appropriate referral to pediatric cardiac services can be done.

Head USG is a useful bedside tool to diagnose intraventricular bleeds in a crashing neonate, when radiology services are not immediately available. Similarly, another time constrained bedside assessment is cerebral hemodynamics in hypoxic ischemic encephalopathy. The resistive index of the middle or anterior cerebral artery may have prognostic value if conducted before therapeutic hypothermia is initiated [8]. Lung ultrasound (LUS) has been used to predict surfactant need, diagnose pneumothorax, pneumonia, transient tachypnea of the newborn and pleural effusion [1,3]. Learning bedside LUS is relatively easy and can be very rewarding in diagnosing tension pneumothorax in a crashing neonate. Gut ultrasound is primarily used to evaluate necrotizing enterocolitis and may be used to predict the need for surgical intervention before the intestine perforates [9,10]. POCUS improves success rate in procedures like central line placement, bladder tapping [11] and lumbar puncture [12,13]. POCUS is also useful in ascertaining central line [14,15] and endotracheal tube position [16] (**Table I**).

An area of increasing utility of POCUS, impacting neonatal outcomes, is in a 'crashing' neonate. An International working group of experts in POCUS have designed a 'Crashing infant protocol' [2] incorporating lung, cardiac, cranial, abdominal, and central line POCUS to assess the underlying mechanism of deterioration (e.g., pneumothorax, pleural effusion, cardiac contractility, cardiac filling, cardiac tamponade, pulmonary hypertension, congenital heart disease, gut injury, intracranial bleed and mispositioned central lines). Similarly, it has been suggested that in the following critical situations, POCUS would play a useful and critical role: *i*) Infants unresponsive in a neonatal resuscitation protocol, *ii*) Unexplained acute respiratory failure or worsening hypoxemia unresponsive to usual respiratory support, *iii*) Unexplained acute circulatory shock or worsening hypotension, lactic acidosis, oliguria, unresponsive to volume expansion, and vasopressors, and *iv*) Unexplained drop in hemoglobin >20% in 24 hours with suspicion of acute bleeding [1].

If USG is, indeed, helpful in safely undertaking a procedure, the greater risk is likely in not learning and employing POCUS during the performance of these procedures. It is beyond the scope of this article to elaborate on the methodology and benefits of each of the POCUS components.

STATUS OF POCUS IN INDIA

A recent survey on uptake of POCUS in Indian neonatal intensive care unit reported an impressive 72% of the respondents having access to POCUS [17]. Only 26% and 40% of the units had round the clock availability of pediatric cardiology and radiology services, respectively. In this context, bedside POCUS trained clinicians might play a key role in rendering emergent imaging services. Though, a good percentage of neonatologists had access to POCUS in India, only 25% had underwent a structured training. Interestingly, about 25% of the participants had

self-learned, with the help of educational materials. The lack of adequate training might adversely affect the providers, the patients, and the institutions. A useful technology should not become hazardous because of its use or lack of use. The major reason for lack of access to POCUS has been non-availability of trained personnel, and the dogmatic application of the pre-conception and pre-natal diagnostic techniques (PC-PNDT) Act [17].

Barriers to Usage

Absence of a comprehensive training program: A POCUS clinician needs to not only performs USG in a standardized manner, but also interpret the study, integrate this information into the clinical setting, and monitor changes associated with the intervention. This level of acumen can only be achieved with a dedicated and structured training program, which is currently lacking in India. Though workshops (*http://iapneocon2023jaipur.com/themes/assets/pdf/workshop/SCAN%20Workshop.pdf*), e-learning modules (*https://www.drpradeepsuryawanshi.com/neopocus-course/*), and classroom teaching exposes clinicians to POCUS, it does not translate into expertise. In addition, the number of experts and centers that run structured POCUS programs are limited. Absence of a formal curriculum and accreditation process limits its utility. Time constraint on the part of trainees and teachers, suboptimal machine maintenance and repair, inadequate access to supervision and review of the scans, and inability to retain previously learned skills are hindrances to successful implementation of a program.

Legal considerations: Legal considerations may also impact successful implementation of POCUS. While the PC-PNDT Act plays a significant role in curbing female feticide in India, it possibly might act as a deterrent to practice POCUS, as even the smallest error in fulfilling the requirements of the Act, is viewed seriously by the authorities [18]. Though, the use of ultrasound in neonatal transport and retrieval is feasible and useful [19,20], the PC-PNDT act precludes use of portable machines. Health practitioners may perform POCUS with little or no training, and without formal accreditation, leading authorities to call for reform and regulation of its use. The study of a major legal database from a developed country suggests that POCUS use and interpretation is not a significant cause of lawsuits against neonatologists [21]. In fact, failure to perform POCUS might be a greater medicolegal issue [22]. Any clinician practicing medicine is prone to misdiagnosis and its medicolegal implications. Development of a robust clinical governance, adequate training, appropriate documentation and record keeping might mitigate such risks.

Infrastructural support: It is important to note that to run a successful POCUS program, clinicians should have access to a dedicated ultrasound machine, power backup, and data storage facility, which needs resource inputs. Many neonatal centers in India are privately owned, where 'cost effectiveness' could be a major consideration. Cost would also be a major consideration in public hospitals.

Support of speciality services: We suggest that pediatric cardiology and radiology services should be part of the program, even if they support it remotely. Limited availability of these services, and resistance from the specialities are important barriers to the successful implementation of this program.

THE WAY FORWARD

There are only a few neonatal POCUS guidelines [2,3] and accredited training programs [23] around the world. Few other medical subspecialties have structured curriculum-based approach to POCUS training (critical care medicine, emergency medicine, obstetrics/gynecology, family practice, and anesthesia) [24-27]. The Australian Society of Ultrasound Medicine (ASUM) runs the neonatology POCUS program (heart, head, lung and abdomen), which includes an online physics course, hospital-based training, completion of basic and advanced training, and logbook requirements. A certification board reviews recommendations for certificate in clinician performed ultrasound and refers to ASUM Council for award. Re-certification occurs at five-yearly intervals [23].

Identifying a core national group comprising of expert neonatologists, radiologists and pediatric cardiologists under the umbrella of a national body (e.g., National Neonatology Forum/Indian Academy of Pediatrics) should be the first step. A proposed design of the POCUS program is depicted in **Fig.1**. A POCUS governance structure should be in place with clearly defined roles. The apex national body should take care of the training, curriculum, liaise with government authorities and do the need assessment. The national body shall define the scope of POCUS practice, its limitations, and guidelines around mandatory consultive service referrals. The regional bodies should do a mentoring role and provide guidance on rules and regulations. The institutional POCUS heads shall look after training and record keeping. Quality assurance is everyone's responsibility.

Need assessment: Newborn diseases are no different in India compared to the rest of the world. However, the prevalence of a higher incidence of pathologies like Gram negative septicemia and intrauterine growth retardation must be factored in while assessing the need for a curriculum. POCUS programs should be aimed at the front level providers in neonatology (practicing neonatologists, neonatal trainees and pediatricians looking after sick neo-

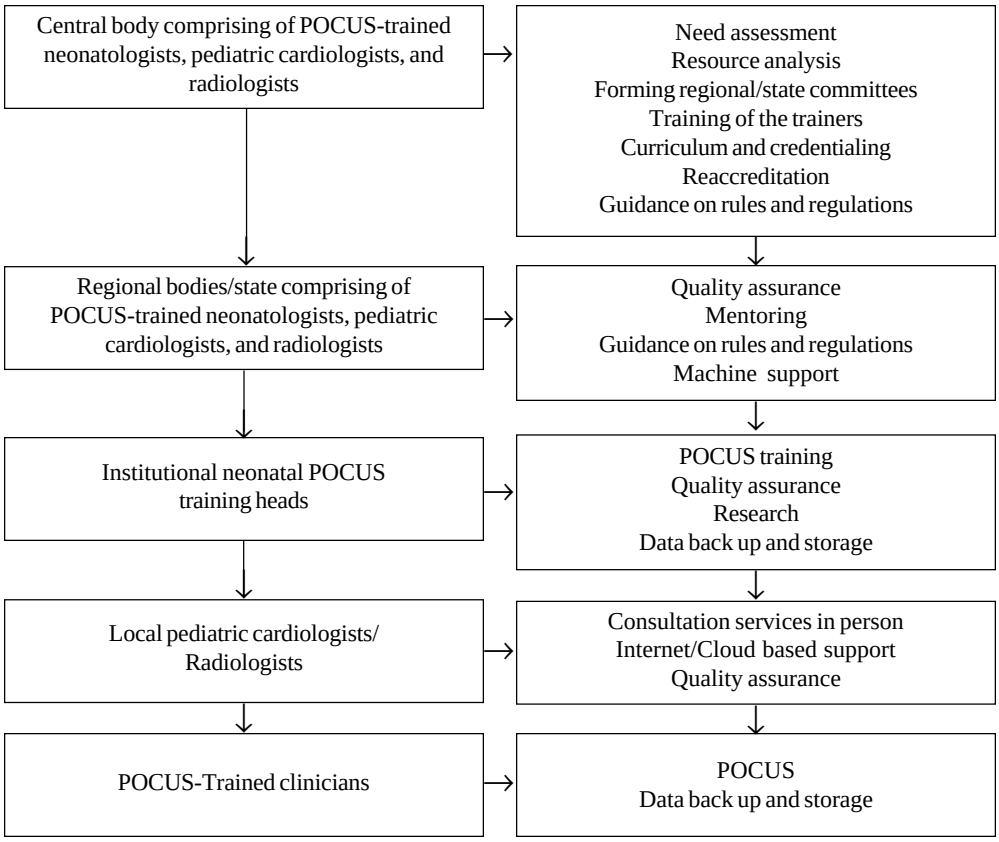

Fig. 1 Proposed design of a point-of-care ultrasound (POCUS) program.

nates). Addition of an ongoing POCUS training, to the neonatal training curriculum might be useful but may overburden the already stretched curriculum. However, it should be noted here that successful implementation has been noted in training programs of other specialities [28,29]. In view of the limited availability of trained faculties and resources, it would be beneficial to start with a targeted core group of potential learners. Potential training centers and infrastructure could be identified by geographical distribution, and financial resources should be considered to run such programs. Incentives to both the trainees and trainers could also be factored in during the planning phase. Post training practice space and resources, mentoring and regulatory requirements need careful deliberation.

Training and curriculum: It must be a longitudinal institute-based training. If trainees are in practice, it is important to secure dedicated time when they will be free from clinical responsibilities and able to concentrate on USG training. Little is known about how much training or hands-on experience is needed to become proficient with POCUS. However, it is important that minimum qualifications appropriate to the performance of each type of examination are prescribed and regulated. A pool of experienced trainers is usually necessary to help with initial training efforts. Though it is ideal to have onsite full-time clinicians as trainers, it may not be feasible all the time and may warrant visiting faculties to run the course. Essential components of the standardized curriculum and credentialing should include ultrasound physics and technical aspects, supervised hands-on/simulation training and completion of a logbook comprising of a certain number of scans. Trainees should have access to videos, images, books, and online materials, as these may otherwise be limited. Stress should be on analyzing and integrating information gained from POCUS with clinical decision making. It will be critically important to depict the scope of practice, and when consultive referral should be man-datory. All the training centers should work in tandem with speciality services like pediatric cardiology and radiology. An exit examination comprising of theory and practical evaluation should be in place to assess competency and safety. Completion of the course should lead to a certification. It is possible that some clinicians may not practice POCUS after certification, and therefore,

limited period certification and re-accreditation at specified intervals could be considered. Program leadership should aim for long term sustainability and attempt to identify potential trainees who would use POCUS regularly and ultimately provide training to their colleagues. POCUS-trained clinicians should maintain a record of their scans for medico-legal reasons. Collaboration with pediatric cardiology/radiology is ideal for periodic review of the studies and interdisciplinary educational activities. Every institution running POCUS program must have radiology/cardiology referral services. If a clinician faces a POCUS-related dilemma, he/she should consult the speciality services either in person or through telemedicine. Telemedicine and cloud-based facilities could be used to facilitate review, if inhouse subspeciality services are not available [30,31]. It should be noted here that telemedicine facilities have been used in India to run retinopathy of prematurity program successfully [32], and could potentially be used successfully here as well.

Machine management: A dedicated USG machine is pivotal, and the most expensive part of the POCUS program. Public sector hospitals should be encouraged to put forward business cases to the authorities or arrange industry sponsors and advise for this could be provided by the coordinating national body. Further, advise on procurement of machines, transducer selection, data storage (internal and external), post sales service, and PC-PNDT recognition could also be provided by the national body.

Quality assurance: Quality assurance is necessary to ascertain operator competence and to ensure patient safety. Quality assurance should be done either by the local/regional experts or by external experts. In the current era, images can be reviewed remotely, and feedback can be given for ongoing safety and quality. The central body can play a constructive role to have quality assurance monitoring system in place.

Misdiagnosis and medicolegal aspects: The risk of misdiagnosis is a real concern, and some of this can be resolved by practicing within the limits of the training, and formulating guidelines about when consultative referral should be mandatory. We believe a structured training and regular accreditation process will also be useful in this context. It is a good practice to disclose the limitations of POCUS to the patients and explain the fact that it is not a replacement for cardiology/radiology services. Integration of policies with the PC-PNDT Act could further help in overcoming medico-legal barriers.

CONCLUSION

POCUS is a useful adjunct to clinical examination and has multiple applications. It is for the policy makers to consider a formal incorporation into neonatology. This would enhance competency of the frontline neonatal physicians, and ensure quality, while undertaking care of the sickest and smallest neonates. This could, eventually, translate into improved outcomes at a national level.

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RESEARCH PAPER

Development and Validation of a Bedside Dengue Severity Score for Predicting Severe Dengue in Children

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Objective: To develop and validate a bedside dengue severity score in children less than 12 years for predicting severe dengue disease.

Methods: We carried out an analysis of data on the clinical and laboratory parameters of patients with confirmed dengue, hospitalized in October, 2019 at our center. A comprehensive patient's score was developed. Predictive models for severity were built using a forward step-wise method. This model was validated on the data of 312 children with dengue admitted during September- October, 2021.

Results: Severe dengue was predicted by the dengue severity score with a sensitivity of 86.75% (95% CI 77.52%-93.19%), specificity of 98.25% (95% CI 95.56-99.52%), a positive predictive value of 95.34% (95% CI 92.18%-97.26%) and a negative predictive value of 94.74% (95% CI 87.16%-97.95%). The overall predictive accuracy was 95.2% (95% CI 92.19%-97.28%).

Conclusion: The proposed bedside dengue severity scoring system was found to have good validity. Validating the score in different settings and patient populations is suggested.

Keywords: *Management, Mortality, Obesity, Outcome, Prognosis*.

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Dengue fever is the most prevalent human arboviral infection and a major public health issue in the tropics [1]. In 2021, the National Vector Borne Disease Control Program (NVBDCP) reported 1,93,254 laboratory-confirmed cases of dengue in the country [2]. With monsoon epidemics overwhelming our hospitals, it is crucial to identify the risk factors for severe dengue. By assessing the validity of such predictors, operational solutions can be established, thereby, reducing the burden on the health care system [3].

Previously available dengue severity scores, proposed from other countries, involve laborious calculations. With modest specificity and sensitivity, these scores rely on extensive laboratory parameters [4]. Derived scores that aim to classify patients into different categories, have overlapping scores amongst the severity categories, thereby limiting their clinical applicability [5]. There is tremendous diversity in dengue endemicity in different parts of the world and even within the same country [6].

We, herein, report the development and validation of a bedside dengue severity score in children less than 12 years, for prediction of severe dengue disease.

METHODS

A model scoring system was built for predicting severe dengue using data from hospital records for 125 children who were admitted with dengue in the month of October, 2019. The derived score was deployed in children with dengue prospectively for validation. Based on total number of dengue cases admitted during peak dengue season (September, 2019 to January, 2021), an initial sample size of 380 was determined. Pilot research was conducted using 10% of this sample size, and the findings of the pilot research were used to estimate the actual sample size for the study. Using G*Power software (version 3.1.9.2), a power of 80%, a level of significance (*P* value) set at 5%, a confidence interval of 95% and prevalence data obtained from the pilot study (5.1%), the sample size was estimated to be 312 for the final study group.

Invited Commentary: Pages 341-42.

The study was approved by the institutional ethics committee of our institute. For the model prediction and validation, the same inclusion and exclusion criteria were used. The study population included children admitted in the inpatient wards of the Institute of Child Heath,

Chennai, with fever and positive NS1 Ag and/or IgM Elisa dengue in the age group of 2 month - 12 year. Co-infection with other tropical diseases, and fever with any identified focus of infection were excluded. Further, for score validation, the children were enrolled in the febrile phase.

Fourteen risk factors for severe dengue were taken from the National guidelines on dengue (2020) [7] to develop the severity score (**Web Box I)**. Obesity, which is claimed to be positively associated with severe dengue [8], was also included. Narrow pulse pressure (≤20 mm /Hg) in the absence of circulatory shock is indicative for fluid leak from the intravascular compartment. Pulse pressure is also considered a reliable indicator of fluid responsiveness [9]. Hence, narrow pulse pressure in the absence of shock was considered as one of the possible risk factors for severe dengue.

Severe dengue was defined by the revised World Health Organization (WHO) 2009 disease classification [10] and NVBDCP 2020 criteria (**Web Box II**) [7]. Disease outcome was primarily classified as severe and non-severe.

Statistical analysis: Data were analyzed using IBM SPSS version 20.0 (IBM Corp). Binary logistic regression was used to develop the prediction severity model. A forward stepwise method was used by the model in three steps to identify three variables as significantly predicting the dependent variable. The Nagelkerke square was used to quantify how much the predicted variables influenced the result. Hosmer-Lemeshow test was used to determine the fitness of the regression model. Using Canonical discriminant function coefficient, the ability of the identified (significantly associated) risk factors to effectively discriminate between severe and non-severe dengue were calculated. Linear discriminant analysis was used for the estimation of coefficients as the risk factors are not completely independent of each other and a predictive score was developed. The means of the discriminant function was given by Functions at group centroids and the score value necessary to differentiate between severe and non-severe dengue were given. Validity of the constructed model was deployed on 2021 data; sensitivity, specificity and predictive accuracy were calculated.

RESULTS

With forward stepwise regression, three variables were identified as significantly predicting the disease outcome viz., the presence of mucosal bleed [OR (95% CI) 29.81 (6.49-136.85); *P*<0.001], narrow pulse pressure [OR (95%CI) 287.48 (80.27-1029.62); P<0.001] and third space fluid accumulation [OR (95% CI) 6.42 (2.11-19.48); *P*= 0.001]. Other risk factors studied were not significantly associated with severe disease in the 125 children used for score development. Nagelkerke R Square showed that these three predictors influenced dengue severity by 80.8%.

Hosmer-Lemeshow test assessed the goodness of fit of the model. In Step 3, the model strengthened and became significant (*P*=0.026), when three variables of good significance were added (narrow pulse pressure, minor mucosal bleed and third space fluid accumulation). Using Canonical discriminant function for all the three variables, the equation for scoring was calculated as follows:

Bedside Dengue Severity Score = -1.297+ 4.234 (narrow pulse pressure) + 1.284 (mucosal bleed) + 0.489 (third space fluid loss)

In the score, -1.297 is the constant and 4.234, 1.284, and 0.489 were the coefficient of narrow pulse pressure, mucosal bleed and third space fluid loss, respectively. The score was calculated, by applying the variables in the formula as number 1 and 0 for presence and absence, respectively. From functions at the group centroid, values closer to -1.056 were predicted to devlop non severe dengue and values closer to 2.913 were proposed to develop severe dengue; the midpoint being 0.9285.

Table I Characteristics of Children With Dengue Fever (*N*=312)

Characteristics	*Value*
Age (y)[a]	6.4 (3.44)
Infants	19 (6)
Obese children	12 (3.8)
Immunodeficient children	9 (2.8)
Chronic illness	7 (2.2)
Bleeding tendency	1 (0.3)
Abdominal tenderness	111 (35.5)
Hepatomegaly	53 (16.9)
Persistent vomiting	148 (47.4)
Lethargy	92 (29.4)
Narrow pulse pressure	73 (23.4)
Hematocrit rise	56 (17.9)
Rapid fall in platelets	39 (12.5)
Minor mucosal bleed	20 (6.4)
Third space fluid loss	122 (39.1)
Dengue severity	
Mild dengue	110 (35.5)
Dengue with warning signs	119 (38.14)
Severe dengue	83 (26.6)
Dengue deaths	8 (2.5)

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

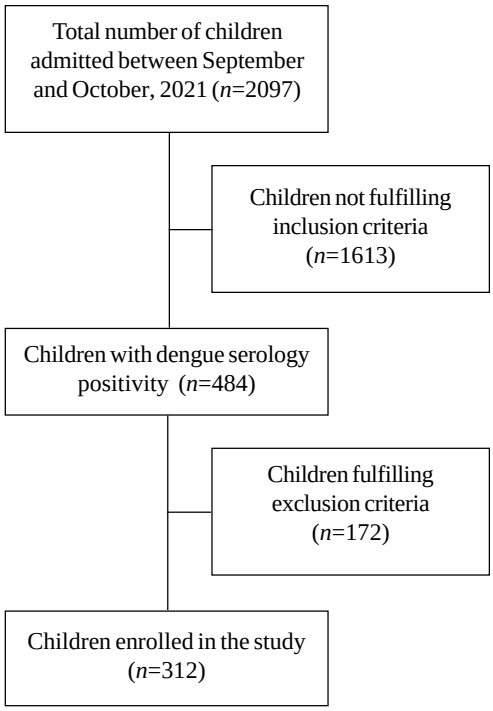


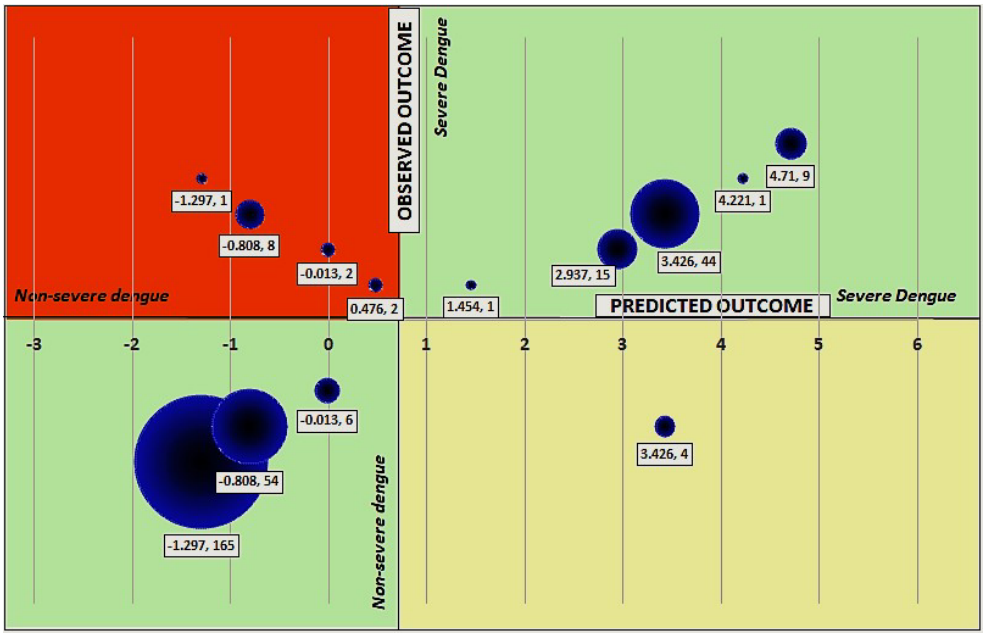
Fig.1 *Flow of patients in the study.*

Table II Diagnostic Performance of the Bedside Dengue Severity Scoring System in Children

Measure	*Value (95% CI)*
Sensitivity	86.75% (77.52-93.19)
Specificity	98.25% (95.59-99.52)
Positive predictive value	95.34% (92.18-97.26)
Negative predictive value	94.74% (87.16-97.95)
Accuracy	95.19% (92.19-97.28)

The score was validated by applying it on the data collected in the year 2021. The clinical characteristics of the 312 children (62.8% boys) enrolled is given in **Table I** and the flow of patients in the study for validation is given in **Fig. 1**. There was no loss to follow-up and no patient was discharged against medical advice in the cohort. Mean (SD) age was 6.4 (3.44) years.

Fig. 2 shows the bubble chart graph illustrating outcome of study sample. Non-severe dengue was predicted by the score in 236 children, and was observed in 225 children; whereas, severe dengue was predicted in 78 and observed in 72 children. The score identified severe dengue with 86.7% sensitivity and 98.25% specificity, and 95.2% overall predictive accuracy (**Table II**).



The label beneath each bubble reads the score, followed by the number of children with that score, from left to right. The size of the bubble is proportionate to the number of children with the specific score. The X-axis represents the outcome predicted by the score as severe and non-severe dengue with values closer to 2.913 being severe and values closer to -1.056 being non-severe dengue with the midpoint being 0.9285. The Y-axis depicts the observed disease outcome, categorized as severe or non-severe. The green quadrants (left lower and right upper) reflect those cases in which the predicted outcome matched the observed outcome. The orange (left upper) quadrant shows those cases where the predicted outcome was non-severe but was observed to have severe dengue. The yellow (right lower) quadrant displays the cases where the cases were predicted to have severe dengue but were observed to have non-severe dengue.

Fig. 2 *Bubble chart graph illustrates the outcome of the study sample.*

WHAT IS ALREADY KNOWN?

- Co morbidities and presence of warning signs predispose to severe dengue, but there is no operational tool to predict the severity.

WHAT THIS STUDY ADDS?

- A scoring system is provided that can be generated rapidly at the bedside and can predict severe dengue with good accuracy.

DISCUSSION

In this study, we devised a severity score that could be reliably performed at the bedside with three validated risk factors. Narrow pulse pressure in the absence of circulatory shock was considered as an important predictor of severe dengue, as it may be an early marker of reduced effective circulating volume. The existing criteria for admission, diagnosis, and discharge were not altered. If the values of 0 and 1 are substituted in the formula, for the presence or absence of narrow pulse pressure, mucosal bleed and third space fluid loss, the score can be calculated manually in less than a minute.

Several researchers have devised scoring system to predict dengue severity, but most of them require extensive investigatory backup. The score developed by Phakounthong, et al. [13] from Cambodia had modest sensitivity and specificity and also requires a good laboratory backup, which may not be available at all levels of care. Compared to this, the score currently described has good specificity and positive predictive values, relies solely on clinical criteria, and can be adapted to most levels of care. Tangnararatchakit, et al. [4] had devised a daily dengue severity score, which consisted of 14 parameters, making the application tedious and cumbersome. In this study, the clinical outcomes depended on quality of patient care. Further, there was a possibility of variation in each parameter for scoring that could affect the final score [4]. Pongpan, et al. [5] had devised a score on a large scale for children in Thailand but the generated score could correctly classify patients into their original severity levels only 60% of the time, and had an unacceptable under-estimation and over-estimation levels of 25.7 % and 13.5 %, respectively [5].

