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*Theme : Algorithms in Pediatric Intensive Care (AI)*



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1. GlaxoSmithKline Biologicals, Infanrix hexa Summary of Product Characteristics, 2017; 2. Samal-Rosenfeld S, Hovvay Summary of Product Characteristics, 2018; 3. Easy six preterm infant information 2017; 4. Omelka F, et al. Pediatrics. 2006;118(2):1792-1798; 5. Wang J, et al. Acta Paediatr. 2008;97(12):1349-1350; 6. Omelka F, et al. Immunization of preterm infants with GSK's hexavalent combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine: A review of safety and immunogenicity. Vaccine 12(18). http://dx.doi.org/10.1016/j.vaccine.2004.05.007; 7. GlaxoSmithKline Dof. ENG 2017/03/4564\_00 (Number of GSK sponsored studies in which Infanrix hexa has been administered).

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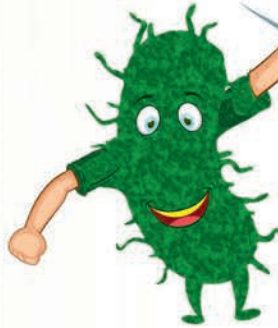
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<sup>^</sup> USFDA - United States Food & Drugs Association    <sup>§</sup> EFSA - European Food Safety Authority

\*Adapted from : Suva MA, Sureja VP, Khenni DB. Curr Res Sci Med 2016;2:65-72.

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## IAP-Child Health Initiative for Urban Slums

**BAKUL JAYANT PAREKH**

*President, Indian Academy of Pediatrics, 2020  
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**S**ocietal inequality is most stark in our urban centers. We have large slum communities living right next to corporate and residential skyscrapers. Almost 40% of Mumbai lives in slums and while it may vary slightly for other metros of our country, the conditions are not starkly different. There is enough data to suggest that urban slums fare very poorly on some of the most basic human development indicators related to child health and nutrition.

Children in urban slums face huge problems related to high prevalence of disease, lack of nutrition and low levels of personal hygiene. Moreover, access to health-care professionals like pediatricians is a challenge. The government's mid-day meal scheme is doing its best to provide adequate nutrition to children at the budgeted price point.

I strongly feel that the Indian Academy of Pediatrics (IAP) must take a leadership role to solve these problems at scale. A collaborative approach with other stakeholders combined with our nationwide reach will help us address these issues across the country. I feel that the solution has three key parts, as listed in **Box I**.

We should fine tune the above program through a field-based pilot. For doing that, I have already identified an Integrated Slum Development Project that is working in partnership with MCGM (Municipal Corporation of Greater Mumbai) in an urban slum in Goregaon West, covering about 20,000 families. A group of eminent non-government organizations (NGOs) under the *aegis* of MCGM is executing various aspects of the project, *e.g.* Pratham ([www.pratham.org](http://www.pratham.org)) is looking at education initiatives and skill development programs, Green communities foundation ([www.greencf.org](http://www.greencf.org)) is an expert in waste management and Apnalaya ([www.apnalaya.org](http://www.apnalaya.org)) is contributing to address citizenship and governance issues at the community level. The screening, medical intervention and nutrition programs will be implemented by Green communities foundation. After successful implementation of this pilot, this program will be scaled up to Mumbai and other urban/ rural centers in collaboration with local branches and other NGO partners like Rotary.

The pilot, the way I have conceptualized it, will address the core project objectives and will be executed in the following manner:

1. Universal screening - Screening of all children door-to-door will be done to identify:
  - (a) Current nutritional status and growth and intervention needs.
  - (b) Current disease status – top 5-10 common conditions.
  - (c) Current health and hygiene gaps and simple interventions that can address those gaps like oral health, footwear, clothes, deworming, etc.

This screening will be conducted by a trained and equipped worker. IAP will design the program so that the trainer should know who would be screened, what would be measured and using which equipment. IAP will also create training material for workers.

### **Box I Addressing Child Health and Nutrition Issues in Urban Slums**

#### *Universal screening at doorstep*

- Door to door screening of children needs to be done to identify current gaps related to healthcare, nutrition and other hygiene issues.

#### *Medical and material intervention*

- The cases that need intervention as a result of the screening exercise should be directed to a local pediatrician who can visit the slum periodically and can provide certain medical and material handouts. The pediatrician can also connect the child to tertiary care, if needed.

#### *Nutritional intervention*

- A low cost protein, lipid and micronutrient supplement that can be distributed through the direct slum intervention combined with the mid-day meal at the nearby municipal schools.

2. Medical attention and related handouts

- (a) We will enable our volunteer pediatrician network to provide consultation or enable doctor consultation with pediatric support.
- (b) At the time of the consultation, apart from medication, certain handouts for oral health, footwear, clothes, deworming etc. will be provided.
- (c) The children will be connected to tertiary care, if needed.

In short, IAP will design a plan of action when any obvious nutrition problems, diseases or underlying conditions needing intervention or any other personal problems are encountered.