Detection of third space fluid accumulation and gall bladder wall thickening can be easily done by point of care ultrasonogram (POCUS) [14]. The current score can be calculated based on history, clinical examination and POCUS, and can be derived at the bedside with the widespread availability of POCUS, and improved competency and training of pediatricians.

Due to the dynamic nature of the disease, which may vary in different phases of illness, it is encouraged that the score be applied frequently in children with proven or suspected dengue, especially in the critical phase, so that, severe disease can be anticipated earlier. Owing to this score's high sensitivity and positive predictive value, it can be used in triaging children with predicted severe dengue to facilitate prompt referral to higher centers. In tertiary care centers, this could be used for better monitoring of children, and improved utilization of resources/infrastructure to increase the survival of children with life threatening disease.

Limitations of the study include that the study subjects predominately were from the poor socio-economic status and may not be representative of the general population. The generation of the score was done from retrospective data, and therefore the fluctuating nature of the risk factors was not accounted for during score formulation. Serum IgG dengue was not performed in our hospital routinely and this was not assessed as a risk factor for severe dengue. Since the study requires performing bedside ultrasound to identify third space fluid accumulation, its utility in primary healthcare facilities remains uncertain.

The Bedside Dengue Severity Scoring developed reliably predicted severe dengue with scores closer to 2.913. It is believed that by promoting early referral, aiding vigilant observation, and better resource allocation in resource-limited settings, this scoring system might contribute to a reduction in morbidity and death associated with severe illness. It is suggested that similar studies may be conducted at different levels of care, before application to the general population.

Ethics clearance: EIC, Madras Medical College; No. 15112021 dated Nov 3, 2021.
Contributors: VG: conceptualized the study, was involved in collecting data, analyzing data, manuscript preparation and case management; SVL: was involved in case management and manuscript preparation; SS: was involved in case management and manuscript preparation; VP: was involved in data collection, management of cases and manuscript preparation; SK: was involved in manuscript preparation, critical review of manuscript and data analysis. 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 the study is available with the online version at *www.indianpediatrics.net*

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Web Box I Risk Factors for Severe Dengue Used for Development of Dengue Severity Score

- Infancy
- Lethargy
- Obesity (BMI >27th adult equivalent)
- Persistent vomiting (≥2 times/d) [10]
- Third space fluid loss[a]
- Narrow pulse pressure (≤20 mm Hg) in the absence of circulatory shock
- Immunosuppressed condition[b]
- Hematocrit rise ≥20% from baseline
- Chronic illness[c]
- Rapid fall in platelets (to <50000/µL from ≥100000/µL taken 24 h apart)
- Bleeding tendency (primary or acquired due to drugs/ diseases)
- Abdominal tenderness
- Mucosal bleeding[d]
- Hepatomegaly[e]

[a]Periorbital puffiness, gall bladder wall edema, Free fluid in pleural/peritoneal cavity identified clinically or by imaging; [b]Primary or acquired due to conditions like SAM, Nephrotic syndrome, drugs like steroids/chemotherapeutic drugs other immunosuppressant drugs; [c]Chronic conditions like Chronic liver/GI disease, chronic kidney disease, chronic lung disease/hematological conditions etc.; [d]bleeding from sites other than skin and visceral organs e.g.epistaxis, gum bleed, not causing hemodynamic compromise; [e]by palpation/percussion method or ultrasonography.

Web Box II Severity Classification

Patients were classified as severe if they had at least one of the following:

- shock – compensated and decompensated;[a]
- fluid accumulation causing respiratory distress;
- severe hemorrhage;
- severe organ failure (central nervous system,[b] acute kidney injury,[c] liver,[d] heart,[e] etc).

[a]defined as per Pediatric emergency medicine course (PEMC) guidelines, which is the standard protocol followed in our institution [11]. [b]impaired consciousness/seizure/altered behavior [Dengue encephalitis- detecting anti DENV IgM/Viral RNA/NS1and exclusion of other causative agents of viral encephalitis by cerebrospinal fluid analysis and/or magnetic resonance imaging findings; Dengue encephalopathy- altered sensorium due to edema/ severe hypo-natremia/renal or liver dysfunction/metabolic acidosis/release of toxic substance even if there is no CSF abnormality]. [c]defined as an abrupt reduction in kidney function defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL,≥50% increase in serum creatinine from baseline, or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours). (as per AKIN criteria)[12]. [d]defined by transaminase levels above 1000IU/L. (aspartate transaminase or alanine transaminase).[e]defined as clinical evidence of congestive cardiac failure with cardiomegaly on chest X-ray and ECHO by trained intensivist or cardiologist showing reduced ejection fraction <55% or left ventricular wall motion abnormality.

RESEARCH PAPER

Correlation of Serum Lactate Levels, Perfusion Index and Plethysmography Variability Index With Invasive Blood Pressure in Late Preterm and Term Infants With Shock

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Objective: To study the correlation of objective parameters for diagnosing shock viz., perfusion index (PI), plethysmography variability index (PVI) and serum lactate (SL) with invasive blood pressure in late preterm and term infants with shock. **Methods**: Prospective observational study (diagnostic test) conducted at the neonatal intensive care unit of Kanchi Kamakoti CHILDS Trust Hospital, Chennai between June, 2018 and May, 2020. Term and late preterm neonates with shock were included in the study. PI, PVI, SL, SpO2 and heart rate were monitored. PI, PVI and SLL were recorded at 0,12, 24 and 72 hours of onset of shock. All the babies were followed up till discharge or death. **Results**: Total 78 neonates were enrolled in the study. At 0 hour, SL and PVI had negative correlation (P =0.002 and P=0.003) while PI had a weak-to-moderate positive correlation (P=0.002) with invasive blood pressure. SL ≥4.65 had a sensitivity of 75% and specificity of 75.8%, and PI <0.455 had a sensitivity of 65%, and specificity of 58.6% for predicting invasive hypotension. PVI ≥23.5 had a sensitivity of 90% and specificity of 63.8% in predicting invasive hypotension. **Conclusion**: PI has moderate positive correlation while SL and PVI have moderate negative correlation with invasive blood pressure. The cutoff values of SL ≥4.65, PI <0.45 and PVI ≥23.5 can predict invasive hypotension with good sensitivity and negative predictive value.

Keywords: *Hemodynamic support, Hypotension, Management, Prediction*.

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Shock in neonates is clinically assessed by monitoring heart rate, blood pressure, capillary refilling time, acid-base status and urine output [1-4]. The clinical parameters are liable to subjective variation, so there is a need for an objective parameter for diagnosing shock, which is less invasive, such perfusion index (PI), plethysmography variability index (PVI) and serum lactate (SL).

PI is an assessment of pulsatile strength, and it is an indirect measure of peripheral perfusion [5]. The signal comprises two components, one of which is arterial and pulsatile and the other, which is non-pulsatile and originates from connective tissue, bone, and venous blood. PVI has recently been proposed to predict fluid responsiveness. It is an automatic measure of the dynamic changes in PI occurring during the respiratory cycle [6]. Serum lactate gives information on metabolism capacity at cellular level and reflects true perfusion and oxygenation status [7]. The combination of measurement of PI, PVI and SL could help in early recognition of hemodynamic instability and thus initiate prompt treatment. Hence, we investigated the correlation of PI, PVI and SL with invasive blood pressure in our study.

METHODS

This prospective observational study (diagnostic test) study was conducted at a tertiary care level 3 neonatal intensive care unit (NICU) of Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu from June, 2018 to May, 2020. Ethics approval was obtained from the institute's ethics committee. Term and late preterm neonates, who were admitted in the NICU and fulfilling the case definition of shock [8], were enrolled in the study.

Invited Commentary: Pages 343-44.

Shock was defined as the presence of at least two of the six criteria [1,9,10]: Heart rate >180 per min, decrease in blood pressure (mean arterial pressure (MAP) <5th centile for gestational age for age), oliguria <0.5 mL/kg/h for preceding 6h, CRT (capillary refilling time) >3s, central to peripheral temperature difference >3°C, and metabolic

acidosis (base deficit (BD) >5 or lactate >2 times upper normal) [11]. Hypotension was defined as mean blood pressure (MBP) value below the 5th centile for the gestational age and postnatal age of the baby [12-14]. Informed consent was obtained from parents in their own language. Gestational age was assigned either by first trimester ultrasonogram or last menstrual period. A detailed structured form, which included demographic data, etiology, risk factors, examination findings and investigation results, was completed. All neonates enrolled in the study had undergone baseline investigations as per the NICU protocol. A 4 Fr umbilical artery catheter or peripheral arterial line was placed for invasive blood pressure (IBP) monitoring by the doctor on duty. Heparin stock solution infusion was started to maintain the arterial line patency. IBP monitoring was done by using Edward kit transducer and pressure bag, and Dash 4000 multipara monitor.

PI and PVI and SL were recorded at 0,12, 24 and 72 hours of onset of shock. PI, PVI, SpO_2 and heart rate were monitored using new generation pulse oximeter (Masimo Rainbow Rad87; Masimo Corp). Pulse oximeter probe was placed on the right hand (preductal) of the subjects soon after diagnosis of shock. PI and PVI values were recorded every 20 seconds for 10 minutes duration during each prespecified assessment points [15]. Average of lowest and highest PI reading was taken each time to eliminate the bias of considering lowest values. Lactate values were obtained from the arterial blood gas (ABG) analysis (Radiometer ABL 700 automated blood gas analyzer). All the babies were followed-up till discharge from the hospital or death.

PI, PVI and SL values were assumed to have strong correlation coefficient value of 0.9 with IBP in neonates with shock. To have 90% power and 95% confidence interval, the required sample size was calculated as 78 neonates undergoing invasive blood pressure monitoring.

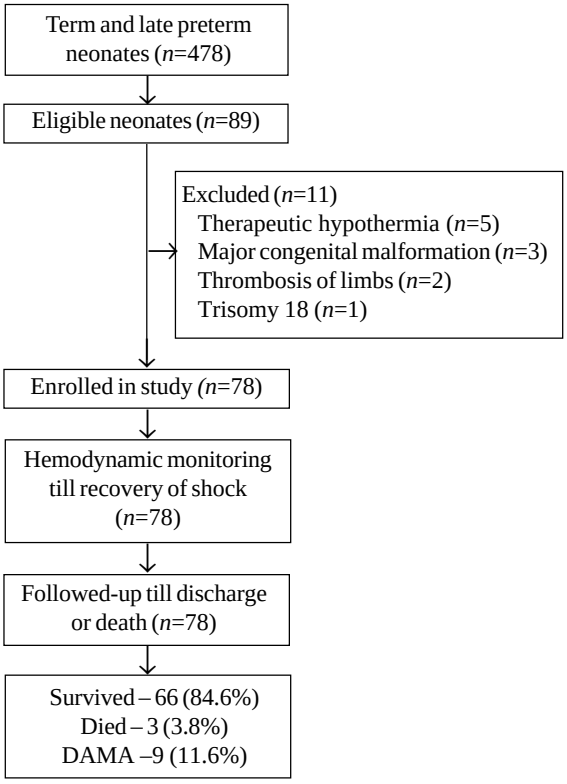
Statistical analysis: Statistical analyses were performed using SPSS 22.0. Statistical significance was assumed for *P* value <0.05. Pearson correlation was performed to identify correlation between PI, PVI and SL and invasive blood pressure. We constructed a 2 × 2 table by taking SL as more than or equal to 4.65, PI less than 0.455 and PVI more than or equal to 23.50 as an index test and presence or absence of shock by invasive hypotension as a reference test. Sensitivity, specificity, positive and negative predictive values were calculated for PI, PVI and SL to predict invasive hypotension. Cutoff values for PI, PVI and SL were derived using ROC curves.

RESULTS

A total of 724 neonates were admitted during the study period, of which 478 were late preterm and term neonates. All late preterm and term neonates were examined for features of shock. Eighty-nine neonates were found to be eligible and 78 were enrolled in the study, and followed-up till discharge or death (**Fig. 1**). Among the study population, 65% participants were male, and 63% babies belonged to term gestational age. Mean gestational age was 37.5 (1.89) weeks, median (IQR) postnatal age was 6 (2, 23.75) days and mean (SD) birth weight was 2.67 (0.67) kg. Out of 78 neonates, 26% required intubation and 15% PPV (**Table I**). The various shock parameters are given in **Web Table I**, and values of PI, PVI, SL, SBP, DBP and mean IBP at the onset of shock (0 hours) and when shock recovered (72 hours) are shown in **Web Table II**.

At 0 hour, SL and PVI had a significant negative correlation while PI had a significant weak-to-moderate positive correlation with IBP. SL ≥4.65 had sensitivity of 75% and specificity of 75.8%, PI <0.455 had sensitivity of 65 % and specificity of 58.6%, and PVI ≥23.5 had a sensitivity of 90% and specificity of 63.8% in predicting invasive hypotension (**Table III**).

SL and PVI had negative correlation with IBP (SBP, DBP and MBP) at 0 hour (*P*<0.05) **(Table II, Fig. 2)**. SL and PVI values were high initially in the neonates with hypotensive shock at the time of admission, which came



DAMA: discharge against medical advice.

Fig. 1 Study flow chart.

Table I Demographic Characteristics of the Study Population (*N*=78)

Characteristics	*Value*
Antenatal risk factors	
Urinary tract infection	3 (3.8)
Maternal fever < 24 h of delivery	3 (3.8)
Meconium stained amniotic fluid	4 (5.1)
Premature rupture of membranes	6 (7.7)
Neonatal characteristics	
Male sex	51 (65)
Gestation category	
Late preterm	29 (37)
Term	49 (63)
Cesarean delivery	62 (79)
Resuscitation required	
PPV	12 (15)
Intubation	20 (26)
No	46 (59)
Gestational age (d)[a]	37.5 (1.89)
Birth weight (kg)[a]	2.7 (0.67)
Postnatal day at admission[b]	6 (2, 23.7)
Final outcome	
Survived	66 (84.6)
Discharge against medical advice	9 (11.6)
Death	3 (3.8)

Values expressed as n (%),[a]mean (SD), or [b]median (IQR).

down when blood pressure improved after correction of shock (negative correlation). PI had a positive correlation with invasive blood pressure **(Table II, Fig 2)**. The PI values were low initially when blood pressure was low, which increased when it improved after correction of shock (P <0.05).

Table II Correlation Between Invasive Blood Pressure and Serum Lactate, Perfusion Index and Plethysmography Variability Index at Admission in Neonates (*N*=78)

Parameter at admission	*Correlation coefficient*	*P value*
Serum lactate		
Systolic blood pressure	-0.314	0.005
Diastolic blood pressure	-0.349	0.002
Mean blood pressure	-0.350	0.002
Perfusion index		
Systolic blood pressure	0.273	0.016
Diastolic blood pressure	0.341	0.002
Mean blood pressure	0.325	0.004
Plethysmography variability index		
Systolic blood pressure	-0.28	0.013
Diastolic blood pressure	-0.34	0.003
Mean blood pressure	-0.324	0.004

Table III Predictive Ability of Serum Lactate (SL), Perfusion Index (PI) and Plethysmography Variability Index (PVI) in Predicting Shock by Measuring Invasive Blood Pressure in Neonates (*N*=78)

Predictors	*SL (≥4.65 mmol/L)*	*PI (<0.455)*	*PVI (≥23.5)*
Sensitivity	75%	65%	90%
Specificity	75.8%	58.6%	63.8%
PPV	51.7%	35.1%	29%
NPV	89.79%	82.9%	87.5%

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

Receiver operating characteristic curve (ROC curve) was constructed to predict invasive hypotension from SL, PI and PVI. Area under the ROC curve was 0.813, 0.666 and 0.707, respectively with a narrow confidence interval (**Web Fig. 1**).

DISCUSSION

In this study, we tried to identify objective parameters for assessment of shock, which are commonly available at the bedside of a sick neonate that would help clinician in the diagnosis of shock and assess the response to its treatment. We found that at 0 hour, SL and PVI had negative correlation while PI had a weak-to-moderate positive correlation with invasive blood pressure.

Increase in serum lactate levels in infants with shock and negative correlation with invasive blood pressure have been reported in previous studies on neonates receiving therapeutic hypothermia and neonates who had septic shock [16,17]. We also found a negative correction of lactate with invasive blood pressure. We found a moderate positive correlation between PI and invasive blood pressure, which is consistent with other studies. PVI as an indicator of volume-responsive hypotension in newborn infants during surgery has been studied and was observed to have negative correlation with arterial blood pressure [18]. Other studies have identified a weak positive correlation between inferior vena cava collapsibility index and PVI [8].

Our study was a prospective observational study conducted in an exclusively out born level 3 NICU. We studied three easily available parameters at point of care to draw a correlation with clinical shock and the invasive blood pressure in a comparatively adequate sample size. Our study was conducted in an extramural unit where more of the sick cases are referred, so results of our study cannot be extrapolated to intramural units. Frequently, babies with shock have already received fluid boluses or inotropes, before referral, which may have disturbed the real values of SL, PI and PVI. We did not evaluate the role of these

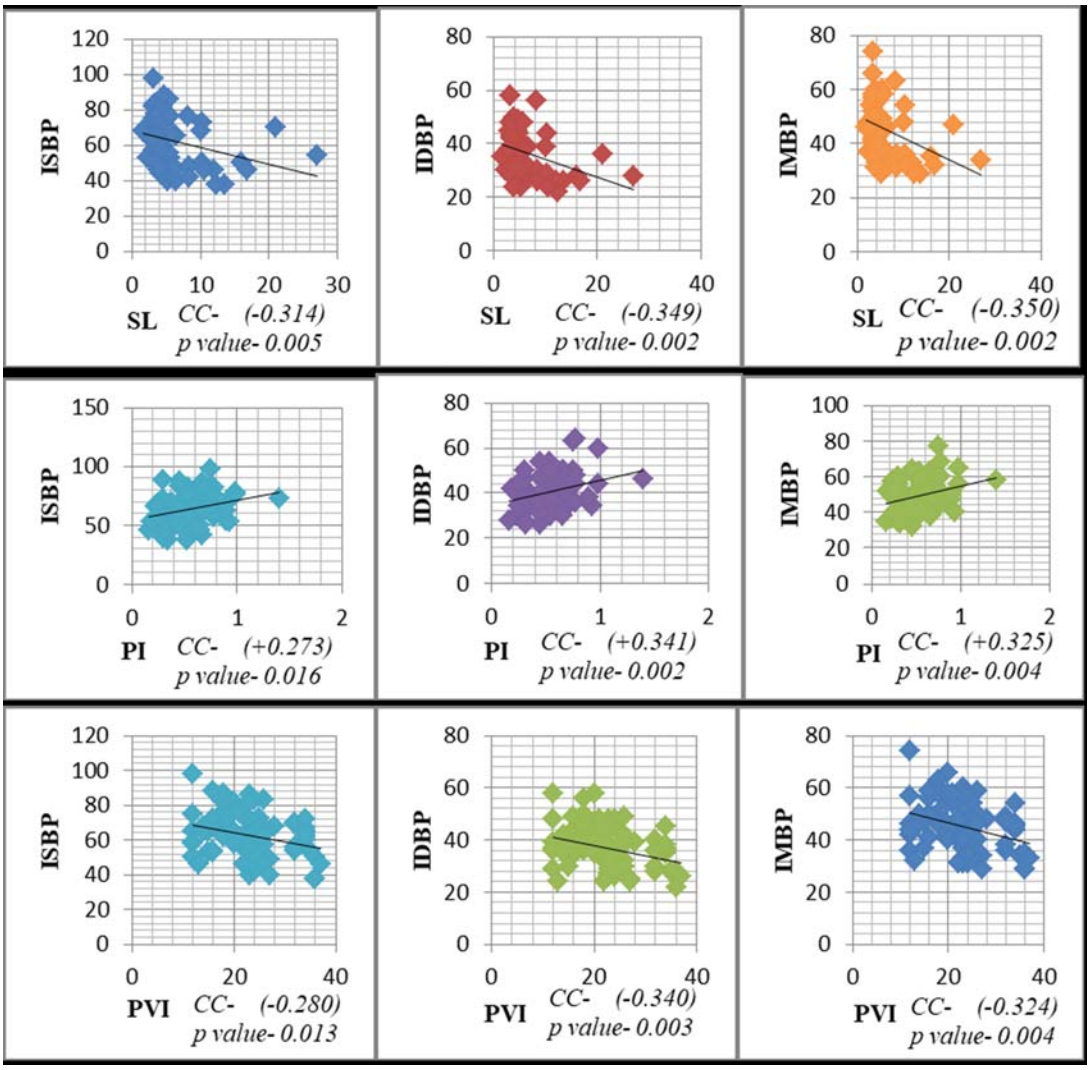


Fig. 2 Correlation between invasive blood pressure (BP) (systolic, SBP; diastolic, DBP; and mean, MBP) and serum lactate (SL), perfusion index (PI) and plethysmography variability index (PVI) at admission. *CC - Correlation coefficient.*

parameters in various types of shock in neonates; even though, majority had septic shock.

Serum lactate levels and PVI had negative correlation while PI had a positive correlation with invasive blood pressure in late preterm and term neonates with shock.

Ethics clearance: Institutional ethics committee, KKCT Hospital; No. IEC-DNB/39/ dated March 28, 2019.
Contributors: SSS**:** contributed in collecting data, analysis, interpretation of data and drafting the manuscript; NCK,VHK,SS: contributed to conception and design of the study, drafting and critically reviewed the content; GK: contributed in collecting 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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WHAT THIS STUDY ADDS?

- Trends of changes in serum lactate levels, perfusion index and plethysmography variability index values have good correlation with invasive hypotension in late preterm and term neonates with shock.

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Web Table I Indicators of Shock in Neonates Enrolled in the Study (*N*=78)

Indicators of shock	*No. (%)*
Heart rate >180/min	78 (100)
Capillary refilling time >3 s	76 (97)
Core-to- periphery difference >3°C	74 (95)
Base deficit >5 meq/L in blood gas	32 (42)
Elevated lactate >2-times	48 (62)
Hypotension	20 (26)
Oliguria	5 (6.5)
Weak peripheral pulses	62 (80)

Web Table II Parameters of Shock at Various Time Points of Assessment

Hemodynamic assessment	*At admission*	*12 h*	*24 h*	*72 h*
Mean heart rate (bpm)	189 (9)	164 (7)	148 (6)	142 (4)
Invasive BP				
ISBP (mm of Hg)	62.73 (13.04)	66.95 (10.92)	69.79 (9.47)	72.03 (8.58)
IDBP (mm of Hg)	36.90 (8.14)	40.31 (7.60)	42.63 (6.56)	44.79 (7.04)
IMBP (mm of Hg)	45.24 (9.64)	49.33 (8.69)	52.28 (7.68)	54.53 (7.17)
Non invasive BP				
SBP (mm of Hg)	68.89 (12.66)	72.07 (11.48)	75.82 (9.73)	76.667 (8.76)
DBP(mm of Hg)	39.69 (9.59)	43.25 (7.87)	46.53 (8.02)	49.00 (7.36)
MBP(mm of Hg)	49.36 (9.92)	53.21 (9.15)	56.68 (8.40)	59.16 (7.82)
Perfusion index	0.52 (0.23)	0.77 (0.27)	1.02 (0.35)	1.52 (0.42)
PVI	22.91 (6.89)	15.6 (4.65)	13.86 (4.95)	12.13 (2.91)
S. lactate	5.71 (2.25)	4.21 (1.93)	2.83 (1.37)	2.16 (1.05)
Base excess	-8.012 (3.97)	-5.017 (2.25)	-3.61 (1.54)	-2.21(1.34)

Values expressed as mean (SD). SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure, PVI: Plethysmography variability index.

RESEARCH PAPER

Identification of Probable Urinary Tract Infection in Children Using Low Bacterial Count Thresholds in Urine Culture

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Objectives: To assess the proportion of children, symptomatic for urinary tract infection (UTI), with urine culture showing single bacterial species >10^4 CFU/mL, and to compare patient and disease characteristics between children having low counts (from >10^4-10^5 CFU/mL) and those with counts >10^5 CFU/mL. **Methods:** Prospective observational study, enrolling symptomatic children aged 1 month to 12 years. Mid-stream clean-void or catheter collected urine were cultured. Children with single species >10^4 CFU/mL were scheduled for imaging studies, following age criteria of Indian Society of Pediatric Nephrology guidelines. The main outcome was proportion with single bacterial species >10^4 CFU/mL in urine culture. **Results:** Of 216 children (132 males) with median (IQR) age of 24 (12, 48) months, 38 (17.6%) showed single species growth >10^4 CFU/mL. Of these, 29 (13.4%) were diagnosed as UTI at cutoff >10^5 CFU/mL, and an additional 9 (4.2%) were found to have 'probable low-count UTI' (from >10^4 to 10^5 CFU/mL). One child in the latter group had bilateral hydroureteronephrosis, vesico-ureteral reflux and renal scarring. There was largely no difference in parameters between children with low counts and those with counts >10^5 CFU/mL. **Conclusion**: An additional proportion of symptomatic children with probable urinary tract infection and possible underlying urological abnormalities may be identified by lowering bacterial colony count cutoff to >10^4 CFU/mL, in clean-voided and catheter-based urine samples.

Keywords: *Bacterial colony, Diagnosis, Urological abnormalities.*

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A reliable diagnosis of urinary tract infection (UTI) in a child is often challenging, because it is difficult to differentiate between contaminants and true bacterial infection [1]. The traditional definition of significant bacteriuria of >10^5 colony-forming units (CFU)/mL in clean-voided urine samples [2,3] has been extrapolated from studies done in adult females nearly 60 years ago [4]. Similarly, the recommended cutoff of >50,000 CFU/mL in transurethral catheter specimen [2,5] was derived in a study nearly 3 decades ago [6]. The accuracy of these cutoffs has been questioned [7], suggesting a possibility of true UTI in children even with lower colony counts [8,9].

There is lack of evidence regarding low bacterial colony count UTI in children, especially in clean-voided or catheter samples [10,11], resulting in variation across different guidelines [2,3,5,12,13]. Our study aimed to identify the proportion of symptomatic children who show growth of a single bacterial species with colony counts >10^4 CFU/mL in urine culture, and to compare the clinical characteristics, bacteriological profile and imaging findings between children having 'probable low bacterial count UTI' (from >10^4CFU/mL up to 10^5CFU/mL) and those diagnosed with UTI at conventional bacterial colony count cutoff (>10^5 CFU/mL).

METHODS

This prospective observational study, in a tertiary care hospital, was conducted from 1 October, 2020 to 30 September, 2021. Following approval by the institutional ethics committee, consecutive children from 1 month to 12 years of age, having clinical features suggestive of UTI, as described in the table of signs/symptoms in infants and children suggestive of UTI, provided by NICE (National Institute for Health and Clinical Excellence, 2018) UTI guidelines [14], were screened for eligibility. Children already on antibiotics, those with indwelling bladder catheter, and those in which the clinical features were better explained by a diagnosis other than UTI, were excluded.

Invited Commentary: Pages 345-46.

After taking informed consent, clinical details were recorded and urine samples were collected in sterile containers for urinalysis and culture. While a mid-stream, clean-voided sample was collected from toilet trained

children, a catheter sample was taken from non-toilet trained children. Centrifuged specimen was used for urinalysis but was used neat to plate for culture. A semi quantitative culture technique was used. Using a loop of 0.002 mL, urine was plated on CLED (Cysteine-Lactose-Electrolyte Deficient) agar. The number of colonies grown per microliter of urine gave the estimate of bacterial growth. One microliter of urine growing 100 colonies, meant growth of 10^5 CFU/mL of urine. Thus, for a growth of 10^4 CFU/mL of urine, 1 microliter grew at least 10 colonies.

All symptomatic children who showed growth of single bacterial species in urine culture with colony counts $>10^4$ CFU/mL were scheduled for radiological investigations following the age criteria as in ISPN 2011 guidelines [2]. Those children with bacterial counts $>10^5$ CFU/mL in urine culture were provided standard treatment with or without antibiotic prophylaxis [2]. However, administering antibiotics to children with low bacterial colony counts ($>10^4$ - 10^5 CFU/mL) in urine culture, was at the discretion of the treating physician, depending upon the sickness and clinical features.

For this study, "probable UTI" was identified if: *a*) clinical features consistent with UTI (as per NICE guidelines 2018 [14], table of symptoms and signs in infants and children suggestive of urinary tract infection), and *b*) urine culture showing growth of a single bacterial species with colony counts ranging from $>10^4$ to 10^5 CFU/mL, with either mid-stream or catheterized sample.

Taking prevalence of UTI of 7-10% in symptomatic children, at conventional colony count cutoffs [15], and expecting 15% [11] would be identified at threshold of $>10^4$ CFU/mL, with a precision of 0.05 and 95% CI, we got a sample size of 196.

Statistical analysis: Mean (SD) or median (IQR) were compared between groups by independent sample *t* test or Mann Whitney *U* test, respectively. Proportions were compared by chi-square test. Analysis was done using SPSS 21 software, taking statistical significance at $P<0.05$.

RESULTS

Of the 850 children assessed for eligibility, 216 children (61.1% males), with median age of 24 (IQR12, 48) months, met the inclusion criteria. The baseline characteristics of the children are shown in **Table I**. Most (*n*=195) of them presented with the "most common symptoms" category of the NICE table [14]. Six children had prior documented history of UTI: two of them having UTI 1 month and 5 months ago, had not been evaluated earlier radiologically. Remaining four had previous UTI between 3-24 months ago. All four had posterior urethral valve (PUV), three of them having hydronephrosis and vesico-ureteral reflux (VUR).

Table I Demographic and Clinical Characteristics of Children With Suspected Urinary Tract Infection (*N*=216)

Parameters	*Value*
Age (mo)[a]	24 (12, 48)
Girls	84 (38.8)
Weight (kg)[b]	12.3 (6)
Height (cm)[b]	87.5 (20.2)
Previous UTI	6 (2.8)
Known CAKUT[c]	7 (3.2)
Duration of symptoms (d)[a]	3 (2,5)
Fever	161 (74.5)
Vomiting	61 (28.2)
Irritability	11 (5.1)
Lethargy	3 (1.4)
Poor feeding	6 (2.8)
Loin tenderness	1 (0.5)
Dysuria	34 (15.7)
Frequency	10 (4.6)
Cloudy urine	3 (1.4)

Values are in n (%), [a]median (IQR) or [b]mean (SD). UTI:urinary tract infection; CAKUT:congenital anomalies of kidney and urinary tract; [c]children with posterior urethral valve and/or vesico-ureteral reflux.

Urine specimens were collected by catheter and by clean-voided method from 123 and 93 children, respectively.

Urine culture results showed 51/216 (23.6%) children having bacterial growth of a single species, 19/216 (8.8%) having mixed growth while rest 146/216 (67.6%) had no growth (**Fig. 1**). Of the 51 pure growths, 38 samples (17.6% of all enrolled symptomatic children) showed colony counts $>10^4$ CFU/mL. While 29 (13.4%) children were diagnosed with UTI at conventional colony count cutoff ($>10^5$ CFU/mL), an additional 9 (4.2 %) were found to have 'probable low-count UTI' (from $>10^4$ to 10^5 CFU/mL). Of the six children having previous history of UTI, two had sterile urine cultures, 3 had UTI at conventional counts and one had low-count UTI. *E. coli* was the most common organism isolated in 31 (81.6%), followed by *Klebsiella*

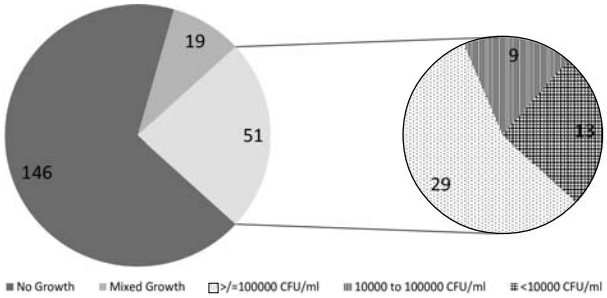

Fig. 1 Results of urine culture of symptomatic children with suspected urinary tract infection (*n*=216).

pneumoniae, *Enterococcus faecium*, *Proteus mirabilis* and *Staphylococcus aureus*.

Radiological investigations revealed abnormalities in one 31-month boy, among the nine children with 'probable low-count UTI.' He was found to have bilateral hydroureteronephrosis on ultrasonography, bilateral VUR (Grade III right kidney, Grade II left kidney) in MCU, and multiple scars in the right kidney in DMSA scan. Ultrasonography was done in 37 children, with eight (21.6%) showing abnormal findings, seven with hydronephrosis (including the boy with 'probable low-count UTI'), and one child with small contracted kidneys. Of the 15 children in whom MCU was indicated, eight (including two with low-counts) underwent the procedure, five (62.5%) of them showing abnormalities. Of the 31 children (eight with low-counts) who were required to undergo DMSA renal scan, 17 children (5 with low counts) could avail it, and four (23.5%) of them showed scars in DMSA, one of them being a child with 'probable low-count UTI.

Comparison of parameters (**Table II)** between children with UTI diagnosed at conventional colony count cutoff and those with 'probable low-count UTI' showed no significant difference in terms of age, gender, method of collection of urine, nor frequency of abnormal imaging findings. While all the children diagnosed with UTI at conventional colony counts received antibiotics as per guidelines, four children with 'probable low-count UTI' were prescribed antibiotics by the treating physician.

DISCUSSION

Our study showed that by lowering the threshold of significance to a bacterial colony count of $>10^4$ CFU/mL, 17.6% children with symptoms could be identified with such bacterial growths. While at conventional colony count cutoff, only 13.4% children would have been diagnosed with UTI, an additional 4.2 % were found with 'probable low-count UTI.'

Taking a cutoff of $\geq 10^4$ CFU/ml, Primack, et al. [16], diagnosed an additional 1.8% symptomatic children with UTI aged 2 months to 6 years. Low bacterial count $<10^5$ CFU/mL in suprapubic urine samples have been reported earlier [10]. Moreover, in catheterized samples, authors have demonstrated that about 9-10% of children with UTI would be missed if the colony count cutoff was not decreased below 50,000 CFU/mL [11].

In our study, a higher proportion of children with 'probable low-count UTI' was below 2 years of age, compared to the conventional-count UTI group. The difference; though, not statistically significant, does reiterate the argument in favor of using low-count cutoffs in infants and young children, who are unlikely to hold urine long enough to allow bacterial growth to reach counts beyond 50,000 or 100,000 CFU/mL. The two children with low counts identified by Primack, et al. [16], were aged 8 months and >2 years, respectively. Another study reported that the number of children with low-counts decreased with increasing age of the children [11].

Table II Characteristics of Children With UTI Diagnosed at Conventional Bacterial Colony Count Cutoff ($>10^5$ CFU/mL) and Probable Low-Count UTI ($>10^4$-10^5 CFU/mL)

Parameters	*Conventional -count UTI* [b] *(n=29)*	*Probable low-count UTI*[c] *(n=9)*	*OR (95% CI)*	*P value*
Age (mo)[a]	29 (13,90)	24 (16,39)	-	0.436
Male sex	13 (44.8)	7 (77.8)	0.58 (0.33 to 0.98)	0.084
Urine collection by catheter	17 (58.6)	5 (55.6)	1.13 (0.25 to 5.12)	0.871
NICE 'most common symptoms'	29 (100)	8 (88.9)	1.12 (0.89 to 1.42)	0.069
Fever	20 (69)	8 (88.9)	0.77 (0.55 to 1.09)	0.236
Vomiting	8 (27.6)	2 (22.2)	1.24 (0.32 to 4.82)	0.750
Dysuria	12 (41.4)	0	1.70 (1.25 to 2.31)	0.020
Antibiotics given	29 (100)	4 (44.4)	2.20 (1.08 to 4.67)	<0.001
Urea (mg/dL) [a]	19 (15.5,28.7)	20 (14, 34.5)	-	0.976
Creatinine (mg/dL) (*n*=90)[a]	0.27 (0.19, 0.52)	0.25 (0.15,0.36)	-	0.377
Abnormal DMSA (*n*=17)	3/12 (25)	1/5 (20)	1.25 (0.17 to 9.31)	0.825
Abnormal MCU (*n*=8)	4/6 (66.7)	1/2 (50)	1.33 (0.29 to 5.95)	0.673
Abnormal USG (*n*=37)	7/28 (25)	1/9 (11.1)	2.20 (0.32 to 15.9)	0.379
E. coli growth	26 (89.7)	5 (55.6)	6.94 (1.17 to 41.67)	0.021

Values are represented as no. (%) or [a]median (IQR). [b]colony count $>10^5$ CFU/mL; [c]colony count $>10^4$ to 10^5 CFU/mL. UTI:urinary tract infection, USG:ultrasonography; MCU:micturating cystourethrogram, NICE:National Institute for Heath and Clinical Excellence (2018) UTI guidelines [14].

WHAT THIS STUDY ADDS

- By lowering bacterial colony count cutoff to >10^4 CFU/mL, in clean-voided and catheter-based urine samples, an additional proportion of symptomatic children with probable urinary tract infection and possible underlying urological abnormalities may be identified.

While most of the symptoms were similar between the groups, as reported earlier [11], symptoms of dysuria were seen exclusively in the conventional-count UTI group, probably because this group had more children of older ages compared to the low-count group.

One of the nine children with 'probable low-count UTI' had underlying urologic malformations and VUR. Prevalence of scars in kidneys or underlying anatomical abnormalities has hardly been studied in children having UTI with low bacterial counts. Our findings somewhat match with those of Kallenopoulos, et al. [11], who reported similar prevalence of reflux and urologic malformations in children with low and high colony counts. The possibility that such children harboring underlying significant urinary tract abnormalities, may be missed if they are not evaluated further, considering their low-count growths as insignificant.

The relatively small number of children in the low-count group may be a limitation for extrapolating this data to the population. Not all children where radiological investigations were indicated could undergo evaluation. The strengths of our study include patients of a wide age-range, and urine samples collected by clean-voiding or catheter.

This study shows that lowering the threshold of significance for bacterial colony count to >10^4 CFU/mL for both clean-voided and transurethral catheter-based specimens of urine, may help in detection of an additional proportion of symptomatic children with probable low-count UTI, over and above those diagnosed with UTI at conventional colony counts. Such children, even with low bacterial colony counts in urine culture, have a possibility of underlying urologic malformations, and hence, may be considered for further evaluation.

Ethics clearance: Institutional Ethics Committee, CNBC, No. F.1/ IEC/CNBC/ 11/07/ 2020/Protocol no. 76/9670, dated Sep 29, 2020.

Contributors: KM: conceived and designed the study, supervised data acquisition and did the data analysis, made the primary draft of the manuscript for publication; RN: helped in data acquisition, compilation and drafting the manuscript; MK: gave critical inputs in designing the study, data analysis and revised the manuscript critically; KS: was involved in designing the study and supervised all laboratory investigations and approved all results. All authors approved the final version before submission and agree to be accountable for all aspects of the work.

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RESEARCH PAPER

Neurological Manifestations of COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C) in Yogyakarta, Indonesia

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Objective: This observational cohort study aims to provide data on pediatric patients with neurological manifestations associated with multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19). **Methods:** Patients aged <18 with neurologic symptoms and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from January, 2021 to January, 2022 at the Dr. Sardjito Hospital in Yogyakarta, Indonesia were evaluated. We used WHO diagnostic criteria to classify patients as MIS-C or non-MIS-C. Demographic information, symptoms, and outcomes were compared between MIS-C and non-MIS-C groups. **Results:** Between January, 2021 and January, 2022, 74 pediatric patients were considered eligible. More than half of the patients were female (54.1%), and 24.3% presented with MIS-C. Length of hospitalization was significantly longer in MIS-C individuals (*P*=0.006). The commonest neurological findings were involuntary movements (43.2%) and paresis (27%). The commonest neuroimaging findings were meningoencephalitis (18.9%) and hydrocephalus (22.9%). Among all the variety of neurologic manifestations in non-MIS-C and MIS-C patients, a statistically significant result was found for fever (71.4% vs 100%; *P*=0.015*)*, altered mental state (14.2% vs 50%, *P*=0.004*)*, and paresis (33.9% vs 5.5%, *P*=0.030*)*. **Conclusion:** MIS-C was found in 24% of our patients with acute neurologic symptoms, and most cases (51.8%) had positive SARS-CoV-2 antibody results.

Keywords: *Hydrocephalus, Neuroimaging, Outcome, Stroke*.

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Until January 10, 2022, there were more than 500,000 pediatric coronavirus disease 2019 (COVID-19) cases in Indonesia, leading to 5,000 deaths in children [1]. Approximately 22-47% of pediatric patients in the US experience neurological symptoms related to COVID-19, such as seizures, status epilepticus, difficulty walking, anosmia, ageusia, head-ache, altered mental status, and fatigue [2]. Whereas, about 5% experienced life-threatening neurologic manifes-tations related to multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C), including severe encephalopathy (white matter hyperintensities and splenial lesions), acute ischemic or hemorrhagic stroke, acute central nervous system infection/acute disseminated encephalo-myelitis (ADEM), acute fulminant cere-bral edema, aseptic meningitis, and Guillain-Barré syndrome (GBS) [2-4]. SARS-CoV-2 may cause neurological damage through two mechanisms: a direct viral infection of the central nervous system (CNS) through ACE2 receptors, and inflammatory injury mediated by cytokine release [5]. Only 20%-46% of patients have positive PCR results in MIS-C-associated neurologic cases, whereas 80-99% have positive serum anti-bodies. This evidence shows that when MIS-C occurs, most children are not experiencing acute COVID-19 infection [6].

Invited Commentary: Pages 347-49.

Patients who experience these severe neurological symptoms may develop residual neurologic symptoms that impact their quality of life [2]. This article aims to provide the data of patients who had neurological mani-festations of COVID-19-associated MIS-C.

METHODS

This observational cohort study was conducted on patients younger than 18 years with acute onset of

neurologic manifestations and SARS-CoV-2 infection based on clinical or laboratory evidence, from January, 2021 to January, 2022 at the Dr. Sardjito Public Hospital, a tertiary referral hospital for Yogyakarta and the southern part of Central Java provinces, Indonesia. SARS-CoV-2 infection was confirmed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay from nasopharyngeal swab or a positive serum IgG SARS-CoV-2 test or presumed (clinical diagnosis). Presumed acute SARS-CoV-2 infection was defined as a patient diagnosed clinically based on clinical suspicion and/or a close contact is positive for the virus; this situation occurred most frequently in the early stages of the pandemic when testing was limited due to a lack of testing facilities. Acute onset neurological manifestations looked for in this study were seizures, seizures with fever, focal/general neurological deficits, decreased consciousness, neuropsychiatric disorders, acute neuromuscular disorders, cerebrovascular accidents, movement disorders, and aphasia in children. The patients were also confirmed to have no other underlying neurological diagnosis. All patients were then classified into MIS-C and non-MIS-C groups based on the WHO diagnostic criteria [4].

All children were subjected to detailed clinical history, and completed physical and neurological examinations to find neurological deficit. Additional data as demographics, comorbidities, neurological symptoms, and supporting examinations (brain magnetic resonance imaging (MRI), head computed tomography (CT) scan, and cerebrospinal fluid analysis), therapy and outcome were taken from the medical record. Blood samples were taken for qualitative and quantitative SARS-CoV-2 serologic examinations, as well as a neutrophil-lymphocyte ratio (NLR), C- reactive protein (CRP), and coagulation profile such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, and D-dimer.

Statistical analysis: Patients were grouped into non-MIS-C and MIS-C based on the WHO criteria of multisystem inflammatory disorder in children [4]. The normality of the data was verified using the Shapiro-Wilk test. Categorical data are presented in frequencies (percentages), normally distributed data are presented in mean (SD), and non-normally distributed data are presented in median (IQR). Independent *t*-test, Fisher exact test, and Kruskal-Wallis test were used to find the association between the non-MIS-C and MIS-C groups, with *P* value <0.05 considered statistically significant. Data entry and analysis were performed using SPSS v.25 (IBM Corp).

RESULTS

From January, 2021 until January, 2022, a total of 74 children presented acute onset of neurologic manifestations with clinical or laboratory evidence of SARS-CoV-2 infection. Most of the patients (28.3%) were aged 1-5 years, and 54.1% were female. Eighteen patients (24%) had MIS-C with a mean (SD) age 7.7 (6.2) years. The median (IQR) length of stay was 14 (1-81) days. There were significant differences in antibody serology test results ($P<0.001$) and hospital length of stay ($P=0.006$) between the non-MIS-C and MIS-C groups. The mortality was found to be higher in the MIS-C group compared to the non-MIS-C group (44.4% vs 33.9%; $P=0.06$) (**Table I**).

Table I Characteristics of Children With Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection and Neurological Findings (N=74)

Characteristics	*Non MIS-C (n=56)*	*MIS-C (n=18)*
Age (y)[a]	6.4 (5.6)	7.7 (6.2)
Male gender	26 (35.1)	8 (10.8)
RT-qPCR positive	3 (4.1)	4 (5.4)
Antibody test positive	13 (17.6)	14 (18.9)
Hospital stay (d)[b,c]	12 (1-66)	26 (5-81)
Death	11	8

Values in no. (%), [a]mean (SD) or [b]median (IQR). MIS-C: multisystem inflammatory syndrome in children; RT-qPCR: reverse transcription-quantitative polymerase chain reaction. [c]P<0.01.

From a total of 18 patients who experienced MIS-C, all had a fever for more than three days, and had elevated markers of inflammation such as erythrocyte sedimen-tation rate (ESR), CRP, or procalcitonin, no other obvious microbial cause of inflammation and evidence of COVID-19 (RT-qPCR, antigen test or serology positive) (**Web Fig. 1**). The mean prothrombin time (PT) was 18.2 s, partial throm-boplastin time (PTT) was 36.1 s, and D-dimer was 2,291 mg/L. The mean (SD) value of inflammatory markers was 65.2 (65.5) mg/dL for CRP, and 13.25 (33.5) ng/mL for pro-calcitonin.

There were significant differences in neurological manifestations and radiographic findings between the non-MIS-C and MIS-C groups (**Table II**), especially for fever [OR (95% CI) 1.4 (1.2-1.7), $P = 0.015$], altered mental status [OR 6.0 (1.8-19.7), $P = 0.004$], and paresis [OR 0.1 (0.01-0.9), $P=0.030$]. Patients who survived had lesser need of inotropes (12.9% vs 36.8%; $P=0.035$), and lesser use of antiviral agents (3.7% vs 26.3%; $P=0.010$).

DISCUSSION

In our study, 18 children (16.2%) out of 74 children with acute neurologic symptoms were confirmed with MIS-C, which is similar to a study conducted in the US that found 12% of cases of neurologic symptoms were associated with MIS-C [7]. Our study population's mean age of MIS-C cases was similar to previous reports [7,8].

Table II Clinical and Radiologic Findings in Children With SARS-CoV-2 Infection in Yogyakarta, Indonesia

Findings	*Non MIS-C (N=56)*	*MIS-C (N=18)*	*OR (95% CI)*	*P value*
Fever	40 (71.4)	18 (100)	1.4 (1.2-1.7)	0.015
Seizure	32 (57.1)	11 (61.1)	1.2 (0.4-3.5)	0.767
Respiratory distress	7 (12.5)	4 (22.2)	2.0 (0.5-7.8)	0.445
Neurological findings				
Altered mental status	8 (14.3)	9 (50)	6.0 (1.8-19.7)	0.004
Paresis	19 (33.9)	1 (5.5)	0.1 (0.01-0.9)	0.030
Aphasia	2 (3.6)	0	-	0.416
Involuntary movement	23 (41.1)	9 (50)	1.4 (0.5-4.2)	0.506
Stroke/transient ischemic attack	6 (10.7)	3 (16.7)	1.7 (0.4-7.5)	0.679
Guillain-Barré syndrome	1 (1.8)	1 (5.5)	3.2 (0.2-54.5)	0.430
Neuroimaging				
Cerebral edema	10 (17.8)	6 (33.3)	2.0 (0.6-7.0)	0.325
Cerebral atrophy	7 (12.5)	1 (5.5)	0.4 (0.04-3.1)	0.669
Hydrocephalus	12 (21.4)	5 (27.8)	1.2 (0.3-4.2)	0.756
Meningoencephalitis	13 (23.2)	1 (5.5)	0.2 (0.02-1.3)	0.086
Microcalcification	9 (16.1)	2 (11.1)	0.6 (0.1-2.9)	0.710
Cerebral ischemia/hemorrhage	7 (12.5)	0	-	0.173

Values in no. (%). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MIS-C: multisystem inflammatory syndrome in children. Neuroimaging included either computed tomography scan or magnetic resonance imaging.

A total of 22.2% of our MIS-C patients had a positive RT-PCR test, 77.8% had a positive antibody test, and one of them had positive findings in both results. Studies in the US showed that 44% of MIS-C patients with neurologic manifestation had positive PCR results, 35% of patients had positive antibody test results, and 30% of patients had both positive results [2]. This may have been due to differing testing strategies and differing healthcare settings of the two studies.

The duration of hospitalization was for the MIS-C group longer compared to a previous systematic review [9]. In our study, hospital stays were longer because most patients were admitted to the hospital in critical condition. For the same reason, the mortality rate in our study was also higher than previous multinational data (1.7%) [9], and that from Latin America (0%) [10].

A study in Germany reported frequent neurologic symptoms associated with MIS-C were altered mental state (33.3%), new paresis (30%), impaired consciousness (23.3%), hypo/areflexia (30%), anosmia/hyposmia or ageusia/hypogeusia (20%, underreported in critical care patients) and seizures (16.7%) [11]. The range of neurologic symptoms associated with COVID-19 in children and adolescents is broad and varies by age, including seizures/ status epilepticus in younger patients and reports of anosmia and/or ageusia, headache, and fatigue/weakness in older patients. Approximately one in every four patients with neurologic involvement, regardless of age group, presented with altered awareness or confusion. The wide range of neurologic complications, including peripheral nerve disorders (GBS and variants), focal central nervous system (CNS) disease (ischemic stroke due to large vessel occlusion, cerebral venous sinus thrombosis, and focal cerebral arteriopathy), and diffuse CNS involvement (CNS infection, ADEM, severe ence-phalopathy with white matter and corpus callosum lesions, and acute fulminant cerebral edema), suggests that multiple mechanisms underpin this wide spectrum of disease [2].

In a study conducted in the United Kingdom, four out of 27 children exhibited corpus callosum splenium MRI or CT alterations. Reversible lesions of the corpus callosum have also been observed in Kawasaki disease [12]. Sixty of our 74 patients underwent neuroimaging, with 27 (45%) receiving a brain MRI and 33 (55%) a head CT scan. The previous study reported acute to subacute infarcts (24%) as the most common neuroimaging finding in patients with COVID-19, followed by cerebral microhemorrhages, acute spontaneous intracerebral hemorrhages, and encephalitis/ encephalopathy [13]. A previous study [14] also reported acute or subacute infarct and hemorrhage as the most common neuroimaging findings. Cerebral edema findings have been reported to be the result of intracranial hypertension associated with multisystem inflammation [15].

This research was conducted as a cross-sectional study with a small sample size from one tertiary referral hospital. Therefore, the results are not representative of

WHAT THIS STUDY ADDS?

- MIS-C was diagnosed in a quarter of patients with acute neurologic symptoms and history of SARS-CoV-2 infection, with the majority of cases being post-asymptomatic infection (positive antibody test).

the entire population. The non-availability of standard drugs and supporting investigation facilities in our country makes it difficult to describe the actual response to therapy.

MIS-C was found in 24% of our patients with neurologic symptoms related to COVID-19, and 77% had positive antibody results. A multicenter study, as well as long-term interdisciplinary follow up, are needed to be done in future research. This will give healthcare providers better understanding concerning the major neurological issues in pediatric patients with SARS-CoV-2, allowing them to make rapid decisions and initiate treatment to reduce morbidity and mortality.

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RESEARCH PAPER

Differentiating Multisystem Inflammatory Syndrome in Children (MIS-C) and Its Mimics – A Single-Center Experience From a Tropical Setting

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Objective: Identifying clinical and laboratory indicators that differentiate multisystem inflammatory syndrome in children (MIS-C) apart from other febrile diseases in a tropical hospital setting. **Methods**: Review of hospital records done in a tertiary care exclusive children's hospital for children admitted from April, 2020 till June, 2021. Laboratory values, severe acute respiratory syndrome coronavirus (SARS-CoV-2) serological status, and clinical signs and symptoms of patients with MIS-C, and those with similar presentations were analyzed. **Results**: 114 children fulfilled the inclusion criteria (age group of 1 mo-18 y) for whom a diagnosis of MIS-C was considered in the emergency room based on the clinical features. Among them, 64 children had the final diagnosis of MIS-C, and the remaining 50 children had confirmatory evidence of infections mimicking MIS-C such as enteric fever, scrub typhus, dengue and appendicitis. **Conclusion**: Older age group, presence of mucocutaneous symptoms, very high C-reactive protein, neutrophilic leukocytosis, abdominal pain and absence of hepatosplenomegaly favor a diagnosis of MIS-C.

Keywords: *Dengue, Enteric fever, Scrub typhus, SARS-CoV-2.*

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Recognition of unique features of multisystem inflammatory syndrome in children (MIS-C) is critical for early recognition and treatment, and this remains a challenge for clinicians, as case definition of MIS-C often overlaps with other common conditions [1-3]. Tropical infections like enteric fever, dengue and rickettsial infection may present with clinical characteristics mimicking MIS-C in low- and middle-income settings [4,5], and may be treated incorrectly as MIS-C, resulting in unnecessary hospitalization and therapy.

We report findings from our retrospective analysis of cases of MIS-C and infections mimicking MIS-C in a pediatric hospital setting.

METHODS

This study was a review of hospital records of all children (aged 1 month to 18 years) admitted between April, 2020 to June, 2021 at our tertiary children hospital, for whom the diagnosis of MIS-C was considered upon arrival in the emergency room. The study was approved by the institutional review board. We compared the clinical and laboratory characteristics of MIS-C group and non-MIS-C groups. Cases identified as having acute coronavirus disease 2019 (COVID-19) were not included.

An initial diagnosis of MIS-C was considered in children with clinical features consistent with World Health Organization criteria for MIS-C [2]. Children who fulfilled the criteria for MIS-C (clinical and laboratory evidence of raised inflammatory markers) was grouped together, while children who had alternative diagnoses, confirmed by laboratory data for other infections including scrub typhus, dengue, enteric fever and appendicitis, were grouped as MIS-C mimics. Complete blood count was done by automated five-part hematology analyzer with Horiba Pentra E60 kit and C-reactive protein was measured with Biosystem CRP reagent by immunoturbidimetry method. Echocardiogram was done for all children who were included in the study as a part of initial evaluation. Dengue fever was confirmed by non-structural antigen/ IgM (Enzyme linked immunosorbent assay) with Bio-Merieux Mini VIDAS kit, and rickettsial infection was confirmed if scrub typhus IgM was positive (Inbios Scrub typhus Detect IgM ELISA). Enteric fever was diagnosed by blood cultures. Appendicitis was diagnosed on the basis of clinical presentation supported by ultrasonographic findings with per-operative confirmation. Confirmed COVID-19 was defined as either positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) performed by Indian Council of Medical

Research (ICMR) approved laboratories, and SARS-CoV-2 IgM and IgG antibody test was performed by ELFA method using ICMR-approved YHLO SARS-CoV-2 IgG and IgM antibody titer assay kits (BioMerieux Mini VIDAS). We also gathered data on exposure to SARS-CoV-2, course in the hospital, and outcomes including coronary artery dilatation (*z* score 2 to 2.5) or aneurysms (*z* score >2.5) and left ventricular dysfunction (ejection fraction <55%).

A final diagnosis of MIS-C was made only after two expert pediatric clinicians concurred with the diagnosis based on clinical features and after exclusion of infections based on laboratory data.

Statistical analysis: Data analyzed included demographic data, symptoms, clinical examination findings and laboratory values at the time of presentation. Clinical symptoms and gender were expressed as proportions and chi-square test was used for comparisons. Laboratory parameters were expressed as median (IQR) with Mann-Whitney test used for comparisons. A *P* value <0.05 was considered as significant.

RESULTS

A total of 114 children were initially included for analysis based on clinical criteria for MIS-C. Among them, 64 children had a final diagnosis of MIS-C, and the remaining 50 children had confirmed infections mimicking MIS-C [enteric fever (*n*=20), dengue (*n*=6), scrub typhus (*n*=15), and appendicitis (*n*=9)]. Among those initially included, there were no cases of complete Kawasaki disease (KD) phenotype or toxic shock syndrome (TSS) [6].

Among MIS-C mimics, we encountered five children with a co-infection. These children had culture positive enteric fever (*n*=20), appendicitis (*n*=9), and dengue (*n*=6), in whom reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 was also positive. However, we considered COVID as a bystander in these cases.

Duration of fever prior to presentation was nearly similar in both the groups, with a median of 4.5 days in MIS-C and 6.5 days in MIS-C mimics (**Table I**). MIS-C was more common among older children (median (IQR) age of 9.65 (5.22-17) years. Mucocutaneous symptoms (including rash, oral mucosal changes, conjunctivital congestion) and abdominal pain were more commonly observed in MIS-C (*P*=0.005) (**Table I**). Presence of rash in children was observed more amongst MIS-C cases (*P*<0.001). Organomegaly (hepatomegaly/hepatosplenomegaly) was more commonly observed in children with conditions mimicking MIS-C (**Table I**).

Table I Baseline Characteristics of Children With MIS-C and MIS-C Mimics

	MIS-C (n=64)	*MIS-C mimics (n=50)*	*P value*
Duration of fever (d)[a,b]	4.5 (3-6)	6.5 (4-9)	0.74
Age (y)[a]	10 (5-17)	4 (3-8)	<0.001
Male gender	40 (62)	26 (52)	0.339
Rash	35 (54.6)	7 (14)	0.001
Oral mucosal changes	12 (18.7)	3 (6)	0.050
Conjunctival congestion	29 (45.3)	5 (10)	0.050
Abdominal pain	29 (45)	10 (20)	0.005
Vomiting	18 (28)	20 (40)	0.230
Diarrhea	15 (23)	15 (30)	0.521
Organomegaly	11 (17)	31 (62)	<0.001
Hypotension[c]	9 (14)	5 (7)	0.57

All values in no. (%) or [a]median (IQR). MIS-C: multisystem inflammatory syndrome in children. [b]at presentation. [c]during hospital stay or at admission.

Children with MIS-C had significantly higher CRP (median CRP 132 mg/L) and higher neutrophil-lymphocyte ratio. Among 64 cases of MIS-C, only 9 (14%) children presented with or had hypotension during the course of hospital stay. LV dysfunction was seen in 7 (11%) children with MIS-C, but only two children had LV dysfunction in MISC mimics (one with dengue and one with scrub typhus). There was no evidence of coronary artery involvement in either of the groups (**Table II**).

Table II Laboratory Parameters in Children With MIS-C and MIS-C Mimics

Laboratory values	*MIS-C (n=64)*	*MIS-C mimics (n=50)*	*P value*
Hemoglobin (mg/dL)	10.4 (7.6, 14.5)	9.8 (5.6,13)	0.217
Leukocyte count (x10^9/L)	10.31 (6.77, 13.0)	8.28 (2.3, 9.34)	0.134
Neutrophil-lymphocyte ratio	5.43 (3.11,8.78)	3.76 (2.1,6.17)	0.006
Platelets (x 10^9/L)	246 (141,356)	186 (79,326)	0.225
C-reactive protein (mg/L)	132 (56,242)	53 (31,74)	0.05
Albumin (g/dL)	3.1 (2.7,4)	3.4 (3.2, 4.8)	0.12
Ventricular dysfunction[a,b]	7 (11)	2 (4)	1.00

All values in median (IQR) or [a]no. (%). MIS-C: multisystem inflammatory syndrome in children. [b]by echocardiography.

WHAT THIS STUDY ADDS?

- Older age group, presence of mucocutaneous symptoms, very high C-reactive protein, neutrophilic leukocytosis, abdominal pain, and absence of hepatosplenomegaly favor a diagnosis of MIS-C.

Leukocytosis was seen in 12 (18.7%) children with MIS-C while leukopenia was seen only in two children (3%). Thrombocytosis was seen in 14 children with MIS-C (21.8%) and thrombocytopenia was seen in 10 children (15.6%). Neutrophil-lymphocyte ratio was found to be higher in MIS-C (P =0.006) compared to MIS-C mimics (5.43 vs 3.46). Extremely high C-reactive protein (CRP) value of more than 100 mg/L was seen in 46 (72%) children with MIS-C, while only 9 (18%) children with enteric fever and scrub typhus had a CRP more than 100 mg/L (P<0.001).

SARS-CoV-2 antibody was positive in majority of the cases of MIS-C (48, 75%) and in MIS-C mimics (37, 74%), while COVID RT-PCR was positive in a few cases of MIS-C (5, 7.8%) and MIS-C mimics (5, 10%). The differences were not statistically significant.

DISCUSSION

The most discriminative predictors of MIS-C were older age group, presence of rash along with significantly raised CRP >100 mg/L and neutrophilic leukocytosis, and absence of hepatosplenomegaly.

Though early reports described MIS-C as a variant of Kawasaki disease, subsequent studies have reported varied presence of KD features and differences in laboratory parameters and demographics between these diseases [7,8]. Among the mucocutaneous symptoms in our study, cheilitis and conjunctival congestion and rash were more commonly observed among the MIS-C cohort. Although, children with MIS-C mimics had various infectious etiologies associated with gastrointestinal system, presence of abdominal pain was more often associated with MIS-C. Presence of hepatomegaly or splenomegaly or both favored a diagnosis of MIS-C mimic. Children with MIS-C may or may not present in overt shock but develop-ment of hemodynamic instability may be an important clinical sign to favor a diagnosis of MIS-C. Among the laboratory parameters, except for CRP >100 mg/L and neutrophilic leukocytosis, lymphopenia and thrombocytopenia have been frequently reported in children with MIS-C [10], but in our series none of these laboratory parameters was statistically significant to differentiate MIS-C and infections. An arbitrary cutoff of >100 mg/L was statistically significant to identify the MIS-C group (P<0.001), unlike the CDC/WHO cutoff of 30 mg/L. Interestingly, leukopenia was observed more often in MIS-C mimics.

Roberts, et al. [9] had reported that children with MIS-C were older; more likely to present with conjunctivitis, oral mucosa changes, abdominal pain and hypotension, and had higher neutrophil-lymphocyte ratios and lower platelet counts. Earlier Indian studies [10,11] have compared the manifestations of MIS-C and dengue and have reported that the presence of mucocutaneous features and highly elevated CRP favored MIS-C while the presence of petechiae, hepatomegaly, and hemoconcentration and high ferritin favored a diagnosis of dengue.

On comparison of both the cohorts, the incidence of seropositive status of COVID antibodies and RT-PCR was nearly equal. Even though the presence of SARS-CoV-2 exposure is considered as one of the diagnostic criteria (PCR/SARS-CoV-2 IgM/IgG positivity), with the reported seropositivity rate of nearly 70% [12] and an expected constantly rising rate, the utility of antibody test positivity in the diagnosis of MIS-C is limited.

Since we included only hospitalized children and our hospital's algorithm suggested considering MIS-C when CRP was ≥30 mg/L, mild cases of MIS-C might have been inadvertently missed. Multivariable logistic regression analysis was not done in our study. Tests for inflammatory makers like ESR, procalcitonin, ferritin, D-dimer were not done for all children. Our study reflects only the local prevalence of alternative diagnoses in a tropical setting. Dengue cases were diagnosed with NS1 ELISA/IgM ELISA and scrub typhus was diagnosed with Scrub IgM ELISA only, and not confirmed with PCR or cultures.

Older age group, presence of mucocutaneous symptoms, very high CRP, neutrophilic leukocytosis, abdominal pain and absence of hepatosplenomegaly favor a diagnosis of MIS-C. Considering seropositivity status alone and overlooking other diagnostic criteria for MIS-C may lead to its over-diagnosis and delay in the initiation of treatment for primary disease. Thorough clinical examination for findings like eschar, organomegaly and appropriate microbiological tests are crucial in the diagnosis of MIS-C mimics.

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Contributors: SBS, JS: concept and design; KD, SLR, DN: acquisition, analysis and interpretation of data; SBS, JS, KD, SLR: drafting of the manuscript; SC, DN: statistical analysis; SLR: analysis of laboratory assays; KD, SBS, JS, AVR: critical

revision of the manuscript for important intellectual content; SBS, JS, KD, SLR, DN, AVR, SC: final approval of the version to be published.

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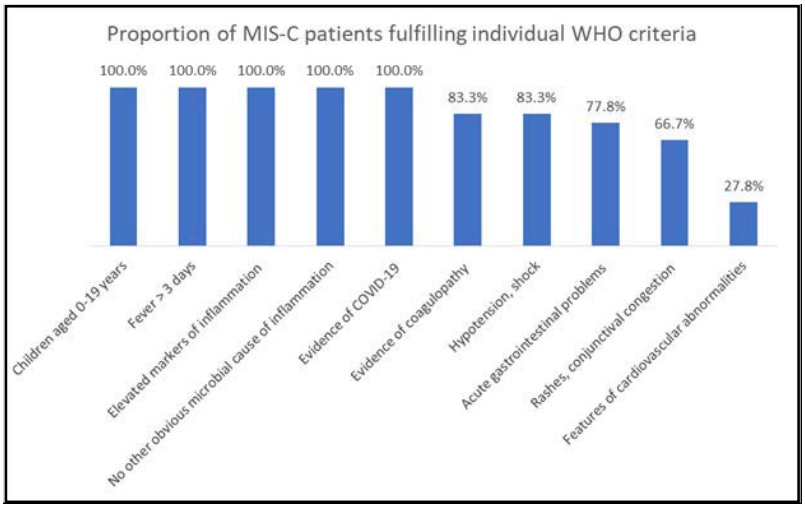

Web Fig. 1 Proportion of multisystem inflammatory syndrome in children (MIS-C) patients fulfilling individual WHO criteria.

RESEARCH PAPER

Cardiac Outcome of Children With SARS-CoV-2 Related Multisystem Inflammatory Syndrome

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Objective: To study the cardiac outcomes of patients with multisystem inflammatory syndrome in children (MIS-C) after 6-month of diagnosis. **Methods:** This review of hospital records was conducted on MIS-C patients (aged <21 years) who completed a six-month follow-up. The baseline demographic, clinical, laboratory, and treatment characteristics during the acute phase, and echocardiographic findings during follow-up were collected. **Results:** 116 patients (61.2% male, median age 7 years) with MIS-C were included in the study. At the time of admission, cardiac abnormalities were present in 70.7% of MIS-C patients, and the most common cardiac abnormalities were valve failure (50.9%), followed by ventricular dysfunction (39.7%), and pericardial effusion (23.3%). Six month after diagnosis, cardiac abnormalities were found in 10.3% of patients, and patients had lower rates of ventricular dysfunction (P<0.001), valve failure (P<0.001), pericardial effusion (P<0.001), and coronary involvement (P<0.001) as compared to the baseline. Intravenous immunoglobulin (IVIG) and steroid treatment significantly reduced the odds of occurrence of ventricular dysfunction (P=0.002), valve failure (P=0.004), and low ejection fraction (P=0.002) in comparison to IVIG treatment alone. **Conclusion:** While most MIS-C patients had abnormal echocardiographic findings at admission, only 10.3% of patients had cardiac abnormalities during follow up.

Keywords: *Echocardiography, Ejection fraction, Management, Ventricular dysfunction.*

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Multisystem inflammatory syndrome in children (MIS-C) is a severe systemic hyper-inflammatory disease with multi-organ involvement that follows severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1]. Patients with MIS-C present with a variety of clinical characteristics, including cardiac manifestations similar to Kawasaki disease (KD). There have been several studies regarding left ventricular (LV) systolic dysfunction and coronary artery dilation in MIS-C [1-4]. The incidence of coronary artery aneurysms ranges from 14-24%, and 31-58% of patients have been reported to have LV systolic dysfunction [1-3]. Few studies reported the incidence of pericardial effusion and valvar regurgitation in MIS-C; however, one study found that 33% of patients had pericardial effusions, 25% had mitral regurgitation, and 17% had tricuspid regurgitation [3].

There is limited data regarding longitudinal follow-up of MIS-C such as cardiovascular involvement. Therefore, we conducted this study to evaluate the cardiac outcomes of MIS-C patients six months after diagnosis.

METHODS

This multicenter study was conducted on children and adolescents with MIS-C who were younger than 21 years, during April, 2020 to September, 2022. The study included patients who were diagnosed with MISC-C six months before presentation and were referred to hospitals affiliated with the two study centers. Patients with congenital heart disease, previous history of cardiac dysfunction, and previous history of Kawasaki disease were excluded from the study. Subspecialty physicians at each hospital had diagnosed patients with MIS-C using CDC criteria [5].

Invited Commentary: Pages 347-49.

Age at diagnosis, gender, clinical manifestations, hospital stay duration, initial laboratory parameters including white blood cell count, hemoglobin, platelet counts, erythrocyte sedimentation rate (ESR), liver function tests, and details of treatments were entered in the study forms. Details of echocardiographic findings on admission and at six-month follow-up were also collected. According to the

vasoactive need (based on vasoactive inotropic score), the need for respiratory ventilation, and organ damage, patients were clinically categorized as having had mild, moderate, or severe MIS-C [6].

Informed consent was obtained at the time of echocardiography from all patients or from their parents/legal guardians. The study protocol was approved by the institutional ethics committee in accordance with the Helsinki Declaration guidelines.

Two-dimensional standard echocardiography was carried out by skilled cardiac sonographers utilizing the GE Vivid E9 Ultrasound System (GE Healthcare). Abnormal echocardiogram findings were described as pericardial effusion, coronary artery involvement (dilation or aneurysms), significant valvulopathy, ventricular dysfunction (diastolic function using E/A wave ratio and E wave deceleration time, and systolic function through Simpson's biplane method), or any combination of the above. According to the Boston Children Hospital *z* score system, coronary artery dilatation or aneurysm were defined as coronary artery diameter ≥2 to <2.5 *z* score and ≥2.5 *z* score, respectively [7]. Based on a modified Simpson method, the left ventricular ejection fraction (EF) was classified as either normal (≥55%) or low EF (<55%) [8].

Statistical analysis: Categorical variables were described as frequencies (%), and continuous variables were des-cribed as mean (SD) or median (IQR). We compared the demographic, clinical, laboratory, and echocardiographic examination of our patients between mild-to-moderate and severe cases. Besides, we divided patients into two groups based on the two commonly used initial treatments, which were intravenous immunoglobulin (IVIG) plus steroid or IVIG alone, and we compared the cardiac outcomes bet-ween these two types of treatment. In order to compare qualitative data, the chi-square test and, whenever needed, Fisher exact test were used. The Mann-Whitney test was used to compare the quantitative data between the two study groups. To compare the changes in echo-cardiography findings as qualitative data at baseline and the end of follow-up, McNemar test was used. Additional analyses were performed using the multiple logistic regression models to compare the echocardiography findings at the 6-month follow-up between the two treat-ment groups by adjusting the effect of MIS-C disease severity. All statistical analyses were performed using IBM SPSS software version 20.0 (SPSS Inc.), at the significance level of 0.05.

RESULTS

A total of 116 patients (71 males) with MIS-C were enrolled in the study with a median (IQR) age of 7 (5-9) years. MIS-C patients were clinically classified into severe cases (*n*=43, 37.1%), and mild-to-moderate MIS-C patients (*n*=73, 62.9%). Patients with severe MIS-C had significantly longer hospital stay than those with mild-to-moderate MIS-C ($P<0.001$) (**Table I**).

At the time of admission, cardiac abnormalities were found in 82 (70.7%) of MIS-C patients, and the most common cardiac abnormalities were valve failure (50.9%), ventricular dysfunction (39.7%), and pericardial effusion (23.3%). Severe MIS-C patients had considerably higher rates of valve insufficiency ($P<0.001$), ventricular dysfunction (P<0.001), and low EF ($P=0.018$) than mild-to-moderate MIS-C patients.

6-month follow up, cardiac abnormalities were found in 12 (10.3%) of patients (**Table II**). There was a significant decrease in cardiac abnormalities 6 month follow-up viz., ventricular dysfunction ($P<0.001$), valve failure ($P<0.001$), coronary involvement ($P<0.001$), and low EF ($P<0.001$).

On multiple logistic regression, after adjusting for the effect of MIS-C disease severity, cardiac outcomes following 6-month follow-up showed that the odds (95%

Table I Baseline Characteristics of Patients (Aged <21 Years) With Multisystem Inflammatory Syndrome in Children (MIS-C)

Variables	*Mild-to-moderate MIS-C (n=73)*	*Severe MIS-C (n=43)*
Male gender	45 (61.6)	26 (60.5)
Age (y)[a]	7 (5.0-8)	7.5 (5.5-9)
Hospital stays (d)[a,c]	8 (7.0-9)	11 (10-12.5)
Clinical characteristics		
Fever	73 (100)	43 (100)
Abdominal pain	37 (50.7)	23 (53.5)
Nausea/vomiting	28 (38.4)	17 (39.5)
Diarrhea	16 (21.9)	11 (25.6)
Respiratory symptoms	30 (41.1)	20 (46.5)
Skin rash	27 (37.0)	17 (39.5)
Lymphadenopathy	7 (9.6)	4 (9.3)
Neurologic symptoms	12 (16.4)	8 (18.6)
Laboratory findings		
Leukocytes (10^9/L)[a]	8.1 (6.9, 9.8)	7.4 (6.3, 11.45)
Hemoglobin (g/dL)[a]	11.4 (10.3, 12.7)	11.0 (10.4, 12.7)
Platlet (10^9/L)[a,c]	220 (185, 73)	187 (161.5, 213)
ESR (mm/h)[a]	37 (29, 42)	39.0 (29.5, 44)
AST (U/L)[a]	33 (25, 45)	30 (20, 47.5)
ALT (U/L)[a]	34 (21, 44)	30 (20.5, 48.5)
Creatinine (mg/dL)[b]	0.59 (0.15)	0.65 (0.16)
Treatment[c]		
IVIG	50 (68.5)	4 (9.3)
IVIG + steroid	23 (31.5)	39 (90.7)

Values in no. (%), [a]median (IQR) or [b]mean (SD). P<0.001. ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; IVIG: intravenous immunoglobulin.

WHAT THIS STUDY ADDS?

- In this retrospective study, only 10.3% patients were found to have cardiac abnormalities on echocardiography, six months after a diagnosis of multisystem inflammatory syndrome in children associated with coronavirus disease (MIS-C).

Table II Echocardiography Findings of MIS-C Patients at Admission and at Six-Month Follow-up

Findings	*Mild-to-moderate MIS-C (n=73)*	*Severe MIS-C (n=43)*
At admission		
Ventricular dysfunction	20 (27.4)	26 (60.5)
Valve failure	27 (37.0)	32 (74.4)
Pericardial effusion	13 (17.8)	14 (32.6)
Coronary involvement	10 (13.7)	6 (14.0)
Low ejection fraction	9 (12.3)	13 (30.2)
At 6-month follow-up		
Ventricular dysfunction	3 (4.1)	4 (9.3)
Valve failure	4 (5.5)	6 (14.0)
Pericardial effusion	0	0
Coronary involvement	1 (1.4)	2 (4.7)
Low ejection fraction	3 (4.1)	4 (9.3)

Values in no. (%). [a]*P<0.001,* [b]*P<0.05.*

CI) of persisting ventricular dysfunction 0.009 (0-0.16), valve failure 0.025 (0.002-0.306), and low EF 0.009 (0 -0.16) in the IVIG plus steroid treatment group were greater than those in the IVIG treatment group, respectively but not for coronary involvement [0.71 (0.03-16.6)].

DISCUSSION

This hospital record review found a 10.3% occurrence of cardiac abnormalities in children who had MIS-C six months back, which were lower in those who were treated with steroids and IVIG both.

According to recommendations, MIS-C patients require long-term follow-up, particularly in the case of cardiac involvement. Due to the similarities between MIS-C and KD, the long-term cardiac sequela has been described in the literature as a coronary artery aneurysm, and it is suggested that it be monitored similarly to KD [4]. Various studies had different rates of cardiac abnormalities on echocardiographic follow-up. One study reported that 16% of MIS-C patients had persisting echocardiographic abnormalities after three months follow-up [11]. Another study found 15.4% of 138 MIS-C patients had residual echocardiographic changes after an average follow-up of 39.9 days [12]. We found that 10.3% of patients had cardiac abnormalities after a 6-month follow-up, which is a longer follow-up than the previous two studies. Bagri, et al. [13] found that following 4-6 weeks of echocardiographic follow-up, one of the 19.4% of MIS-C patients who had a coronary artery abnormality at admission still had coronary artery involvement [13]. Farooqi, et al. [14] reported that 80% of MIS-C patients had mild echocardiographic abnormalities, while 44% of them exhibited moderate-to-severe abnormalities such as coronary involvement. None of the patients had coronary involvement, and 18% still had mild echocardiographic abnormalities following 1-4 weeks of cardiac follow-up [14].

With regards to the treatment, IVIG and steroids are the main treatment options for MIS-C patients. Previous studies demonstrated that IVIG plus steroids was linked to better fever course than IVIG alone [15]. Son, et al. [16] reported that patients who received IVIG plus steroids had decreased risks for the left ventricular dysfunction (8% vs 17%). Our findings are in line with this study that IVIG plus steroid treatment significantly reduced the odds of ventricular dysfunction in comparison to IVIG treatment alone. Similarly, Ouldali, et al. [15] demonstrated that treatment with IVIG plus steroids was linked to fewer severe acute consequences, such as acute left ventricular dysfunction and the need for hemodynamic support. Another single-center study [17] concluded that cardiac recovery in those who received IVIG plus steroids was shorter in comparison to those who received IVIG alone. Further studies are required to comprehend the mechanisms underlying the potential effect of steroids in patients with MIS-C.

In conclusion; although, MIS-C is a severe multisystem disorder throughout its acute stage, it has a generally encouraging long-term cardiac outcome. Furthermore, treatment with IVIG plus steroids may reduce the risk of cardiac complications on follow-up.

Ethics clearance: Institutional Ethics Committee, AJA University of Medical Sciences; No. IR.AJAUMS.REC.1401.136 dated Nov 20, 2022.
Contributors: MYZ: conceptualized the study design; analyzed and interpreted the results, and wrote the manuscript; ARG, AM, SS, A Aminian, BD, A Azarfar: recruited patients, collected demographic and clinical data analyzed and interpreted the results; ARG: conceptualized the study design, analyzed and interpreted the results, and commented on and revised the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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RESEARCH PAPER

Profile of Cardiac Involvement in Children After Exposure to COVID-19

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Objective: To evaluate the incidence and pattern of cardiac involvement in children post-COVID (coronavirus disease) infection in a tertiary care referral hospital in India. **Methods**: A prospective observational study was conducted including all consecutive children with suspected MIS-C referred to the cardiology services. **Results**: Of the 111 children with mean (SD) age 3.5 (3.6) years, 95.4% had cardiac involvement. Abnormalities detected were coronary vasculopathy, pericardial effusion, valvular regurgitation, ventricular dysfunction, diastolic flow reversal in aorta, pulmonary hypertension, bradycardia and intracardiac thrombus. The survival rate post treatment was 99%. Early and short-term follow-up data was available in 95% and 70%, respectively. Cardiac parameters improved in the majority. **Conclusion**: Cardiac involvement post COVID-19 is often a silent entity and may be missed unless specifically evaluated for. Early echocardiography aids in prompt diagnosis, triaging, and treatment, and may help in favorable outcomes.

Keywords: *Coronary aneurysm, Intracardiac thrombus, MIS-C, Pericardial effusion, Ventricular dysfunction.*

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In the global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV- 2), most children showed minimal symptoms; however, a subset developed hyper-immune multiorgan inflammation [1,2]. The Centers for Disease Control and Prevention (CDC) defined this as multisystem inflammatory syndrome in children (MIS-C) [3], with some similarities with Kawasaki disease. The cardiovascular manifestations of MIS-C included arrhythmias, coronary vasculopathy, ventricular dysfunction, valvular regurgitation, and pericardial effusion. Other complications like intracardiac thrombus, shock and myocarditis were infrequently reported [4-7]. Immunomodulation has been found to have a promising role in the management of MIS-C.

METHODS

A prospective observational study was conducted between June, 2021 and September, 2021, enrolling consecutive children with suspected MIS-C [3], referred to pediatric cardiologists in a tertiary care hospital in northern India, post second wave of coronavirus disease (COVID-19). Children with bacterial sepsis and other alternative diagnosis, were excluded. Demographic, anthropometric and clinical data including clinical presentation, treatment and early and short-term outcomes were recorded. Laboratory data were assessed under three broad categories, organ function tests, and inflammatory and cardiac markers.

Invited Commentary: Pages 347-49.

Cardiac evaluation was done by twelve lead electrocardiogram (ECG), and echocardiography as per American Society of Echocardiography guidelines [8] and cross evaluated by another cardiologist blinded to clinical data. As per American Heart Association guidelines [9], the coronary arteries were classified as no involvement (*z* score <2), dilatation only (*z* score ≥2-<2.5), small aneurysm (*z* score ≥2.5-<5), medium aneurysm (*z* score ≥5-<10) and large aneurysm (*z* score ≥10). The first cardiac evaluation was performed within 7 days of onset of symptoms and follow-up between 10-14 days post therapy. Survivors were planned for subsequent cardiac assessments at 1 month, 3 months and at 1 year.

Statistical analysis: Data were analyzed by SPSS v 20.0 trial version. Fisher exact test was used to compare categorical data. Kruskal-Wallis test was used to compare data which was not normally distributed. *P* value <0.05 was considered statistically significant.

RESULTS

A total of 111 children (74 males), with mean (SD) age of 3.5 (3.6) years were studied. Seven (6.3%) were neonates, 26 (23.4%) were infants, and majority 78 (70.2%) were between 1 and 14 years of age. SARS-CoV-2 antibodies were positive in 94.5%, none were RT-PCR positive, and contact tracing was positive in 13.5%.

The mean (SD) time from onset of symptoms to presentation to cardiologist was 5.4 (2.2) days. Pyrexia was the predominant feature in 92 (82.8%) children, followed by gastrointestinal symptoms in 35 (31.5%) (vomiting 16.2%, loose stools 5.3%, abdominal pain 6.3%), rash in 15 (13.5%), altered sensorium in 4 (3.6%) and generalized swelling in 4 (3.6%). Respiratory distress was universal in neonates while it was observed in 26 (23.4 %) in pediatric group (8.1% had severe and 15% had mild-to-moderate distress). Bradycardia was found in 7 children.

Laboratory investigations revealed anemia in 30 (27%), which was severe (hemoglobin <7g/dL) in 7 (6.3%). Leucolytosis was seen in 15 (13.5%), with increased neutrophil-lymphocyte ratio in 5 (4.5%) and thrombocytopenia in 13 (11.7%). Inflammatory markers were elevated in 105 (94.5%). Mean (SD) C-reactive protein and procalcitonin were 22.3 (30.4) and 8.1 (9.1), respectively. Deranged renal function was noted in 12 children while 15 had elevated transaminases. Abnormal levels of troponin T were seen in 22 (20%) and elevated D-dimer was noted in 40 (36%). D-dimer was >4 times of normal in all children with MIS-C.

ECG evaluation showed all children to be in sinus rhythm, except seven who had bradycardia. Bradycardia was secondary to sinus node dysfunction in six children and Wenckebach phenomena in one child. The findings of echocardiography are shown in **Table I**. A total of 45 (40.5%) children showed ventricular dysfunction with left ventricle affected in 36% and right ventricle in 4.5%. Coronary vasculopathy was detected in 67 children (60.3%) (**Fig. 1**). Left main coronary artery was most commonly affected (56%) followed by left anterior descending (31%). Mean ratio of velocity time integral of reversed and antegrade flows was 0.25. Diastolic flow reversal was associated with low cardiac output in two children and with severe anemia in seven, while in others it may be arteriopathy affecting vascular compliance. Two had moderately severe pulmonary artery hypertension (all neonates). Pulmonary venous hypertension (PVH) was present in one patient with severe left ventricular dysfunction. Two children showed intracardiac thrombus.

Table I Echocardiographic Findings in Patients With MIS-C (*N*=111)

Parameters	*No (%)*
Coronaries	
Normal	44 (39.6)
Dilated	17 (15.3)
Small aneurysm	48 (43.2)
Moderate aneurysm	2 (1.8)
Large aneurysm	0 (0)
Dilated chamber	17 (15.3)
LA/LV	10 (9)
RA/RV	7 (6.3)[a]
LV dysfunction (EF%)	40 (34.2)
Mild (45-<55%)	33 (27.9)
Moderate (30-44%)	6 (5.4)
Severe (<30%)	1 (0.9)
RV dysfunction	5 (4.5)
Pericardial effusion	54 (48.6)
Diastolic flow reversal	19 (17.1)
Structural abnormality	
Ventricular septal defect	2 (1.8)
Left SVC to coronary sinus	2 (1.8)
Coronary artery origin from different sinus	3 (2.7)
Patent foramen ovale	18 (16.2)
Valve regurgitation	87 (78.2)
Tricuspid	
Mild	79 (71.1)
Moderate	8 (7.2)
Severe	1 (0.9)
Mitral[b]	
Mild	51 (45.9)
Moderate	6 (5.4)
Aortic[c]	
Mild	24 (21)

[a]*All neonates.RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, EF: ejection fraction, SVC: superior vena cava, CS: coro-nary sinus, PFO: patent foramen ovale, DFR: diastolic flow reversal.* [b]*none had severe regurgitation;* [c]*none had moderate or severe regurgitation.*

Table II shows association between increased CRP level and coronary artery involvement. Significantly higher proportion of patients with normal CRP had small aneurysms than the patients with abnormal CRP [OR (95% CI) 3.31 (1.28-8.57); *P*=0.014]. There was no significant association between duration of admission, age in years, BMI, BSA with coronary involvement and ventricular dysfunction.

All patients received immunomodulation. Intravenous immunoglobulin (IVIG) alone was given to 34 (31%), both

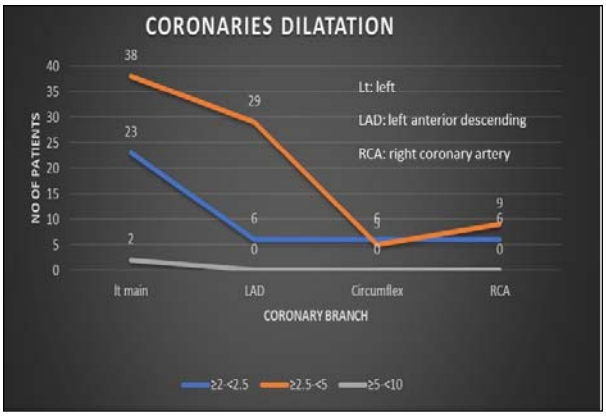

Fig. 1 Coronary artery (left main), left arterior descending (LAD) artery, right coronary artery (RCA) and circumflex artery among children with MIS-C.

IVIG and corticosteroids were administered to 45 (40%), while 32 (29%) received only steroids (due to resource constraints). Low molecular weight heparin was administered to those with documented intra-cardiac thrombi. All were discharged on oral aspirin and continued till normalization of coronaries. Ionotropic support and mechanical ventilation were required for 6 (5.4%) and 11 (10%) children, respectively. The mean (SD) duration of hospital stay was 5.7 (1.9) days. All children, except the infant with giant right atrial thrombus, recovered. Immediate survival rate was 99%.

Early (mean, 12 days) and short-term (mean, 95 days) follow-up data was available in 95% and 70% of children. Early follow-up echocardiography showed improvements in most parameters. Proportion of children with coronary involvement decreased to 56% while 11.3% had increased *z*-scores in first follow up. Cardiomegaly persisted only in five children while significant valvular regurgitation disappeared in all. Ventricular function normalized in 95.5%, pericardial effusion decreased to 1.8% as compared to 48.6% at the onset, while none had pleural effusion. At short-term follow-up, 11 (10%) children showed persistent coronary aneurysm. Ventricular function, pulmonary artery pressure and rhythm normalized in all. The child with Wenckebach phenomenon was lost to follow-up.

DISCUSSION

Our study included mostly young children, in contrast to studies by Dufort, et al. [5] and Rajapakshe, et al. [10]. This may be due to increased awareness among pediatricians who referred all suspected MIS-C to pediatric cardiologists. Our data revealed cardiac involvement in 95.4% of cohort in the form of coronary vasculopathy, ventricular dysfunction, valve regurgitation, and rhythm abnormalities.

As per previous data [11], cardiac involvement was common and reported in 67-80% of MIS-C. Common cardiovascular manifestations were cardiac dysfunction (31-58%), coronary vasculopathy (14-48%), and rhythm abnormalities (6.3-25%).

Our study demonstrated that echocardiography provides significant value to clinical information. Although, none of them are per se diagnostic for MIS-C, rapid exclusion of alternative diagnosis and initiation of therapy provided survival benefit to 99% of the patients. Therapeutically, the recommended protocol of immunoglobulin and steroids could not be initiated in all patients. Data from low- and middle-income nations suggested that steroids can be an acceptable alternative in such situations [12].

MIS-C in neonatal group presented a diagnostic dilemma. Findings observed were cardiomegaly, severe

Table II Association Between C-Reactive Protein and Coronary Artery Parameters

	C-reactive protein, n (%)		*Odds ratio (95% CI)*	*P value*
	Normal	*Abnormal*		
Left anterior descending artery				
Dilated	1 (3.8)	5 (6)	0.938 (0.101-8.718)	0.955
Small aneurysm	12 (46.2)	17 (20.5)	3.312 (1.280-8.574)	0.014
Left main coronary artery				
Dilated	5 (19.2)	16 (19.3)	1.354 (0.392-4.672)	0.631
Small aneurysm	11 (42.3)	27 (32.5)	1.765 (0.644-4.839)	0.269
Moderate aneurysm	1 (3.8)	1 (1.2)	4.333 (0.247-76.046)	0.316
Circumflex artery				
Small aneurysm	3 (11.5)	2 (2.4)	4.891 (0.770-31.082)	0.092
Right coronary artery				
Dilated	1 (3.8)	5 (6)	0.617 (0.069-5.560)	0.667
Small aneurysm	2 (7.7)	7 (8.4)	0.882 (0.171-4.548)	0.881

WHAT THIS STUDY ADDS?

- Ventricular dysfunction and coronary vaculopathy were the most common cardiac abnormalities seen with multisystem inflammatory syndrome in children (MIS-C).
- Most of the echocardiographic parameters improved over a short-term follow-up.

pulmonary hypertension, significant valvular regurgitation, ventricular dysfunction, coronary involvement, thrombus and arrhythmia [13]. Presence of such findings should alert the neonatologists towards presence of MIS-C. However, other respiratory causes and cyanotic congenital heart diseases must be excluded.

The major limitation of our study is that the study was conducted only on children referred by pediatricians to cardiologists; thus, referral bias cannot be ruled out. Advanced cardiac imaging like coronary angiography or MRI was not done due to the emergent situation. Echocardiography was the best rapid diagnostic modality available, and was helpful in early management.

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RESEARCH PAPER

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With COVID-19 – Single-Center Experience

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Objectives: To describe the clinical presentation, phenotype and outcome of multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) from a tertiary care center in southern India. **Methods:** 257 children fulfilling the inclusion criteria of MIS-C were prospectively enrolled from June, 2020 to March, 2022. **Results:** Median (range) age at presentation was 6 year (35 day to 12 years). Presenting features were fever (98%), vomiting (75.8%), red eyes (63%), rashes (49%), pain abdomen (49%), shock (45.9%), lymphopenia (73%, thrombocytopenia (58.3%) and anemia (45%). 103 (39.7%) children required intensive care admission. Shock phenotype, Kawasaki-like phenotype and no specific phenotype were diagnosed in 45.9%, 44.4%, and 36.6% children, respectively. Left ventricular dysfunction (30.3%), acute kidney injury (13%), acute liver failure (17.4%), and hemophagolymphohistiocytosis (HLH) (13.6%) were the major system involvement in MIS-C. Mitral regurgitation (*P*=0.029), hyperechogenic coronaries (*P*=0.006), left ventricular dysfunction (*P*=0.001) and low ejection fraction (*P*=0.007) were significantly associated with shock. Overall mortality was 11.7%. **Conclusions:** Kawasaki-like and shock-like presentation were common in MIS-C. Coronary abnormalities were seen in 118 (45.9%) children. Children with acute kidney injury, HLH, need for mechanical ventilation, and echocardiogram evidence of mitral regurgitation in MIS-C have a poor outcome.

Keywords: *Coronary artery, Kawasaki disease, Outcome, Shock*.

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Coronavirus disease 2019 (COVID-19) in children is usually a mild disease, but the associated multisystem inflammatory syndrome in children (MIS-C) presenting with toxic shock syndrome or Kawasaki-like presentation is a severe manifestation. The reported incidence is uncertain, but it occurs in less than 1% of children with SARS-CoV-2 infection. Probable immune-mediated mechanisms have been suggested for this major post-infectious complication, which sometimes requires intensive care admission. The World Health Organization (WHO) has given the clinical definition of this new disease [1].

In India, there are limited studies on MIS-C. This study from a single center in southern India, describes the clinical presentation, phenotype, complications and outcome among children with MIS-C.

METHODS

We prospectively enrolled children admitted with MIS-C, from a pediatric tertiary care center in Chennai during June, 2020 to March, 2022. The study was approved by the institutional ethics committee, and informed written consent was obtained from the parents/legal guardians. Consecutive children aged 1 month to 12 years, diagnosed as MIS-C as per the WHO criteria [1], were included. Children referred as MIS-C from other centers and whose complete treatment details were not available, and children with acute COVID-19 were not enrolled.

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Detailed history, clinical features, phenotype, laboratory investigations, complications and outcome were recorded. Clinical parameters like tachycardia, tachypnea and shock were defined as per Indian Academy of Pediatrics, Advanced Life Support guidelines [2]. Anemia was defined according to the WHO definition as hemoglobin <11 g/L up to 5 years, <11.5 g/L for 5 -11 years and <12 g/L for 12-14 years [3]. Thrombocytopenia was defined as platelet count $<150\times10^9$/L while thrombocytosis was platelet count $>450\times10^9$/L, and lymphopenia was defined as lymphocyte count $<3.0\times10^9$/L. Standard definitions

were used for complications like acute kidney injury (AKI) [4], acute liver failure (ALF) [5], hemophagocytic lymphohistiocytosis (HLH) [6], and pediatric acute respiratory distress syndrome (pARDS) [7]. On admission, children were evaluated for sepsis, common tropical infections and baseline laboratory workup including inflammatory markers like erythrocyte sedimentation rate, C-reactive protein, ferritin, liver enzymes, alongwith complete blood counts, electrolytes and renal parameters. Cardiac evaluation for all children was done by a qualified pediatric cardiologist using GE Vivid S6 ultrasound machine with phased array cardiac transducer. Coronary artery abnormalities were categorized as normal (*z* score <2), dilated (*z* score 2-2.5) or aneurysm (*z* score >2.5) and aneurysms were sub-categorized as small, medium and giant based on their *z* scores of 2.5-5, 5-10 and >10, respectively [8]. An ejection fraction less than 55% was considered left ventricular dysfunction [9]. Severe acute respiratory (SARS-CoV-2) IgG antibody test was performed with Indian Council of Medical Research (ICMR) approved assay kits as per the manufacturer's instructions, and titers more than 10 AU were considered reactive. All children were followed-up till discharge from the hospital, or death, in case of mortality.

Statistical analysis: All analyses were performed using Epi Info 7.0 and SPSS statistical software (version 20). Descriptive statistics were used to present the data. *P* value <0.05 was considered statistically significant. Multiple regression analysis was done to identify the risk factors for mortality.

RESULTS

Among the 312 children with acute febrile illness and features of multisystem inflammatory syndrome, 257 were included for the study. Children with sepsis (*n*=3), tropical infections like enteric fever (*n*=2), dengue (*n*=24), scrub typhus (*n*=18), leptospirosis (*n*=2) and other bacterial infections (*n*=2), and children who were treated outside with no details of therapy, were excluded (*n*=4).

Overall, we studied 257 children for their clinical and laboratory parameters and outcome. Of these,147 (57.2%) children had consulted elsewhere prior to attending our Institute and 110 children came directly for the first consult. Two children had received one dose of methylprednisolone prior to referral. Other children had received antipyretics, antibiotics, antiemetics, oral rehydration fluid and intravenous fluids. The median (IQR) age of the population was 6 (2-9) years and the male:female ratio was 1.19:1. Median (IQR) duration of illness was 5 (3-7) days. Twenty one children (8%) had documented COVID infection in the past, while 51 children (19.8%) had epidemiological link with COVID-19.

Table I Clinical and Laboratory Characteristics of Children With MIS-C (*N*=257)

Parameter	*Value*
Clinical features	
Fever at admission	252 (98.0)
Red eye	163 (63.4)
Red lips	98 (38.1)
Cracked lips	113 (43.9)
Rashes	127 (49.4)
Pain abdomen	128 (49.8)
Vomiting	195 (75.9)
Diarrhoea	137 (53.3)
Edema	114 (44.3)
Strawberry tongue	88 (34.2)
Altered sensorium	85 (33.1)
Breathlessness	61 (23.7)
Oliguria	47 (18.3)
Lymphadenopathy	32 (12.9)
Comorbid illness	39 (13.2)
Myalgia	27 (10.5)
Sore throat	20 (7.7)
Acute kidney injury	34 (13.2)
Acute liver failure	45 (17.5)
Peeling of skin	31 (12.1)
Seizures	21 (8.1)
Headache	19 (7.3)
Aneurysm of 1 coronary	45 (17.5)
Aneurysm of 2 coronaries	31 (12.1)
Aneurysm of 3 coronaries	24 (9.3)
Ascites	38 (15.4)
Laboratory parameters	
aPTT (s)[a]	30.2 (26.7-97)
International normalized ratio[a]	1.2 (1.05 -1.49)
Alanine aminotransferase (U/L)[a]	30 (17 -59)
Aspartate aminotransferase (U/L)[a]	38 (25 -78)
D-dimer (ng/mL)[a]	2.83 (1.23 -4.78)
C-reactive protein (mg/L)[a]	48 (12-106)
Erythrocyte sedimentation rate (mm/h)[a]	67.5 (38-96)
Ferritin (pmol /L)[a]	454 (218 -1104)
Hemoglobin (g/L)[a]	10 (8.8 -10.9)
Lymphopenia	190 (73.93)
Anemia	137 (53.31)
Thrombocytopenia	118 (45.91)
Sodium (mmol/L)[a]	131 (128 -134)
Neutrophil:lymphocyte ratio[a]	3.84 (2.2-7.9)
Platelet at admission ($x10^9$/L)[a]	2.02 (1.2 -3.5)
Procalcitonin (ng/mL)[a]	9.11 (1.46 -42.36)
Prothrombin time (s)[a]	15.6 (13.95 -18.35)
White blood count ($x10^9$/L)[a]	11.4 (7.6 -16.5)
Interleukin 6 (pg/mL)[a]	61.6 (13.5 -313)
Triglycerides (mmol/L)[a]	224 (160-303)

Values in no. (%) or [a]median (IQR). aPTT: activated partial thromboplastin time.

MIS-C presented as an acute febrile illness with gastrointestinal symptoms and mucocutaneous features like red eye, red lips, red tongue and rashes. Among the 128

children with pain abdomen, 7 (5.5%) had undergone surgical management for intussusception and appendicitis prior to the diagnosis of MIS-C, out of which one child died. Neck swelling and submandibular lymphadenopathy at presentation was observed in 20 children (7.7%). Clinical and laboratory features of the study group are given in **Table I**. Fluid boluses at admission for shock, ranged from 10 mL/kg to 110 mL/kg with a mean of 18.5 mL/kg. Among the 118 (45.9%) children with shock, 100 (38.9%) children required inotropes with 55 children requiring one inotrope, 37 needing two inotropes and 8 children requiring 3 inotropes. Oxygen supplementation was required in 140 (54.5%) children out of whom 42 (16.4%) were mechanically ventilated;103 (39.6%) children required pediatric intensive care admission. Five children had discoloration and dermal gangrene which resolved over a few weeks without sequelae. Another five children had digital gangrene, out of whom two died. Six children had underlying immunocompromised conditions like leukemia, nephrotic syndrome and steroid treatment for immune thrombocytopenia, and they were IgG antibody negative despite a documented SARS-CoV-2 RT-PCR positivity in the previous 12 weeks. Other noted comorbid states were diabetic ketoacidosis, febrile seizures, reactive airway disease, autoimmune encephalitis, chronic idiopathic thrombocytopenia, congenital heart disease, developmental delay, achondroplasia, febrile seizures and seizure disorder.

Kawasaki disease (KD) phenotype was present in 114 (44.4%) children with a median age of 5.75 (2-9) years, and 118 (45.9%) had shock phenotype with a median age of 6 (2-9) years. 94 children (36.6%) had no specific phenotype, among whom 35 children had features of hemophagocytic lymphohistiocytosis (HLH). Sixty nine children (26.85%) had combination of more than one phenotype. 118 (45.9%) children had coronary abnor-malities in the form of dilatations, aneurysms, hyper-echogenic and non-tapering coronaries. LV dysfunction was observed in 78 (30.35%) and this normalized at the time of discharge in 70 children. Intracardiac thrombi was encountered in one child. The echocardiogarphic features such as mitral regurgitation (P=0.029), hyperechogenic coronaries (P=0.006), left ventricular dysfunction (P<0.001) and low ejection fraction (P=0.007) were significantly associated with shock.

Common hematological features were lymphopenia, anemia and thrombocytopenia (**Table I**). Hyponatremia and hypoalbuminemia were seen in 76% and 55%, respectively, while elevated AST and ALT enzymes were seen in 47% and 40% of children at admission. Two thirds of the study group had ferritin more than 500 pmol/L.

Along with supportive treatment, 155 (60%) children received IVIG, 191 (74.31%) children received methylprednisolone/prednisolone and 27 (10.5%) children received no therapy. All the 230 treated children were on aspirin. Tocilizumab was given to five children who were febrile without clinical improvement and with rising inflammatory markers despite IVIG and methylprednisolone. Children who fulfilled the MIS-C criteria but without the Kawasaki or HLH phenotype and who became afebrile during hospital stay with declining trend of inflammatory markers did not receive any treatment. The outcome among children who were treated and those who were not treated for MIS-C did not show statistically significant difference (P=0.36). Children with elevated liver enzymes received NAC infusion and among the 34 children with renal failure, three received peritoneal dialysis, six received hemo-

Table II Clinical and Laboratory Parameters of Children With MIS-C (N=257)

Parameters	*Died*	*Recovered*	*P value*
Clinical parameters			
Pain abdomen	12 (9.4)	116 (90.6)	0.26
Diarrhea	17 (12.4)	120 (87.5)	0.47
Bleeds	8 (53.3)	7 (46.6)	<0.001
Breathlessness	14 (22.9)	47 (77)	0.003
Altered sensorium	18 (21.1)	67 (78.8)	0.002
Red eye	15 (9.2)	148 (90.8)	0.045
Red lips	10 (10.2)	88 (89.8)	0.289
Seizures	8 (38.1)	13 (61.9)	<0.001
Vomiting	26 (13.3)	169 (86.7)	0.141
Rash	15 (11.8)	112 (88.2)	0.47
Skin necrosis	4 (26.7)	11 (73.3)	0.08
Edema	13 (11.4)	101 (88.6)	0.56
Shock	27 (22.9)	91 (77.1)	<0.001
Ascites	8 (21.1)	30 (78.9)	0.36
Gangrene	3 (60)	2 (40)	0.012
Hypotension	18 (29.5)	43 (70.5)	<0.001
Oliguria	10 (21.3)	37 (78.7)	0.043
Strawberry tongue	8 (9.1)	80 (90.9)	0.242
Skin peeling	3 (9.37)	29 (90.6)	0.49
Acute liver failure	21 (46.7)	24 (53.3)	<0.001
HLH	19 (54.3)	16 (45.7)	<0.001
Acute kidney injury	22 (64.7)	12 (35.3)	<0.001
MODS	18 (64.2)	10 (35.7)	<0.001
Mechanical ventilation	26 (61.9)	16 (38.1)	<0.001
ARDS	1 (50)	1 (50)	0.21
LV dysfunction	24 (30.8)	54 (69.2)	<0.001
Laboratory parameters			
Thrombocytopenia	25 (21.2)	93 (78.8)	<0.001
Hyponatremia	22 (11.3)	172 (88.7)	0.461
Thrombocytosis	4 (5.5)	68 (94.4)	0.039
Lymphopenia	17 (12.2)	122 (87.8)	0.38
Mitral regurgitation	17 (22.4)	59 (77.6)	<0.001
Coronary z score >2	17 (14.4)	101 (85.6)	0.287

All values in no. (%). HLH: hemophagocytic lymphohistiocytosis; MODS: multi organ dysfunction syndrome; ARDS: acute respiratory distress syndrome; LV: left ventricle.

WHAT THIS STUDY ADDS?

- Mortality in multisystem inflammatory system (MIS-C) is high.
- Acute kidney injury, hemophagolympho-histiocytosis (HLH), need for mechanical ventilation, and mitral regurgitation are associated with a poorer outcome.

dialysis and one child was on continuous renal replacement therapy (CRRT).

No statistically significant difference was observed in clinical presentation, complications and outcome among children referred from elsewhere and those who came directly. Comparison of laboratory parameters among the children who survived and died is summarized in **Tables II** and **Web Table I**. Urea, creatinine, AST, ALT, LDH, IL-6, ferritin, D-dimer, aPTT and INR were the laboratory parameters significantly higher in the children who died compared to the survivors; while platelet count, serum albumin and ejection fraction were significantly lower in those who died compared to the survivors. Pre-hospital illness duration and duration of hospital stay were significantly lower in the children who died when compared to the survivors (P=0.005 and P=0.004, respectively). The median (IQR) hospital stay was 9 (2-13) days. Multiple logistic regression revealed aOR (95% CI) for AKI [1709 (3.78-77.23); P<0.001], HLH [29.29 (4.43-102.27)], need for ventilatory support [25.45 (5.59-115.92)] and mitral regurgitation [7.16 (1.55-32.57)] as significant factors associated with mortality. Overall mortality (95% CI) was 11.67% (8.02-16.24).

DISCUSSION

In this prospective study, we report the clinical presentation, complications and outcome of MIS-C. Kawasaki-like illness and shock were the common phenotypes. Acute kidney injury, need for mechanical ventilation and HLH were poor prognostic factors. The median (IQR) age group of the study was 6 (2-9) years, which is similar to 7.2 years and 6 years as noted in studies from Mumbai [9] and Chennai [10], respectively. Shock was seen in majority of our children, as also reported in a study from Mumbai [11].

The common presentation of acute febrile illness of MIS-C is also seen in sepsis and common tropical infections like dengue, scrub typhus and leptospirosis. MIS-C mimicking acute appendicitis and MIS-C co-existing with acute appendicitis has been reported in literature [12].

While coronary measurements more than 2.5 z score are 98% specific for KD [13], literature reveals that non-KD conditions are rarely associated with coronary dilatation and aneurysm [14]. Coronary involvement varies across different studies from 9-25% and studies have also reported giant aneurysms [15]. In the present study, in majority of cases, left ventricular dysfunction normalized before discharge and is similar to the existing published literature on MIS-C [16].

Mortality of MIS-C in the current study was 11.67%. Being a tertiary care referral center, the proportion of sick cases was much higher in this study group. Mortality up to 10.9% and as high as 18% from pediatric intensive care units have been reported [17,18]. Reported risk factors for mortality are need for ventilation, renal replacement therapy, higher ferritin and cardiovascular complications [17]. No mortality was encountered among children without Kawasaki or shock phenotype. This could be because the untreated children were the mild cases who were recovering at the time of hospitalization. Multicentric studies done elsewhere have shown no significant difference in death among children treated with different modes of immunotherapy However, the influence of immunotherapy and its outcome needs to be assessed by well-planned RCTs.

Limitation of this study is that cardiac enzymes were not done in all children. Severity of the illness might vary with the different strains, and this was not analyzed in this study. The proportion of children presenting with MIS-C following COVID-19 may depend on many factors, which needs to be addressed in future research.

We conclude that Kawasaki-like and shock phenotype were the common presentations in MIS-C, and a high proportion of children present with coronary abnormalities (45.9%). Majority of left ventricular dysfunction resolved before discharge. Acute kidney injury, HLH, mitral regurgitation and need for ventilation are indicators of poor outcome in MIS-C.

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of manuscript; SS: data acquisition, analysis and interpretation of data, drafting of manuscript; RS: data collection and analysis, manuscript writing, contributed to the critical revision of manuscript for intellectual content; NR: designed the study, data acquisition, data analysis, manuscript writing, revision of manuscript; GS: designing of the study, statistical analysis, manuscript writing and drafting of manuscript. All authors approve 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 Comparison of Study Parameters Among the Study Group (*N*=257)

Parameter	*Died*	*Recovered*	*P value*
Prothrombin time (s)	19.9 (15-24.5)	34.2 (27-39)	<0.001
International normalized ratio	1.59 (1.18-2.07)	1.16 (1.04-1.33)	<0.001
Creatinine (µ mol/L)	0.65 (0.4-1.4)	0.4 (0.3-0.5)	0.001
Urea (mmol/L)	35.5 (22-65)	22 (16-32)	<0.001
C-reactive protein (mg/L)	34 (6-96)	48 (12-107)	0.219
Leukocyte coun ($\times 10^9$/L)	19.2 (13.2-34)	14.45 (9.7-19.6)	0.004
Lowest platelet count ($\times 10^9$/L)	0.59 (0.35-1.06)	1.58 (0.95-2.69)	<0.001
Neutrophil-lymphocyte ratio	6.5 (3-11.49)	3.5 (2.2.-7.4)	0.289
D-dimer (ng/mL)	5.3 (3.8-7.6)	2.2 (1.1-4.2)	<0.001
Interleukin-6 (pg/mL)	319 (24.1-1131)	59 (12.5-200)	0.078
Ferritin (pmol/L)	1577 (284-2701)	446 (288-891)	0.002
Fluid bolus (mL/kg)[b]	15 (10-20)	10 (10-30)	0.502
Triglycerides (mmol/L)	260 (119-397)	222 (162-297)	<0.001
Lactate dehydrogenase (U/L)	1194 (597-1878)	386 (298-546)	<0.001
Alanine aminotransferase (U/L)	63 (31-151)	28 (16-52)	<0.001
Aspartate aminotransferase (U/L)	96 (38-330)	36 (25-66)	<0.001
Erythrocyte sedimentation rate (mm/h)[a]	35 (25.5)	56 (35.21)	<0.001
Albumin (g/L)[a]	2.7 (0.69)	3.07 (0.57)	0.009
Ejection fraction (%)[a]	44.29 (12.73)	53.45 (10.72)	<0.001

All values as median (IQR) or [a]mean (SD). [b]Fluid bolus in the emergency room.

RESEARCH PAPER

Hand Foot Mouth Disease During the SARS-CoV-2 Pandemic: A Multicentric Study

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Objectives: This prospective observational study aimed to identify the current trend of the circulating viral strains responsible for hand foot mouth disease (HFMD) outbreak in four tertiary care centers in Rajasthan, amidst the coronavirus disease (COVID-19) pandemic (April-October 2022). **Methods**: Cases with suspected HFMD, presenting to our skin outpatient department were assessed clinically and serologically (IgM antibodies against coxsackie virus (CV) A6, A16 and enterovirus 71) for evidence of the disease. **Results**: We identified 718 new HFMD patients (161 adults) with peaks in May and August, 2022. Male:female ratio decreased with increasing age. Most children were asymptomatic. A total of 385/409 patients assessed serologically, were found positive, most commonly against CV-A6. **Conclusion**: Though HFMD typically affects young children, an unusually higher proportion of adults were affected during the current pandemic. There were some differences between pediatric and adult presentation of HFMD.

Keywords: *Co-Infection, Picornavirus, Coxsackie virus*.

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Hand, foot and mouth disease (HFMD) is a cutaneous viral infection that commonly affects children under 5 years of age. The disease is caused by enterovirus 71 (EV-71), coxsackievirus A6 (CV-A6) or coxsackievirus A16 (CV-A16). CVA6 is responsible for more severe dermatological manifestations than the other two viruses [1]. In the majority of cases, the disease is asymptomatic or has only mild symptoms, including vesiculation over hands, feet, and oral mucosa [2]. The non-pharmacological interventions implemented by the Indian Government, for prevention of coronavirus disease (COVID-19) transmission [3], has helped in reducing the incidence of not only COVID-19 but also other viral infections, including HFMD [1]. With subsidence of the pandemic, and gradual reopening of schools and other daycare centers, there have been reports of HFMD across the nation [4].

In this prospective observational study, we investigated the current trend of the circulating viral strains responsible for HFMD outbreak in four tertiary care centers in Rajasthan, amidst the COVID-19 pandemic. A secondary objective was to identify the differentiating features between the disease in pediatric and adult population.

METHODS

This multicentric study, conducted between April and October, 2022, was initiated after obtaining approval from the institutional ethics committee from the involved centers. Cases with suspected HFMD, presenting to our dermatology and pediatrics outpatient departments were assessed for the clinical signs of the disease and were recruited after obtaining written informed consent. The diagnosis of HFMD was made in a patient having maculopapular or vesicular rash on their hands, feet, buttocks, or oral mucosa, with or without fever. Those having at least one of the following were diagnosed with severe HFMD: acute flaccid paralysis, myocarditis, encephalitis, pulmonary edema, pulmonary hemorrhage, cardiopulmonary collapse, aseptic meningitis, encephalitis, or death. Patients with underlying immunodeficiency, or concurrent presence of any other vesicular disease were excluded. Blood samples were collected for detection of IgM antibodies against Coxsackie virus A6 (CV A6), Coxsackie virus A16 (CV A16), and enterovirus 71 (E71).

Most of the samples were collected at the time of the two outbreaks in May, 2022 and August, 2022.

RESULTS

We identified 718 new HFMD patients (161 adult cases) with the first peak of cases in May, 2022 (27.6%), followed by another peak in August, 2022 (29.7%), with a slight rise again in September, 2022 (14.1%) (**Fig.1**). The clinicoepidemiological characteristics of cases are shown in **Table I**. We divided the cases into two groups according to age: Group A including cases under 18 years of age, and Group B including cases over 18 years. We observed that as the age increased, there was a linear fall in male to female ratio (**Fig. 2**).

Of the 161 adults with HFMD, 23 had a positive family history of HFMD (mainly in child members of the family). In 341 (61.2%) children and 29 (18%) adults, mild fever and constitutional symptoms appeared 24-48 hours before the onset of typical cutaneous and mouth lesions (**Table I**). Oral involvement was seen in the form of labial, palatal, buccal, and tongue lesions. The patients had varying degrees of the typical vesicular lesions on their hands, feet, elbows, or buttocks. Clinical features seen exclusively in children included upper respiratory catarrh in 10.5%, painful deglutition in 18.5%, and lethargy or irritability in 16.3% cases. For mild dehydration or high grade fever fever (>39.4°C), 19 (3.41%) of children required hospitalization. Most admissions were done due to high grade fever. None of the hospitalized cases had any clinical signs consistent with meningitis.

Of the 409 patients whose samples were sent for, 385 cases were positive for IgM CV-A6, CV-A16 and EV-71 antibodies, most commonly detected viral antibodies were against CV-A6.

DISCUSSION

India has experienced a sudden resurgence of HFMD in the last six months, with the virus spreading to many cities

Table I Clinical Features of Patients With Hand Foot Mouth Disease, Rajasthan, April-October, 2022 (*N*= 718)

Clinical features	*Age (≤18 y) (n=557)*	*Age (>18 y) (n=161)*
Involvement of buttocks	302 (54.2)	23 (14.3)
Acral	549 (98.6)	156 (96.9)
Mucosal	469 (84.2)	74 (46)
Associated symptoms		
Fever	341 (61.2)	29 (18)
Pruritus/burning sensation	202 (36.3)	128 (79.5)
Nail changes during recovery	9 (1.6)	1 (0.6)

All values are in frequency (%).

of the country [4]. Between 2009 to 2019, the epidemiological map of India [5] reported only 38 sporadic cases of HFMD from Rajasthan, depicting a significantly lower incidence of HFMD than what we observed during the pandemic outbreak. Though, HFMD is a contagious virus typically affecting young children, it rarely involves adults [6]. During the current outbreak, our study encountered a significant proportion of adult cases. This plethora of adult cases could perhaps be attributable to a viral mutation in the picornavirus family amidst the COVID-19 pandemic. Other peculiar features of our cases, which differ from the traditional clinical description of HFMD, were the involvement of buttocks in a large number of cases and presence of large bullous lesions, unlike the classical lesions of HFMD.

Though infection with EV-71, CV-A6 and CV-A16 are self-limiting, they may rarely lead to serious complications like aseptic meningoencephalitis [7,8]. We did not find any such case. We encountered 10 patients with shedding of nails or onychomadesis, as reported earlier [6].

Conventionally, HFMD cases tend to cluster between February and May [6]. We believe that since the COVID-19 outbreak took place from January to March, 2022, the upsurgence of HFMD patients got delayed. COVID-19

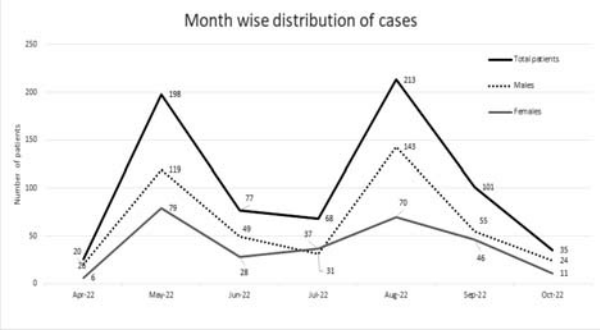

Fig. 1 Month-wise incidences of patients with hand foot mouth disease.

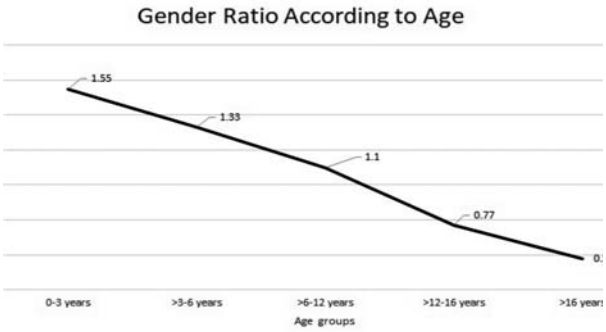

Fig. 2 Change in sex ratio of patients presenting with hand foot mouth disease with increasing age.

WHAT THIS STUDY ADDS?

- We report a sudden surge in cases of hand foot and mouth disease in both children and adults in Rajasthan, during the ongoing COVID-19 pandemic.
- Majority of cases were caused by coxsackie virus A6.

could cause genetic changes in the existing strains of these viruses. Considering the sudden resurgence of cases post-pandemic, it is advisable to perform genome sequencing on these strains to find out how it is currently different from its ancestral form.

Co-infections with SARS-CoV-2 and EV-71 are very likely to happen in the spring. Additionally, the HFMD and COVID-19 share routes of transmission including the hands-to-oral pathway and respiratory droplets. In this study, the highest frequency of HFMD was seen in cases between the ages of 0-3 years (38%). These findings are in concordance with previous reports [9]. Jiang, et al. [10] has raised concerns about children being infected with both COVID-19 and another viral infection, such as dengue virus, influenza virus and enterovirus. A report by Wu, et al. [11] also found that around half of children with COVID-19 also had another respiratory illness at the same time. Our study; however, did not assess the presence of co-infection with COVID-19.

Due to the absence of any existing literature, our study was limited by the absence of any comparison of the current outbreak from pre-pandemic outbreaks and outbreaks from other places during the same time.

In conclusion, our study highlights that there has been a sudden surge in cases of HFMD in both children and adults in Rajasthan during the ongoing COVID-19 pan-demic. Surveillance programs are needed to identify the causes behind this spike and researchers, healthcare pro-viders, and the medical community should play a vital role in enhancing public awareness, especially among mothers, to decrease or even prevent the incidence of future HFMD outbreaks.

Ethics clearance: SPMC ethics committee; No. F/SPMC/IERB/2022/2219 dated April 4, 2022.
Contributors: AM: concept and designed the study, analyzed data and drafted the manuscript; SP,MKS,AA,KV,HP,SKJ: collected the data and helped in data analysis. All authors reviewed and approved the final manuscript.
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Clinical Characteristics and Interventions for Ingested Magnetic Foreign Bodies in Children: A Systematic Review and Meta-analysis

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Background: Ingested foreign materials are a common cause for hospital emergency department visit. Foreign objects such as magnets found in the gastrointestinal tract can cause serious problem because magnets attract to each other across the intestinal wall, often resulting in severe damage. We aimed to review the magnitude of the problem, the clinical characteristics and the interventions related to this problem.

Methods: A systematic review and meta-analysis of the retrospective studies published in PUBMED, MEDLINE, Web of Science, Embase and Cochrane was conducted. The search was limited to studies published from Jan 1, 2000 to July 31, 2022, with the last search done on August 1, 2022. No publication restrictions or study design filters were applied.

Results: Data from 24 retrospective cohort studies with 2014 patients were included in the review. 63.6% (95% CI 59.9%-67.3%) of children who had swallowed foreign bodies were male, and 43% (95% CI 29.3%-57.3%) children presented with non-specific symptoms or had a complete absence of symptoms. Only 74.7% (95% CI 58.7%-88%) of the children has clear history of ingested foreign bodies. Abdominal surgery was the most prevalent interventions (43.3%, 95%CI 32.5%-54.1%) among the inpatients, while conservative treatments were the second common intervention (40.3%, 95%CI 27.8%–52.9%) among the inpatients and outpatients. Intestinal perforation or fistula occurred in 30.2% (95%CI 22.5%–37.8%) children.

Conclusions: Despite significant heterogeneity among primary studies, our results detail the morbidity, clinical characteristics and interventions associated with ingested magnetic foreign bodies in children.

Keywords: *Emergency department, Management, Outcome, Surgery*.

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Ingestion of foreign bodies in young children is a common cause for emergency department visit. In recent decades, high-powered magnets were widely used in commercial and various areas [1]. As a result, the incidence of ingestion of more hazardous items such as high-powered magnets has increased rapidly in the last decade [2]. Magnetic foreign bodies consumed into the gastrointestinal tract or squeezed into the upper respiratory tract, may cause obstruction in nasal, tracheal, auricular and anal area. Ingested magnets travel through the esophagus and stomach into the intestine. Multiple magnets in the gastrointestinal tract adhere to each other across the intestinal wall, often resulting in severe damage [3], which was previously called "the force within." To understand the extent of the problem, this review was conducted to describe the clinical characteristics and the interventions related to the problem.

METHODS

Our study reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [4]. The study was registered on PROSPERO. A systematic review of retrospective studies published in PUBMED, MEDLINE, Web of Science, Embase and Cochrane was conducted. The search had a cap on date from Jan 1, 2000 to Jul 31, 2022, with the last search done on August 1, 2022. No publication restrictions or study design filters were applied. The search strategy for the databases was as follows: ((magnetic foreign body) [all fields]) AND ((children) [all fields]OR (child) [all fields]). Reference lists from related articles were also scanned to broaden the search. A hand search was performed in all five databases.

The study inclusion criteria were *i*) case series reporting the pediatric operations related to the magnetic foreign bodies; *ii*) study reported at least one of the following outcomes: clinical symptoms, interventive method, perforation or fistula, witnessed ingestions, postoperative complications, length of hospital stay, and geographic regions; *iii*) study provided appropriate statistical

estimates or counts; and *iv*) only studies that were reported in English. The study exclusion criteria were; *i*) case reports (<5 cases); *ii*) review articles; *iii*) the foreign body was not in the digestive tract; *iv*) conference abstracts; and *v*) studies with no comparative outcomes in the paper.

The following information was extracted and entered in the database: name of first author, year of publication, type of study, mean age, gender, number of populations, history of ingesting foreign bodies and primary outcomes, including clinical symptoms, interventive method, perforation or fistula, witnessed ingestions, postoperative complications, length of hospital stay, and geographic regions. The Newcastle Ottawa scale (NOS) score [5] for those studies focused on three categories: selection, comparability and outcome. The maximum stars of NOS score is nine stars. An article assessed ≥6 stars was considered to be of high quality and was adopted in the study.

Statistical analysis: This was conducted by STATA version 16.0. The pooled proportions of foreign bodies were calculated using the DerSimonian and Laird approach [6]. All studies with missing values or zero counts were excluded from the analysis. First, a test for homogeneity of proportions among the different studies was performed using the Cochran method. Thus, the pooled proportions of foreign bodies were estimated along with the corresponding 95% confidence intervals (CI), and the DerSimonian-Laird random effects weighting scheme for the studies was included in the analysis. Some study outcomes were reported as medians with ranges or mid-quartiles with ranges. According to the methods intro-duced by Luo, et al. [7] and Wan, et al. [8], those data were converted to means with deviations, thus the results for each group are presented as the mean (SD). The I^2 statistic was used to test the degrees of heterogeneity, the P value of I^2 <0.05 was used to indicate high heterogeneity and vice versa. The random-effects model was applied to pool the high heterogeneity results and the fixed-effects model was used for low heterogeneity (P value of I^2 >0.05). Begg test and Egger test were performed to assess the risk of bias; a P value <0.05 was considered to have a high risk of publication bias.

RESULTS

We identified 556 papers through the literature search. After removing duplicates, 331 records were excluded from title and abstract evaluation, and 201 records were excluded after full-text review because they did not meet the inclusion criteria (**Fig. 1**). Finally, data from 24 retrospective cohort studies with 2014 patients were included in our study.

Table I summarizes the characteristics of 24 records with 2014 patients enrolled in the meta-analysis. The baseline characteristics of the 24 records are listed in **Table II**. The NOS scores ranged from 6 to 8 stars, reflecting the quality of cohort studies. Pooled proportions of dichotomous variables are presented in **Table III**. The pooled effect size (95% CI) for age in years [5.08 (4.29, 5.87); I^2=99%; P<0.001] was based on 2014 cases from 24 articles with a random effect model. The pooled effect size (95% CI)

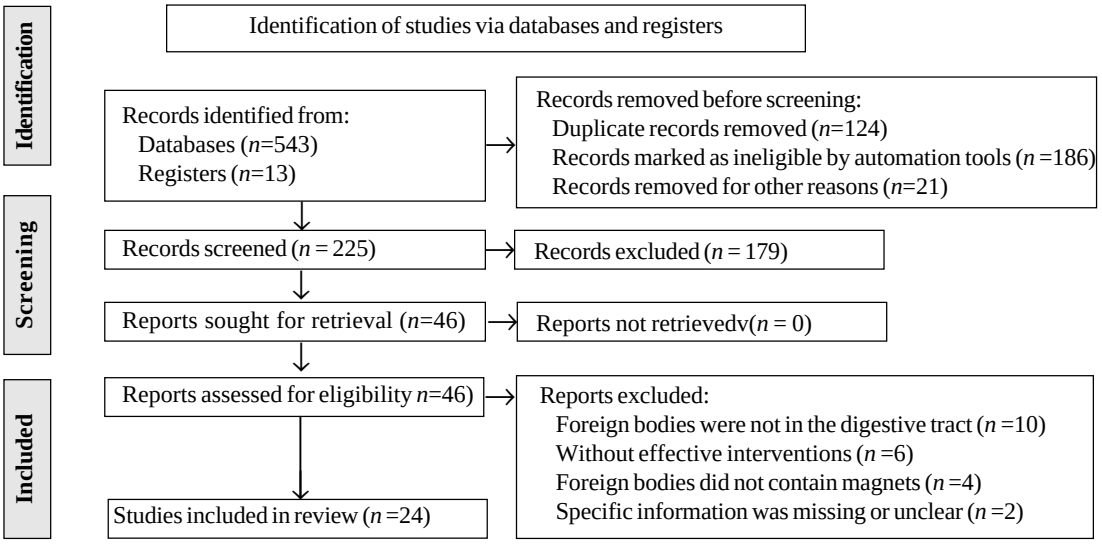

Fig. 1 Adapted PRISMA flow diagram, showing the number of papers identified in the initial search, numbers excluded for various reasons and the final number of papers which are the basis of the data presented.

Table I Characteristics of 24 Records Included in the Meta-Analysis (*N*=2014)

Clinical characteristics	*No. of cases (%)*
Male gender	1250 (62.1)
Geographic region	
North America	1301 (64.6)
Asia	591 (29.3)
Oceania	23 (1.1)
Europe	99 (4.9)
History of ingesting foreign bodies	
Witnessed ingestions	868 (43.1)
Unwitnessed ingestions	699 (34.7)
Not reported	447 (22.2)
Clinical symptoms[a]	
Abdominal pain	211 (10.5)
Vomiting	150 (7.4)
Fever	37 (1.8)
Excessive crying	34 (1.7)
Obstructive symptoms	13 (0.6)
Coughing and chocking	10 (0.5)
Decreased oral intake	5 (0.25)
No symptoms	524 (26.0)
Clinical interventions	
Abdominal surgery	655 (32.5)
Endoscopic removals	393 (19.5)
Conservative treatments[b]	890 (44.2)
Perforation or fistula	364 (18.1)
Postoperative complications[c]	
Wound infection	11 (0.5)
Intestinal obstruction	4 (0.2)
Anastomotic leak	5 (0.25)

[a]melena in 2 children and chest pain in 1 child. [b]including inpatients and outpatients; [c]One child had fever, and another died after hemorrhage from an esophago-aortic fistula.

for days of hospital stay [8.70 (6.51, 10.9); I^2=99.6%; P<0.001] was based on 1225 cases from 12 articles with a random effect model.

Web Table I exhibits the Begg and Egger test for publication bias of clinical characteristics, such as gender, age, witnessed ingestions, clinical symptoms, interventive method, perforation or fistula, length of hospital stay. Egger funnel plots were drawn for the enrolled 24 records (**Fig. 2**).

DISCUSSION

Among all the ingested inorganic foreign bodies, magnets are recorded to be in the highest proportion. Ingestion of magnets warrants specific attention, because it can be particularly destructive to the local tissue [33], especially when multiple magnetic foreign bodies adhere to each other. In 2007, the Consumer Product Safety Commission (CPSC) issued the first warning, noting the possibility of high-powered magnets detaching from children's toys causing injury and even death, if swallowed [34]. In October, 2014, the CPSC published its final rule, Safety Standard for Magnet Sets, prohibiting sales of these small high-powered magnet sets [35], which was later overturned, resulting in a resurgence of these magnets on the market in the later years [36]. From 2011 to 2016, a mean of 1.6 patients per year attended with multiple magnet ingestions vs 9.5 patients per year from 2017 to 2020 in some parts of Europe [37]. North America and Asia appeared to be the regions with the highest number of reports about these foreign bodies. Data showed increase incidence of ingested magnetic foreign bodies commonly in boys.

The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) algorithm [34] published in 2012, should be applied in clinical evaluation and surgical treatment of the affected pediatric patients. If one single magnet was ingested, observation is an appropriate intervention, same treatment as with other smooth, small foreign bodies (except batteries). Magnetic foreign bodies are "*innocent in solitude, harmful in groups*"; however, if numerous magnets were swallowed, thorough evaluation is warranted. If ingestion was recent and the particles are still in the stomach, the magnets should be retrieved by endoscopy using a magnetic probe [38,39]. If signs of intestinal distress develop, prompt laparotomy should be considered to prevent serious gastrointestinal complications [40], especially in multiple magnetic foreign bodies ingestion.

The clinical interventions of ingested magnetic foreign bodies were surgical interventions and/or conservative treat-ments. Surgical interventions include laparotomy, laparoscopy and endoscopic removals among the inpatients. Conservative treatments were also common among the inpatients and outpatients. Multiple magnets adhered together can easily be misinterpreted as a single entity in the single bowel lumen [41], while they are actually located in different bowel sites and attracted to each other causing intestinal wall perforation or fistula. The foreign bodies were mainly found in the jejunum and ileum, followed by colon, duodenum, stomach and esophagus, which are also the predilection sites for bowel perforation or fistula. Approximately, the average hospital stay was 8.7 (95% CI 6.51-10.9) days indicated in 12 articles with 1225 cases recorded.

Although, foreign bodies type was usually reported, only a relatively small proportion of articles provided detailed information on clinical characteristics, diagnostic

Table II Baseline Characteristics of 24 Records Included in the Meta-analysis

Study (year)	*Country*	*No. of patients*	*Gender (M/F)*	*Age (y)*[a]	*NOS score*
De Roo, et al. (2013) [9]	America	72	39/33	2.7 (3.0)	6
Brown, et al. (2013) [10]	America	56	28/28	7.8 (1.3)	8
Agbo, et al. (2013) [11]	America	112	60/52	6.1 (1.3)	6
Tavarez, et al. (2013) [12]	America	38	22/16	5.2 (2.2)	6
Strickland, et al. (2014) [13]	Canada	72	47/25	6.3 (5.0)	8
Waters, et al. (2015) [14]	America	99	66/33	4.2 (3.0)	7
Sola, et al. (2018) [15]	America	89	50/39	7.9 (1.6)	6
Li, et al. (2020) [16]	China	24	17/7	3.5 (1.7)	8
Cai, et al. (2020) [17]	China	56	45/11	4.7 (3.0)	8
Zhang, et al. (2020) [18]	China	49	39/10	3.3 (1.3)	7
Huang, et al. (2020) [19]	China	35	24/11	5.6 (4.0)	7
Lai, et al. (2020) [20]	China	13	10/3	5.5 (3.2)	6
Wang, et al. (2020) [21]	China	74	50/24	3.1 (0.9)	7
Yireh, et al. (2020) [22]	Korea	9	3/6	3.9 (2.9)	6
Mostafa, et al. (2021) [23]	England	46	28/18	6.8 (2.3)	8
Huang, et al. (2021) [24]	China	14	12/2	4.9 (3.1)	8
Miyamoto, et al. (2021) [25]	Japan	104	62/42	2.7 (2.1)	6
Zheng, et al. (2021) [26]	China	51	36/15	4.8 (1.9)	8
Price, et al. (2021) [27]	England	53	27/26	7.2 (3.1)	6
Ding, et al. (2022) [28]	China	71	48/23	2.7 (2.5)	7
Jin, et al. (2022) [29]	China	91	66/25	3.6 (0.8)	6
Nataraja, et al. (2022) [30]	Australia	23	10/13	5.8 (3.6)	8
Middelberg, et al. (2022) [31]	America	596	362/234	7.7 (2.6)	7
Shaul, et al. (2022) [32]	America	167	99/68	6.0 (1.1)	8

M: Male; F: Female; NOS: Newcastle-Ottawa Quality Assessment Scale. [a] *mean (SD). All studies were retrospective studies.*

Table III Pooled Proportions of Clinical Characteristics of Ingested Foreign Bodies in Children

Characteristics	*No. of studies*	*Cases (n)*	*Total cases (N)*	*Pooled proportion (95% CI)*	I^2	*P value*
Gender						
Male	24	1250	2014	0.636 (0.599 - 0.327)	61.9%	<0.001
Female	24	764	2014	0.364 (0.673 - 0.401)	61.9%	<0.001
Witnessed ingestions	15	868	1567	0.747 (0.587 - 0.880)	97.4%	<0.001
Clinical symptoms						
Abdominal pain	11	211	620	0.382 (0.202-0.562)	96.5%	<0.001
Vomiting	11	150	678	0.272 (0.179-0.364)	90.3%	<0.001
Fever	8	37	520	0.068 (0.028-0.108)	76.6%	<0.001
Excessive crying	4	34	167	0.216 (0.016-0.415)	91.2%	<0.001
No symptoms	18	524	1041	0.430 (0.293-0.573)	95.0%	<0.001
Perforation or fistula	21	364	1755	0.302 (0.225-0.378)	95.0%	<0.001
Clinical interventions						
Abdominal surgery	24	655	2014	0.433 (0.325-0.541)	97.8%	<0.001
Endoscopic removal	24	393	2014	0.124 (0.083 - 0.172)	86.3%	<0.001
Conservative treatments[a]	24	890	2014	0.278 (0.403-0.529)	98.2%	<0.001

[a] *including inpatients and outpatients. Random effects model used for all pooled proportions.*

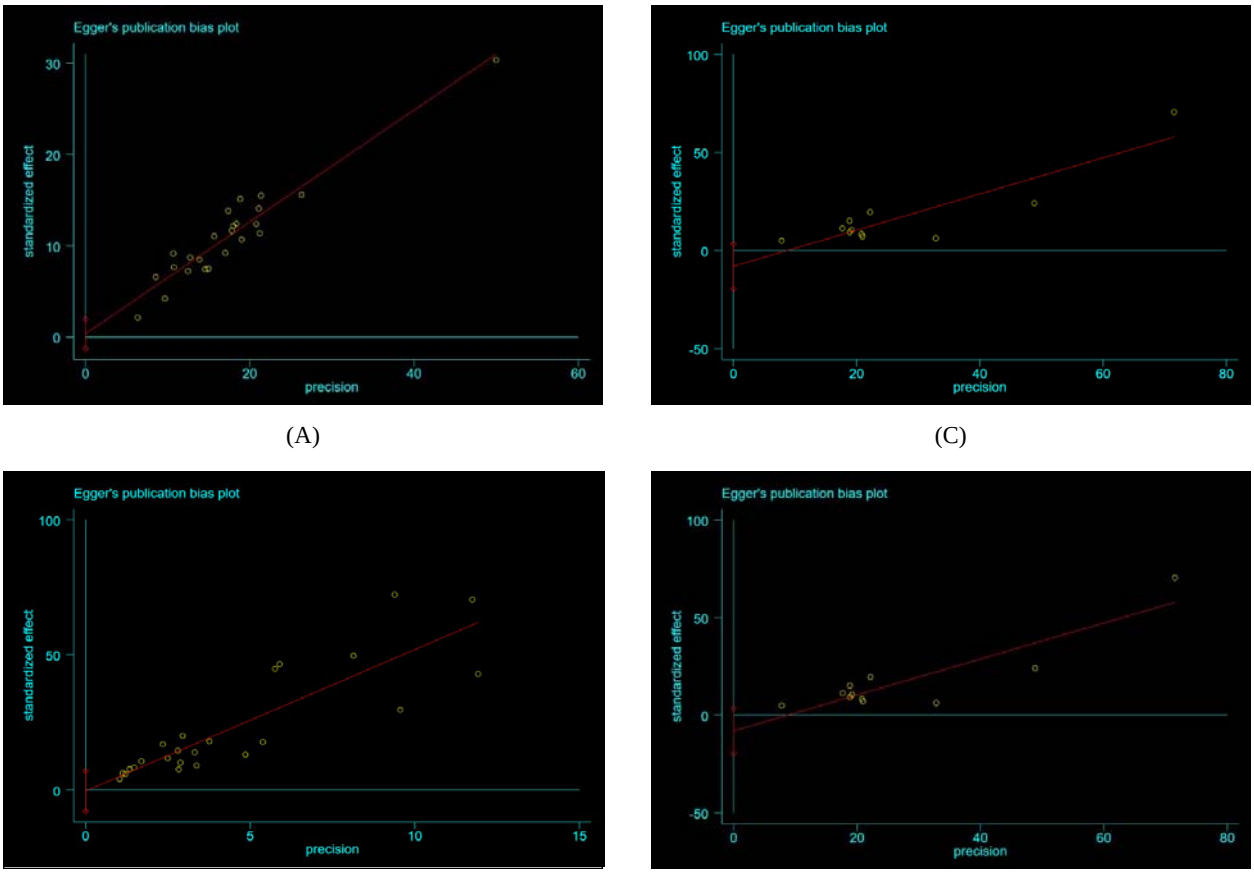

Fig. 2 Publication bias plot (Egger test) for ingested magnetics foreign bodies in children with respect to: *a*) male gender, *b*) age, *c*) witnessed ingestions, and *d*) abdominal pain.

procedures, and complications; suggesting there is a lack of attention in post treatment follow-ups after foreign bodies extraction, and there is insufficient focus on long-term outcomes.

There are limitations in our meta-analysis. Firstly, only data from observational studies or retrospective cohort studies are available, selection bias was inevitable. Secondly, the surgical teams were also the report authors, and there might be a certain risk of bias. Thirdly, only 24 records were analyzed, some clinical presentation and postoperative outcomes were significantly hetero-geneous. Fourthly, there was indication of high risk of publication bias. In addition, long-term follow up data is limited for further analysis.

Ingested foreign bodies in children have become one of the imperative problems that merit special attention in the pediatric emergency, especially the magnetic foreign bodies because it can induce serious consequences. Strict legal regulations should be in place to prevent the use of magnets in pediatric products and the importance of preventive measures needs to be emphasized to parents and caregivers. More importantly, protocols on vigilant diagnostic procedures and standardized treatments should be established when encountered ingested magnetic foreign bodies. Although the extreme diversity of epidemiological study designs and characteristics could make it challenge to analyzing research summaries, meta-analyses of observational studies remain to be one of the few methods to resolve crucial problems in clinical and public health.

Though an enormous heterogeneity among primary studies may impair study comparability, our study results confirmed the relevant morbidity, clinical characteristics and interventions associated with ingested magnetic FBs in children. Protocols for more vigilant diagnostic procedures, treatment and post treatment follow up should be developed; lastly, preventive measures such as parental education and legislation should be emphasized in protecting the pediatric population.

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Contributors: SX, JB: systematic search, data extraction, Formal analysis, article writing; YH, SL, HZ: formal analysis, quality assessment; YF: quality assessment; BZ: corresponding author who determined the main idea of the manuscript. All authors designed, reviewed and approved the manuscript.
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Web Table I Begg and Egger Test of Publication Bias of Clinical Characteristics

	Number of studies	*P value*[a]	
		Begg Test	*Egger Test*
Male	24	1.000	0.650
Age (yrs)	24	0.862	0.917
Witnessed ingestions	15	0.350	0.149
Clinical symptoms			
Abdominal pain	11	0.436	0.984
Vomiting	11	0.087	0.002
Fever	8	0.035	0.013
Excessive crying	4	0.734	0.229
No symptoms	18	0.964	0.491
Perforation or fistula	21	0.001	0.001
Clinical interventions			
Abdominal surgery	24	0.206	0.000
Endoscopic removals	24	0.065	0.372
Conservative treatments	24	0.785	0.070
Postoperative stay (days)	12	0.193	0.001

P value < 0.05 was considered to have a high risk of publication bias.

Necrotizing Enterocolitis: An Enduring Enigma

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Necrotizing enterocolitis (NEC) is one of the most destructive gastrointestinal emergencies in premature neonates. First described over a century ago, this disease still poses a conundrum. The evidence on pathogenesis is exiguous, diagnostic criteria are nebulous, management is arduous and frequently fruitless, and prevention strategies are often inefficacious. This is especially exasperating to neonatologists because it mainly affects preterms who have often survived the initial stormy days, and when everyone believes the battle to be won, they are surprised by a vexatious disease with high fatality and crippling sequelae. Published fifty years back, the article on necrotizing enterocolitis in the newborn by Karan and Pathak [1] was the first reported case series from India, and deserves a thorough review in view of the persisting perplexities posed by this disease.

THE PAST

The case series by Karan and Pathak was done over a nine-month period in the neonatal nurseries in the Institute of Child Health, Niloufer Hospital Hydera-bad, between January and September 1972. During this period, 24 cases were diagnosed as NEC, with an incidence of 1.9% and a nearly equal male to female ratio. All but three babies had low birth weights and were preterm. The seven hospital born babies and a few extramural cases were admitted by 16 hours, while the rest of referred cases were admitted between 2 to 18 days. Nine of the babies had suffered from severe birth asphyxia or respiratory distress in the early neonatal period.

The authors found that while diarrhea of varying severity was almost always the initial event in combination with abdominal distention (75%), other presentations included blood stained stools (67%), and bilious, blood stained, or fecal vomiting (54%). The full blown picture of NEC emerged within seven days of onset of diarrhea in a majority of cases. Refusal to feed and lethargy, along with jaundice, were the most common nonspecific signs and symptoms, followed by temperature instability, respiratory difficulties, and shock and pallor in terminal cases. Stool culture was done in nearly half the cases and revealed multidrug-resistant coli-form organisms. In radiological features, intestinal distention with or without fluid levels, pneumatosis intestinalis, hepatic portal venous gas, and pneumoperitoneum were classical findings. Aspiration pneumonia or staphylococcal pneumonia were the most common associated features. Serial *X*-rays were important in delineating clinical stage, as features were determined largely by the timing of the *X*-rays. Histological features were characterized by necrosis and ulceration of mucous membranes, inflammatory exudates, gas spaces in submucosa and subserosa, and pseudomembrane formation. The babies were kept nil per orally, gastric decompression done, intravenous fluids infused, and blood transfusion planned as required. Local and systemic antibiotics were given in all cases. One case underwent ileal perforation repair and anastomosis but succumbed postoperatively. Despite the aforesaid therapy, mortality was ubiquitous, with only one survivor.

The first reported case resembling NEC was described by Billard in 1928, while working at the Hspital des Enfants-Trouvés (Hospital for Foundling Children) in Paris [2]. Terming the disease as 'gangrenous enterocolitis,' he described a nine-day-old, sick neonate with swollen abdomen, copious green diarrhea, subsequently having tense abdomen with passage of bloody stool, slowing of heart rate, and finally death. Autopsy revealed red and swollen and blood covered terminal ileum. The

mucosa was friable and "*so soft that it turns to mash when scraped with fingernail*" [2]. Similar reports came from Berlin (Siebold, 1825) and Vienna (Bednar, 1850), and due to clustering of cases was often regarded as a nosocomial infection. Around 1950, Schimdt and Quaiser described 85 preterm deaths in Graz in two reports from a disease causing ileocecal enterocolitis and coined the term 'enterocolitis ulcerosa necrotisans' [3]. In 1951, radiologist Steinnon observed peumatosis intestinalis, while Wolfe and Evans described pneumatosis portalis, which have now become the radiological hall-marks of NEC [4,5]. During the next decades, increased survival of premature infants and rapid development of intervention therapies led to increased incidence of NEC. An 'outbreak' in New York Babies Hospital prompted extensive analysis and animal experimentation, which concluded that mesenteric hypoperfusion was an important initiator of intestinal injury, but that multifactorial models with immaturity, enteral feedings, intestinal microbiome, immune dysfunction, and inflammation all contributed to the final common pathway of disease [6]. Those days, surgical intervention was considered inevitable, and despite vigorous therapy, fatality was almost invariable.

THE PRESENT

NEC is often described as an inadvertent side-effect of advancement of obstetric and neonatal care. It never occurs in utero, and the risk is inversely proportional to birthweight and gestational age. A systematic review has shown global incidence of 7% in very low birth weight (VLBW) infants in NICU [7]. Incidence is difficult to ascertain in India as many cases of NEC get coded as 'sepsis.' A vexing aspect of NEC is the continued poor understanding of etiopathogenesis despite extensive research. The pathogenesis of NEC is proposed to be complex multifactorial cascade in response to developmental immaturity of gut motility, digestive enzyme secretion, barrier protections, and circulatory regulation exacerbated by formula feeding, intestinal ischemia, and bacterial effects. Recent studies have highlighted the role of platelet aggregation factor (PAF), an endogenous phospholipid initiator of inflammatory response. Premature infants have low PAF degrading enzymes, and human milk contains PAF antagonists. In another exciting discovery, it was shown that mice deficient in the pathogen recognition molecule, toll-like receptor 4 (TLR-4), were protected from NEC, proving the role of TLR-4 in inducing enterocyte apoptosis in response to altered bacterial enterocyte signalling. Timing, content, modality, and advancement of feeding were always suspected as major triggers for NEC. As the cases were mounting in 1970s, Brown and Sweet at Mount Sinai Hospital in New York popularised a strict enteral feeding regimen based on delayed initiation and very slow prolongation of feeding. However, as lower gestational age born babies continued to survive and develop NEC, the confidence in this regimen fell, and early feeding protocols with prog-ressive and infact total enteral feeding were reinstituted. Despite wide divergence in practices, evidence mostly shows that human milk in standardized feeding regimens reduces NEC, especially in VLBW babies, and incidence is unaffected by early initiation, rapid advancement or by off-label fortification of expressed human milk with infant milk formula widely practiced in developing countries [8].

The diagnosis of NEC is hampered by lack of a single pathognomonic sign or test. Just five years after the case series under review was published, Bell, et al. [9] combined clinical and radiological data to classify NEC into three stages, which were modified and subdivided by Walsh and Kliegman [9]. Despite the understanding that NEC is a potpourri of phenotypes and Bell criteria are both outdated and insensitive to distinguish the multiple diseases masquerading as NEC, there is a dearth of pragmatic replacements that can easily fit into clinical care algorithms. Bowel ultrasound, with its advantages of non-ionizing radiation, repeated assessments, improved spatial specificity for pneumatosis intestinalis, increased sensitivity for intermittent gas bubbles in portal venous system, and doppler-guided detection of bowel wall ischemia has the potential for improving staging of NEC. Other modalities being tried are bowel magnetic resonance imaging (MRI) and near-infrared spectroscopy (NIRS). The classic triad of NEC i.e., thrombocytopenia, hyponatremia, and acidemia is present in minority of cases. Biomarkers like plasma and urinary levels of intestinal fatty acid binding protein (I-FABP) and urinary I-FABP: Cr (creatinine) ratios have been studied for diagnosis and assessment of severity but wider acceptance is somewhat limited by small size of the studies [10]. There has been little change in the approaches for conservative management of NEC, characterized by bowel rest, bowel decompression, and intravenous antibiotics with adjunctive therapy for cardiopulmonary and hematological support. The dependence on blood sampling, denial of feed, and use of antibiotics in a disease caused by anemia, hypoperfusion, intestinal dysfunction, and dysbiome is ironical and needs further research. Other therapies like lactoferrin supplementation and intravenous pentoxifylline still lack concrete evidence. In surgical cases, primary peritoneal drainage has emerged as an alternative to laparotomy. Preventive strategies revolve around standard feeding protocols using human milk feeding with dose-dependent relation between breast milk consumption and decline in risk of NEC. Antenatal steroids, avoidance of anti-reflux medications, and antibiotic stewardship are the other strategies. One of

the most controversial topics in NEC prevention is the role of enteral probiotics. Despite evidence of some benefits, concerns about timing, dose, formulation, lack of pharmaceutical grade quality, and concerns regarding cross-contamination prohibit recommendations for routine use. Other potential preventative strategies involve prebiotics (nondigestible dietary supplements like human milk oligosaccharides), postbiotics (bacterial metabolites like butyrates), isolated MAMPs, or bioavailable TLR ligands. Mortality ranges from 10-50%, and common sequelae like neurodevelopmental delay, failure to thrive, strictures, and short bowel synd-rome with or without intestinal failure can debilitate the survivors.

THE FUTURE

NEC is an enduring challenge, especially poignant due to its crippling affliction of seemingly stable, very small babies weeks after birth. Changed understanding of NEC pathogenesis has ignited much optimism. While genomic identifiers may aid in identification of at-risk infants, stool microbiome analyses and metabolomics, and vola-tile organic compounds (VOC) analyses can ease diag-nosis of NEC precursors [11]. Increased attention to NEC prevention must include better comprehension of feeding practices for premature infants and probiotic-mediated manipulation of the microbial environment. For management of devastating sequelae of short bowel syndrome, newer therapies like autologous artificial intestine with bioscaffold of collagen or synthetic polymers coated with biologic matrix seeded with growth factors like VEGF that can recruit endogenous blood supply or implantation of stem cells hold out hope [12]. With thorough and focused research, in time, a specific cure might be available for premature infants who develop this devastating disease.

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SARS-CoV-2 Infection in Children with Idiopathic Nephrotic Syndrome: A Multicentric Study

A multicenter retrospective study was conducted to assess the clinical spectrum of 30 severe acute respiratory syndrome coronavirus (SARS-CoV-2)-positive children with idiopathic nephrotic syndrome. Difficult to treat nephrotic syndrome was found to be a high-risk group with a high incidence of acute kidney injury and mortality.

Keywords: *Acute kidney injury, Difficult to treat nephrotic syndrome.*

During the global pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection, 'shielding' was advocated for children with underlying chronic disease and/or on long-term immunosuppression to prevent adverse outcomes. However, it did not prove to be useful. A study across 30 countries, of over 100 children with renal diseases, including those on immuno-suppression, reported mild SARS-CoV-2 infection with a low mortality restricted to low- and middle-income countries (LMICs) [1]. As data on children with renal diseases and coronavirus infection (COVID-19) in LMICs is lacking, we studied the epidemiological profile, clinical manifestations and complications in children with neph-rotic syndrome with SARS-CoV-2 infection.

We retrospectively reviewed 30 SARS-CoV-2 infected children (21 hospitalized) with idiopathic nephrotic syndrome across four tertiary care hospitals between 1 April, 2020 to 15 February, 2021 [2]. Patients were diagnosed by either nasal or oropharyngeal swabs using reverse transcriptase polymerase chain reaction (RT-PCR) and/or serum SARS-CoV-2 antibody levels and categorized based on national guidelines [3].

Treatment regimens were modified in hospitalized patients - *i*) Those currently on steroids or having received in last year were prescribed stress dose of steroids (0.3-0.5 mg/kg/day daily) till clinical and biochemical improvement; *ii*) Immunosuppression like mycofenolate mofetil (MMF), calcineurin inhibitors (CNIs) were withheld and restarted at same dose later; and *iii*) Biologicals like rituximab etc. were deferred. Out-patient management continued unmodified. Therapy for COVID-19 was largely supportive. Baseline serum creatinine was estimated using height independent method by Hoste (age) equation and estimated creatinine clearance (eGFR) of 120 mL/min/1.73 m^2 for children older than two years, while age-based normative eGFR was used for children ≤2 years of age. The rise from baseline to peak serum levels categorized the stage of AKI [4,5]. Complications including sepsis, shock, pneumonia, myocarditis and multisystem inflammatory syndrome in children (MIS-C) were treated. Steroid resistant NS (SRNS) and/or steroid dependent NS (SDNS) with failure of ≥2 immunosuppressive drugs or those with features of steroid toxicity were labelled as 'difficult to treat' NS (DTTNS) [2]

Of the 30 children reviewed, 21(70%) children with moderate to severe illness were hospitalized for a mean (SD) duration of 7.23 (6.43) days. With 23 (76.6%) children in relapse, the most common presenting complaint was fever (33.3%) followed by cough (30.0%) (**Web Table I**). Majority were SRNS (33.3%), and 12 (40%) were DTTNS. Respiratory support was required in 8 (26.6%) (3 mechanical ventilation) while 9 (30%) children developed AKI: 1 in stage 1, and 4 each in stage 2 and stage 3. A total of four children in the study progressed to stage 3 AKI, of which 3 succumbed (75%) as no patient could avail dialysis (**Web Table I**).

The most common immunosuppression was oral glucocorticoids (96.6%) followed by both MMF (23.3%) and CNI (23.3%) (**Web Table I**). Two patients received rituximab, one of whom had received a single dose one week prior to testing SARS CoV-2 positive and eventually died. The second patient had received two doses in last 2 years and was admitted for hypovolemia and edema control. In our study, 7 patients were diagnosed as first episode of nephrotic syndrome (FENS) of which four were RT-PCR positive, one diagnosed after 6 weeks of therapy and 2 retrospectively with positive SARS-CoV-2 antibodies. They all achieved complete remission after standard therapy.

Five (16.6%) children died and all of these had DTTNS. Three patients succumbed to respiratory failure with pneumonia; two patients had refractory shock while one had both as the immediate cause of death. Shock and use of nephrotoxic drugs was significantly higher in children with DTTNS than other categories of NS (**Table I**). Among children with DTTNS, 6 (50%) developed AKI with 33.3% progressing to stage 3 AKI (P<0.05).

While majority of children reported a mild-moderate type of illness, DTTNS was recognized as a high-risk group significantly associated with mortality. This may be due to the underlying etiology and higher use of immunosuppressive drugs. Onset of nephrotic syndrome after other viral illnesses like H1N1 is known, with occasional reports of cases after SARS CoV-2 infection [6,7]. In our

TABLE I Clinical and Management Characteristics of Children With Nephrotic Syndrome (*N*=30)

Characteristics	*DTTNS (n=12)*	*Other categories (n=18)*	*OR (95% CI)*	*P value*
Sepsis	8 (66.6)	9 (50.0)	2.0 (0.43-9.09)	0.367
Methylprednisolone	2 (16.7)	0	8.8 (0.38-201)	0.073
Nephrotoxic drugs	9 (75)	0	100 (4.68-2152)	-
Pneumonia	5 (41.7)	4 (22.2)	2.5 (0.50-12.2)	0.255
Ventilation	2 (16.7)	1 (5.6)	3.4 (0.27-42.4)	0.32
Mortality	5 (41.7)	0	27.13 (1.32-554)	0.003
Shock	3 (25.0)	0	13.6 (0.63-292)	0.025

DTTNS: difficult to treat nephrotic syndrome.

study, four among seven children with FENS were RTPCR-positive, while two were retrospectively diagnosed with positive COVID anti-body levels. Whether this is a temporal or a causal associa-tion with SARS-CoV-2 remains to be ascertained. Renal biopsy with definitive histological changes may clarify the pathogenesis.

Though, chronic illness, long-term immunosuppression and frequent hospital visits are known to increase risk of infections, including COVID-19; overall, a good outcome of non-renal pathologies on immunosuppression like hematological neoplasia/solid tumors and rheumatic diseases has been reported [8,9]. Associated sepsis and limited availability of hemodialysis could be responsible for a higher mortality in our study (17.2%) [10]. Lack of assessment of urine output, response to therapy and association of degree of proteinuria with AKI and mortality, limited our inference regarding these associations.

To conclude, children with DTTNS with SARS-CoV2 infection, comprise a high-risk group among children with NS, and require careful monitoring for complications like AKI. Availability of dialysis facilities in COVID wards may improve outcomes. Further research on larger number of children with NS may help understanding viral clearance time, time to achieve remission and long-term outcomes.

Ethics clearance: IEC, LHMC; No. LHMC/IEC/2021/03/64 dated July 7, 2021.
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WEB TABLE 1 Characteristics of Children with Nephrotic Syndrome having COVID-19 Infection

Characteristics	*Value*
Age (y)[a]	6.20 (3.81-9.0)
Male sex	16 (53.3)
History of contact	14 (46.7)
Symptoms of COVID-19	
Fever	10 (33.3)
Cough	9 (30.0)
Fast breathing	4 (13.3)
Myalgia	4 (13.3)
Headache	3 (10.0)
Nausea and Vomiting	3 (10.3)
Abdominal Pain	7 (23.3)
Diarrhea	4 (13.3)
Severity of COVID-19	
mild/moderate/severe	12 (40)/11 (36.6)/(23.3)
Respiratory support	
Oxygen	8 (26.6)
Invasive Support	3 (10.0)
Outcome	
Discharge	25 (83.3)
Death	5 (16.6.)
Type of Nephrotic Syndrome	
FENS/IFRNS/FRNS/SDNS/SRNS	7 (23.3)/ 3(10.0)/ 2(6.66)/ 8(26.6)/ 10(33.3)
DTTNS	12 (40)
Status of Nephrotic syndrome	
Relapse	23 (76.6%)
Remission	07 (30.4%)
Immunosuppression	
Steroids	29 (96.6)
Mycophenolate mofetil	07 (23.3)
Calcineurin inhibitor	07 (23.3)
Rituximab	02 (6.66)
Cyclophosphamide	03 (10.0)
Levamisole	04 (13.3)
Hospital stay (d)[a]	7.23 (7.5)
Baseline serum creatinine (mg/dL) [a]	0.37 (0.113)
Peak serum creatinine (mg/dL) [a]	0.50 (0.45)
AKI	9 (30)
Stage 1	1 (3.33)
Stage 2	4 (13.3)
Stage 3	4 (13.3)
Complications	
Pneumonia	9 (30.0)
Sepsis	17(56.6)
Shock and vasopressor support	3 (10.0)
Antibiotics	17 (56.6)
Nephrotoxic medications	9 (30.0)
Laboratory Results	
Hemoglobin (gm%)[b]	11.3 (2.57)
Total leukocyte count (mm^3) [b]	11000 (4283.24)
Absolute neutrophilic count (mm^3) [b]	5951 (8098.90)
PMN/Lymphocyte Ratio [b]	2.32 (2.12)
Platelet Count (mm^3) [b]	445000 (231387.7)

Values are expressed as n(%),or [a] (median IQR), or [b] (mean SD)
FENS, first episode nephrotic syndrome; IFRNS, Infrequent relapsing nephrotic syndrome; FRNS, frequent relapsing nephrotic syndrome; SDNS, steroid dependent nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; DTTNS, difficult to treat nephrotic syndrome; AKI, acute kidney injury; PMN, polymorph nuclear cell

Bile Acid Conjugation Defect in an Infant

Bile acid conjugation defect 1 (BACD) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutation in *bile acid-CoA: amino acid N-acyltransferase* (*BAAT*) gene located on chromosome 9q31 [1]. In BACD, low levels of intraluminal bile acids in the intestine result in steatorrhoea, failure to thrive and malabsorption of fat-soluble vitamins. Symptoms usually respond to treatment with ursodeoxycholic acid (UDCA) [2]. We report a 9-month-old girl with BACD who mani-fested with steatorrhoea, pruritus and vitamin K deficiency without jaundice.

The child was first born to a non-consanguineously married couple with birth weight of 2.4 kg. At 5 months of age, there was a history of fever with watery loose stools lasting for two days. Following which she developed ecchymotic patches over the chest and abdomen. The child was evaluated in another medical facility. Pro-thrombin time (PT) was 180 s with an International normalized ratio (INR) of 12, and activated tissue thromboplastin time (aPTT) was 120 s (control 30sec). Hemoglobin was 8.6 g/dL, platelet count was 3.9×10^9/L. The child was administered vitamin K injection 5 mg intravenously. Following vitamin K injection, PT/INR and aPTT tests normalized, suggesting vitamin K deficiency.

At 9 months of age, the child presented to our hospital with history of steatorrhea and pruritus for two months. The child's weight was 7.5 kg and length of 68 cm, which were appropriate for age. Examination showed scratch marks due to pruritus. The child had no ecchymotic patches or any features of rickets. Similar to previous hospitalization, the child had prolonged PT/INR, which normalized after parenteral vitamin K. Liver function tests were normal with total bilirubin 0.3 mg/dL, aspartate transaminase (AST) 60 IU/L, alanine transaminase (ALT) 41 IU/L, alkaline phosphatase (ALP) 783 IU/L, gamma-glutamyl transferase (GGT) 5 IU/L, total protein 6.8 g/dL, and serum albumin 4.2 g/dL. Serum bile acid level was high (134 µmol/L, reference range 0.5-10 µmol/L). Clinical exome sequencing showed homozygous missense variation in exome 4 of *BAAT* gene (chr9:g. 101362505C >T; Depth L: 240x) that results in amino acid substitution of threonine for alanine at codon 394 (p.ala394Thr; ENST00000259407.7) consistent with diagnosis of BACD. This variant has not been reported previously. Silico predictions of the variant are probably damaging by PolyPhen2 (HumDiy) and damaging by SIFT, and LRT. This variant was classified as a variant of unknown significance as per the American College of medical genetics and genomics criteria [3]. The child was started on ursodeoxycholic acid (UDCA) orally, 30 mg/kg/day in three divided doses along with supplementation of vitamin K 5 mg parenterally every 3 weeks and other fat-soluble vitamins orally and also medium-chain triglycerides. The child showed improvement in pruritus, no steatorrhea and normal PT/INR at the last follow-up at 14 months of age. Her growth was normal with weight of 8.9 kg and height 80 cm.

Steatorrhea, fat-soluble vitamin deficiency and pruritus with normal GGT in infancy can be due to bile acid transporter defects, bile acid conjugation disorders and bile acid synthesis defect (pruritus being rare). With the absence of jaundice, possibility of bile acid transporter defects was unlikely. High serum bile acid levels ruled out bile acid synthesis defects. Steatorrhea and fat-soluble vitamin deficiency can also occur in intestinal malabsorption, but pruritus is not seen in that disorder.

In a previous case series of BACD [2], the age at diagnosis was 3 months - 14 years, and one child had progressive liver disease with decompensation requiring a liver transplant. Mild to moderate cholestatic liver disease in BACD is presumably because cholic acid is synthesized at normal rate and its efficient intestinal absorption leads to a recycling pool of bile acids that can generate bile flow. Thus, BACD patients can develop variable liver disease in later age that needs follow up [2]. Thus our patient will require follow up to look for progression of liver disease.

UDCA displaces endogenous hepatotoxic bile by hydrophilic bile acid pool [4]. Alteration of the bile acid pool might help increasing the intestinal concentration of hydrophilic bile acids in this disorder. In a previous case series [5], children treated with glycocholic acid (conjugated bile acid with glycine) showed improvement in fat soluble vitamin absorption and growth. However, it is not yet available in Indian market. BACD cases are rare, but once diagnosed effective medical treatment with a good outcome is possible with simple medical management. However, these children need to be maintained on UDCA to control the disease.

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Clinical Profile of Hepatitis Associated Aplastic Anemia (HAAA) in Six Children

Hepatitis associated aplastic anemia (HAAA) is a rare condition, characterized by onset of pancytopenia, usually occurring within a period of six months from developing acute hepatitis (an elevation of alanine transaminase (ALT) more than five times the upper limit of normal), with or without acute liver failure [1]. The trigger is thought to be an autoimmune mechanism with viral induced proliferation of activated cytotoxic T-lymphocytes, mediated by tumor necrosis factor alpha (TNF-α) and inter-feron-gamma (IFN-γ) [1-3]. We report six children with this condition who were managed by us (**Table I**).

The median age of the patients was 5.5 years (range 2-9 years). The median duration to onset of pancytopenia, from the onset of acute hepatitis / acute liver failure (ALF) was 7 weeks (range 0-15 weeks). One each tested positive for anti-nuclear antibodies (ANA, titre 1:160) and anti-mitochondrial antibodies (AMA, titre 1:80), as part of extended autoimmune workup. Routine viral markers including all hepatotropic viruses (Hepa-titis A, B, C, D, E) as well as extended viral markers (including parvovirus B19) were negative in all six patients. Case 1 recovered from hepatitis with supportive care, but failed Immunosuppressive Therapy (IST) for aplastic anemia (AA) and received a haploidentical hematopoietic stem cell transplant (HSCT). Case 2 developed ALF but responded to supportive care, and was started only on eltrombopag for AA, which supported count recovery. Case 3 underwent a liver transplant for ALF, and subsequently received immunosuppre-ssive therapy (IST) for aplastic anemia (AA), failing which he underwent a matched sibling donor (MSD) HSCT. Case 4 was started on steroids and azathioprine for autoimmune hepatitis (AIH). While on treatment, he developed severe AA, and eltrombopag was added while he underwent workup for a planned HSCT. However, counts recovered without needing further treatment. Case 5 underwent a liver transplant for ALF, while counts recovered spontaneously. Case 6 presented with hepatitis and AA together, was diagnosed with AIH and started on steroids, azathioprine and eltrombopag. He responded well with resolution of both hepatitis and AA.

Three of these children are being continued on immuno-suppression, which includes one of the patients who has under-gone HSCT recently. After a median follow-up (from onset of hepatitis) of 27 months (range 6-72 months), all patients are alive with normal liver/graft functions and trilineage hematopoiesis.

A non-exhaustive review of previously reported literature is detailed in **Web Table I**. The incidence of HAAA amongst all cases of AA differs geographically ranging from 2-5% in the West to 15-20% in the Far-East where hepatitis is more common. The severity of hepatitis can be mild and self-limiting, to fulminant requiring liver

Table I Clinical Profile of Patients With Hepatitis Associated Aplastic Anemia

No.	*Serostatus (viral markers/ autoimmune)*	*Age (y) / sex*	*ALF*	*LT*	*Onset to pancyto-penia from hepatitis/ALF*	*Degree of aplastic anemia*	*Bone marrow cellu-larity*	*Spon-taneous recovery of marrow*	*Immuno-suppressive therapy*	*BMT*	*Others*	*Follow-up (mo)*
1	ANA positive (1:160)	9/M	No	No	4 wks	VSAA	<5%	No	ATG, CsA: (failed)	Yes (haplo)	Eltrombopag	30
2	Seronegative	4/M	Yes	No	8 wks	NSAA	50-60%	Yes	No	No	Eltrombopag	6
3	Seronegative	5/M	Yes	Yes	15 wks	VSAA	10-15%	No	ATG, CsA (failed) Post BMT: Tacrolimus	Yes (MSD)	Eltrombopag	12
4	Seronegative	7/M	No	No	12 wks	SAA	5-10%	No	Steroids, azathioprine	No	Eltrombopag	24
5	Seronegative	2/F	Yes	Yes	4 wks	SAA	10-15%	Yes	No	No		72
6	AMA positive (1:80)	6/M	No	No	Simultaneous	NSAA	50-60%	No	Steroids, IVIg, azathioprine	No	Eltrombopag	18

AA: Aplastic anemia, ALF: Acute liver failure, ANA: Anti-nuclear antibody, AMA: Anti mitochondrial antibody, ATG: Anti-thymocyte globulin, BMT: Bone marrow transplant, CsA: Cyclosporine A, MSD: Matched sibling donor, Haplo: Haploidentical, IVIg: Intravenous immune globulin, NSAA: Non-severe aplastic anemia, SAA: Severe aplastic anemia, VSAA: Very severe aplastic anemia.

transplantation, as seen in our cases [4]. The duration to onset of AA in our cases was similar to other reports [5,6], and the range has been reported to vary from a few days up to even a year [7]. Although, all of our patients tested sero-negative for hepatotropic viruses, non-A non-B hepatitis (NANBH) is thought to be the causative factor of nearly 80% of HAAA.

HAAA is managed similar to non-hepatitis aplastic anemia, with IST and HSCT as established primary treatment modalities [1,2,4,7,8]. Four of our patients received immunosuppression, with two treated for AIH with steroids and azathioprine, which is standard first line of treatment for AIH [9]. These immunosuppressants presumably contributed to recovery from subsequent HAAA as well, further supporting the basis of an underlying immune etiology. Eltrombopag, a thrombopoietin receptor agonist has shown promising results in adults either in isolation or in combination with IST as it is effective in stimulating trilineage hematopoiesis, even after discontinuation of the drug [10]. We used it in five of our patients.

Children developing hepatitis should be monitored closely with regular blood counts during the first year to identify possible development of pancytopenia, to initiate early therapy. A multidisciplinary approach involving the pediatric hepatologists and hematologists is vital to optimize care for such patients.

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Kangaroo Mother Care During Follow-up Visits

Kangaroo mother care (KMC) is a cost effective intervention that reduces morbidity and mortality in preterm and low birth weight neonates [1,2]. KMC is practiced during hospital stay, and mothers are also encouraged to continue home-based KMC [3]. We share our experience of KMC for preterm infants during follow up visits.

Data were obtained for preterm infants who visited the high-risk follow up clinic (after hospital discharge) in the outpatient department (OPD) of our hospital between 1 December, 2022, and 15 January, 2023. A total of 31 infants [mean (SD) birth weight 1236 (197) g, gestation age 31.25 (2.69) wk] visited the follow up clinic at mean (SD) post menstrual age of 36.80 (2.37) wk. Axillary temperatures were recorded by digital thermometer as a part of vitals monitoring. Newborns with body temperature of 36.0-36.4°C and 32.0-35.9°C were considered as cold stress and moderate hypothermia, respectively. Eight neonates (25.8%) in cold stress and one neonate with moderate hypothermia (axillary temperature 35.9 ºC) underwent KMC under the supervision of a staff nurse in a designated area of the outpatient department. The mean (SD) neonatal axillary temperature before initiation of KMC, at 30 min after KMC and 60 min after KMC were 36.16 (0.15) ºC, 36.6 (0.1) ºC and 36.64 (0.07) °C, respectively (P = 0.001). All of the babies became euthermic 30 min after starting KMC, and were discharged from the outpatient clinic. In our cohort, mothers were providing KMC to their infants during NICU stay, so it helped them in continuing KMC with minimal support.

The increase in neonatal axillary temperature during KMC is well-known [4]; however, there are no reports on implementing KMC during outpatient visits. Preterm neonates are vulnerable to cold stress after discharge and the risk increases during hospital visits, particularly during the winter season. Establishing a KMC corner in the outpatient department is a low cost intervention not only to prevent hypothermia but also to motivate the mother and family members to continue KMC at home. Like establishing a breast feeding corner in public areas, the KMC corner in the outpatient area may also spread the message of the importance of KMC among other families visiting the area. Preterm babies may remain in a better physiological state during KMC in the waiting area of a busy high risk follow-up clinic. KMC in the outpatient department; however, needs a earmarked area with privacy, and one nursing staff member is needed for KMC monitoring.

In conclusion, providing KMC is feasible during follow-up visits, and beneficial to preterm neonates for better temperature stability. Further large scale studies are needed to explore the benefits of this practice.

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Whether Millets Can Be Part of Our Staple Diet?

Millet is a generic term used for a heterogenous group of small size seeded cereal crops, which are grown in semi-arid tropics of Asia and Africa. In order to feed the ever-growing world population the focus has shifted towards resilient crops, which are easier to grow, affordable as well nutritious to meet the demands. Millets fulfil all the above conditions, as these grow in half the time, do not require rich soil for their survival and growth, their requirement of water is significantly less and need less than half of the energy in processing as compared to the traditional crops. Sorghum (*Jowar*) and Pearl millet (*Bajra*) are the major millet crops grown, constituting 92% of the world millets production followed by Finger millet (*Mandua*), Foxtail millet (*Kangni/Kakum*), Proso millet (*Barre*), Barnyard (*Sanwa/Jhangon*), Little millet (*Kutki*) and Kodo millet (*Kodon*), which altogether constitute about 7.9%. Globally, India is the topmost producer of millets, where millet grains account for about one sixth of the total food grain pro-duction. For emphasizing the importance and to bring millets to the global forefront, during the 75th session of the United Nations General Assembly a resolution was passed to observe the year 2023 as the International Year of Millets.

Millets contains ~ 65% carbohydrates, 6.0-12.5% protein, 1.5-5.0% fat and 7-12% fiber, with a range of essential fatty acids, amino acids, vitamins and minerals (iron, calcium, phosphorus, zinc and magnesium), which makes them energy-dense and rich source of nutrients. The protein, macro- and micro-nutrient content of millets are higher than the staple cereals like wheat, rice and maize. Millets has been entitled as the Nutri-Cereals *(Sri Anna)* by the Government of India.

Studies have found that millets have lower glycemic index, are gluten free, non-acid forming foods rich in dietary fiber and anti-oxidants, which can help in reducing the risk of metabolic syndrome, diabetes, heart disease, inflammatory bowel disease and certain cancers. These benefits emphasizes the need to reintroduce these grains in our routine diet. (*https://pib.gov.in/PressReleasePage.aspx?PRID=1887847;01 January, 2023*)

Daag Achchhe Hain

With the advent of technology daily life of humans is getting more and more convenient, but on the other hand this is increasing the exposure to the environmental chemicals from intrauterine period. Long term effects of such exposure on human body are still not clear. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) is one such group of chemicals which are being used extensively in our daily life. They are characterized by a fluorinated carbon chain, which makes them dirt, water, and oil repellent. PFAS being utilized in most of the common items ranging from non-stick cookware, stain and water-repellent clothing (hiking pants, shirts, athletic wear, yoga pants, and raincoats), and items coated with Teflon and made from Gore-Tex fabric. These fabrics contaminate the environmental air by emission and water bodies during wash, and persists for a longer duration leading to the continuous exposure and accumulation in human bodies, thus also known as "forever chemicals".

Some researchers postulated that ADHD is the result of environmental effects on neurodevelopment during early years of life. Studies have established the association between prenatal exposure to PFAS and ADHD symptoms. In a recently published prospective cohort study from the republic of Korea, researchers studied the association between early-childhood exposure to PFAS and onset of ADHD symptoms in later childhood. Serum levels of six different forms of PFAS were measured in 521 enrolled children at 2 years and 4 years age. Presence of ADHD symptoms was evaluated at 8 years age using ADHD Rating Scale IV (ARS). Poisson regression models were used to analyse the association between PFAS and ARS scores. Levels of exposure to individual PFAS and the summed value were divided into quartiles to examine possible nonlinear relationships. Results showed that at 2 years children lying in the 2nd and 3rd quartile levels of PFAS have higher ARS scores than those in 1st quartile, while no such association was found between PFAS and ARS at 4 years. This suggest that early life exposure to PFAS can have neurotoxic effects in children and predisposes them to ADHD. Thus, use of clothes made of conventional fabric and traditional washing techniques can help in avoiding the extensive use of PFAS containing items and protect children from their harmful effects, "Daag Achchhe Hain" (*Science of The Total Environment 25 March, 2023*).

Impact of Family Mealtime on Children's diet

A balanced diet must contain items from all food groups. Adequate intake of fruit and vegetable reduces the risk of chronic noncommunicable diseases. Globally children take diet containing high quantities of refined flour, sugar and carbonated drinks, and considerably less fruits and vegetables than the recommended amount. Family serves as important learning environment in early years of a child, and family meals decides the food preferences and choices of children. This is important as children gets about two-thirds of their calorie intake from food prepared at home, and most meals being eaten along with parents and siblings.

In a recently published randomized control trial, the effect of increase in the family mealtime on the fruit and vegetable intake in children was evaluated. In this trial, 50 parent-child dyad with children aged between 6-11 years were enrolled and randomized into control (regular family mealtime duration) and intervention (50% longer mealtime duration) groups. Number of pieces of fruits and vegetables eaten by the child during a meal was the primary outcome measured. Analysis revealed significantly more number of pieces of fruits and vegetables were eaten by children in the intervention group than in the control group. Concluding that even a simple step of increased mealtime duration can improve the children's eating behaviour significantly, and can acts as an important public health intervention. (*JAMA Network Open 03 April, 2023*).

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CLIPPINGS

Guideline for the management of fever and neutropenia in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2023 update (Journal of Clinical Oncology 2023; 41:1774-85)

Fever and neutropenia (FN) is one of the most common complications of cancer treatments. The management of pediatric FN continues to be heterogeneous across and within centers; this heterogeneity can be reduced through implementation of clinical practice guidelines (CPGs). This guideline gives an updated CPG for the empiric management of FN in pediatric patients with cancer and hematopoietic cell transplantation recipients. The International Pediatric Fever and Neutropenia Guideline Panel reconvened to conduct the second update of this CPG. Using the Grading of Recommendations Assessment, Development and Evaluation framework, evidence quality was classified as high, moderate, low, or very low. The panel updated recommendations related to initial management, ongoing management, and empiric antifungal therapy. Ten new RCTs in addition to the 69 RCTs were identified in previous FN CPGs to inform the 2023 FN CPG. Changes from the 2017 CPG included two conditional recommendations regarding *a*) discontinuation of empiric antibacterial therapy in clinically well and afebrile patients with low-risk FN if blood cultures remain negative at 48 hours despite no evidence of marrow recovery and *b*) preemptive antifungal therapy for invasive fungal disease in high-risk patients not receiving antimold prophylaxis. The panel created a good practice statement to initiate FN CPG-consistent empiric antibacterial therapy as soon as possible in clinically unstable febrile patients. The updated FN CPG incorporates important modifications on the basis of recently published trials. More high-quality RCTs are required to better inform pediatric FN clinical care. Implementation may be improved through creation and adaptation of institution-specific care pathways on the basis of CPGs. Future work should focus on addressing knowledge gaps, improving CPG implementation, and measuring the impact of CPG-consistent care.

Impact of minimal residual disease on relapse in childhood acute lymphoblastic leukemia: Lessons learnt from a tertiary cancer center in India (Pediatr Hematol Oncol 2023 Mar 17;1-12)

Outcome of children and adolescents with acute lymphoblastic leukemia (ALL) has improved significantly in the past two decades. Accurate risk stratification and minimum residual disease (MRD) based decisions have helped clinicians immensely to assign appropriate treatment to the patients. Prognostic predictive value of end of induction minimal residual disease (EOI-MRD) is well established in acute lymphoblastic leukemia (ALL). Factors likely to affect EOI-MRD positivity (>0.01%) by flowcytometry and relapse in different BFM-95 (Berlin–Frankfurt–Munich) risk groups among children and adolescents were evaluated.This is a single-center, retrospective study conducted at a tertiary care cancer institute in Northern India. Data of 223 children and adolescents diagnosed with ALL up to 18 years of age, from January 2015 to December 2019 was analyzed. Association between demographic and pretreatment characteristics with EOI-MRD was assessed. Risk factors for relapse were analyzed using univariate and multivariate Cox regression. Proportion of the SR (standard risk), MR (moderate risk), and HR (highrisk) patients was 18.8%, 60.9%, 20.3%, respectively. Positive EOI-MRD among these risk groups was observed in 11.9%, 18.3%, and 55.5% patients, respectively. MRD positivity was more likely to be associated with older age (>10years) and BFM-HR patients. Thirty-four (15.2%) patients relapsed in the whole cohort. On univariate analysis, statistically significant factors for RFS (relapse-free survival) included hyper-leukocytosis, high-risk cytogenetics, NCI (National Cancer Institute) high risk, poor day-8 prednisolone response, BFM–HR and positive EOI-MRD status. Of all these only EOI-MRD retained its impact by multivariate analysis. Positive EOI-MRD significantly predicted relapse in BFM-MR with 5-year RFS of 88.0% and 68.4%. Five-year RFS of EOI-MRD negative and positive groups were 86.4% and 65.5%, respectively. EOI-MRD is a powerful tool to predict relapse in children and adolescent with ALL, especially in BFM-MR. Application of MRD in HR patients needs to be redefined in conjunction with other variables.

Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group (Lancet Oncol. 2023;24: E108-20)

Survivors of childhood, adolescent, and young adult cancer, previously treated with anthracycline chemotherapy (including mitoxantrone) or radiotherapy in which the heart was exposed, are at increased risk of cardiomyopathy. Symptomatic cardiomyopathy is typically preceded by a series of gradually progressive, asymptomatic changes in structure and function of the heart that can be ameliorated with treatment, prompting specialist organizations to endorse guidelines on cardiac surveillance in at-risk survivors of cancer. In 2015, the International Late Effects of Childhood Cancer Guideline Harmonization Group compiled these guidelines into a uniform set of recommendations applicable to a broad spectrum of clinical environments with varying resource availabilities. Since then, additional studies have provided insight into dose thresholds associated with a risk of asymptomatic and symptomatic cardiomyopathy, have characterised risk over time, and have established the cost-effectiveness of different surveillance strategies.

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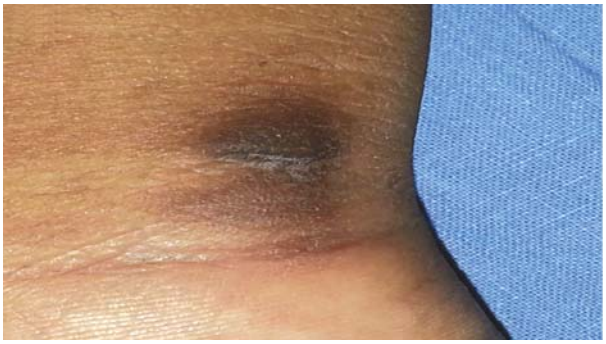
Mousing Callus

A 12-year-old boy presented with complaints of a progressively darkening black-colored circular lesion in right wrist since 8 weeks. He was using desktop computer for 4 to 5 hours/every day for the past two years during the coronavirus pandemic. Examination revealed single hyperpigmented hyperkeratotic plaque of size 2×1 cm in medial side of volar aspect of the wrist (**Fig. 1**). Reduced skin markings were noted over the plaque. A diagnosis of mousing callus was made, and the child was advised to reduce computer mouse usage.

Mousing callus occurs due to prolonged usage of computer mouse. It occurs in ulnar side of ventral wrist due to repeated friction of pisiform bony prominence against the table. The two differentials to be considered are wart and dermatofibroma. Wart has a verrucous surface with black dots, whereas dermatofibroma is characterized by dimpling of lesion upon pinching. Mousing callus gradually improves on reducing mouse use.



(*a*) (*b*)

Fig. 1 *a) Hyperpigmented hyperkeratotic plaque suggestive of mousing callus measuring 2x1 cm in medial side of volar aspect of the right wrist; b) Close up picture of the mousing callus.*

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Lip-Licking Dermatitis

A 3-year-old boy was brought with complaints of dry chapped lips for two weeks. Examination revealed scaly plaques involving both lips and curvilinear scaly plaque below the lower lip (**Fig. 1**). There was history of repeated licking of lips. A diagnosis of lip-licking dermatitis was made. He was prescribed petrolatum jelly thrice a day and parents were advised to get him to stop licking his lips. The lesions improved over the next week.

Lip-licking dermatitis presents with dry, scaly, bleeding lips. It is triggered by dryness of lips due to harsh weather or underlying atopic dermatitis. Patients lick their lips to replenish the moisture, resulting in temporary relief of symptoms. However, it can further aggravate the condition due to dryness resulting from evaporation, and digestive enzymes present in saliva leading to breakdown of protective skin barrier. Regular application of bland, non-irritating lip balm can prevent development of lip-licking dermatitis. Mild topical steroids or topical calcineurin inhibitors such as tacrolimus or pimecrolimus may be required in some cases. Contact dermatitis, actinic cheilitis, granulomatous cheilitis and lichen planus are some of differential diagnosis that need consideration. Untreated disease can result in secondary bacterial or fungal infections.

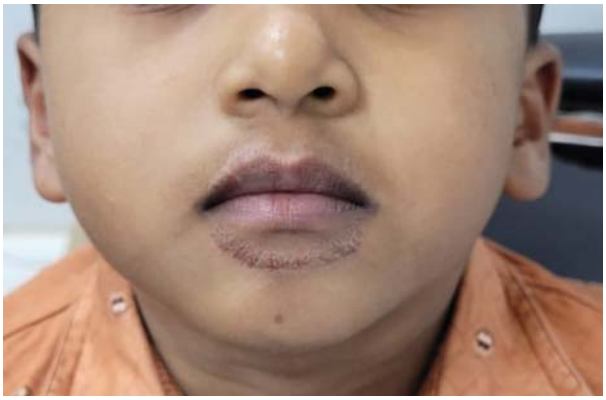

Fig. 1 *Scaly plaques involving both lips and curvilinear scaly plaque below the lower lip.*

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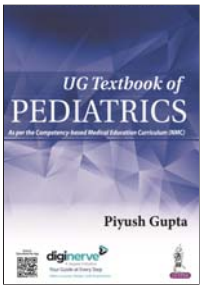
BOOK REVIEW



UG Textbook of Pediatrics

Piyush Gupta, Nidhi Bedi
Jaypee Brothers Medical Publishers
Pages: 1123; *Price*: 1195/-

There have been many pediatric textbooks published for undergraduate medical students in this country, each of which has their own style and approach. But what makes this multi-authored book (contributed by more than 60 pediatric teachers) edited by an eminent pediatric academician and medical educationist is that it has been written with its focus being the new competency-based medical education (CBME) curriculum for undergraduate medical training introduced in 2019.

The 32 chapters in this book cover 35 pediatric topics in the CBME curricula (spanning 399 core pediatric and additional integrated competencies). The 'competency index' provided at the start of the book linking the individual competencies to the chapter and page in the book would make it easy for the student and the faculty to navigate through the book.

Each chapter begins with a listing of the applicable competencies, has a text that is simple and easy to read, and a summation at the end of the chapter titled "In a nutshell." What makes this book particularly interesting and useful is the linking of the cognitive to its practical application through the numerous case studies of problems frequently encountered in pediatric practice. The section on Social Pediatrics covers all the current national programs that target children and adolescents, the IMNCI approach, what the student ought to do when visiting a rural health center, and the role of the physician in the community. The multi-colored book has color coding to highlight headings, boxes, tables, figures, flow diagrams, treatment, revision points and suggested reading. The numerous colorful diagrams are easy to follow and comprehend. The colored flow diagrams would allow the student to initiate standardized treatment for the most common and critical conditions amongst children. All these make the book attractive and readable for the student. The book provides the most recent treatment protocols, a ready reference to drug therapy, growth charts, and pediatric laboratory values.

This is a book that all undergraduate medical students would find most useful while they work through their pediatric training and prepare for their examinations. The faculty too would find this book an *aide-memoir* while planning their teaching sessions for the undergraduate medical students.

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