3. Nutrition intervention

- (a) The product that we have designed is a scientifically formulated fortified dal/ khichdi which is a '10g protein + 50% RDA of 10 micronutrient' solution at a cost lower than the current lowest cost product. It is a completely

natural product – no chemical additives or preservatives, and is 100% vegetarian.

- (b) It will be handed out at all nutrient deficient homes identified during screening and also included in the mid-day meal at two government schools covering about 5000 students.

The Academy's role will be to recommend the correct formulation for fortification and guidelines for consumption.

I feel confident that this pilot will be a significant milestone towards creating a long term solution for the problems I have listed above. It will provide us immense learnings and also pave the path for scale up of this program nationwide. While I have conceptualized this project, its success will solely depend on the valuable inputs and contribution of the entire pediatrician community. I take this opportunity to request your wholehearted support for this initiative. Let's do this together!

*Jai Hind!  
Jai IAP!*

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## Preterm Birth: A Risk-factor for Chronic Kidney Disease?

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The concept of the origin of most chronic illnesses in the prenatal period was introduced by Dr. David Barker, back in the 1990s [1]. This concept was later extended to kidney diseases by Brenner, *et al.* [2]. As more than 60% of the nephrogenesis occurs in the last trimester of pregnancy, it is believed that preterm births before 36 weeks have a lower nephron mass [3]. This results in a decreased estimated glomerular filtration rate (GFR) at birth. However, despite the fewer glomeruli, they manage to achieve a GFR similar to that of a term neonate. This compensatory response due to the single nephron hyperfiltration eventually results in glomerular damage, proteinuria and hypertension, thus setting them on the path of development of chronic renal disease in due time.

In small for gestational age (SGA) newborns; however, the cause for a decreased GFR is different. A difference in the genetic composition of the renal cells with an overall increased rate of apoptosis are the proposed mechanisms [4,5]. The ongoing inflammation along with placental insufficiency in these growth restricted newborns affects the organogenesis, leading to a lower nephron mass [6]. In this issue of the journal, Reddy and colleagues [7] have reported on their study on renal growth and function in appropriate for age (AGA) and SGA preterm neonates with a gestation <35 weeks. They have concluded that preterm infants, especially SGA infants, are at an increased risk of impaired renal function with a poor renal growth at 12 to 18 months of corrected gestational age [7].

The extra-uterine course of each newborn is different. Sepsis, birth asphyxia and use of nephrotoxic drugs may additionally impact the GFR [8]. With an increased risk for renal vascular thrombosis and a poor tubular function, some of these newborns may suffer a second hit, *i.e.* neonatal acute kidney injury (AKI) [9]. These factors predispose this cohort to the development of chronic kidney disease (CKD) in later life [10-12].

As the growth of the kidneys to attain adult

glomerular filtration levels continues till two years of age, the evaluation of kidney function in this dynamic period remains difficult [13]. Therefore, a one-time assessment by a cross-sectional study may potentially lead to biased results. Moreover, baseline renal functions after birth require serial repeated measurements over time to ensure consistency in the results and a valid final outcome.

The use of serum creatinine as a neonatal renal biomarker has been questionable. Being affected by the muscle mass and hydration status, it has a high inter-individual variability among neonates itself [14]. The superiority of Cystatin C over serum creatinine has been extensively studied and evaluated with meta-analyses. Being independent of age, sex, muscle mass and various inflammatory conditions, the constant production rate with a minimal placental transfer makes it a preferred biomarker for estimation of GFR, especially in neonates. Even though, further validation by more extensive studies remains necessary, its importance cannot be undermined.

Iyengar, *et al.* [15] in 2016, studied the kidney growth and changes in GFR during this dynamic period in a cohort of southern Indian infants using serial renal volume measurements by an ultrasound and cystatin C derived glomerular filtration rate. While the renal growth was reported to be slower in the low birthweight and SGA infants, the GFR at 18-24 months of age was similar. This supported the concept of hyper-filtration in the smaller kidneys which may act as a precursor to the development of CKD in the adult life.

Various studies support the concept of the mean renal volume as a surrogate *in vivo* marker for the nephron number in neonates [16,17]. However, the extrapolation of this concept to renal length, as done in the current study, may lead to biased results. Moreover, most of the studies conducted previously for assessment of the renal function and the progression to CKD in this cohort, have enrolled large subject numbers. A small number of total enrolled patients by Reddy, *et al.* [7] might lead to confounded results and hence, a decreased generalizability of the study.

A newer innovative method of assessing nephron number by magnetic resonance imaging (MRI) of the kidney, with cationic ferritin labelled glomeruli is currently being evaluated [18]. The ongoing research in metabolomics with urinary novel biomarkers including beta-trace protein, beta-2 microglobulin, urinary neutrophil gelatinase associated lipocalin, urinary kidney injury molecule, serum cystatin C and uromodulin will open new doors for early detection of kidney injury and better techniques for estimation of GFR in children. The manipulation of the modifiers of nephrogenesis, including variants in the *PAX2* or *RET* genes and epigenetic factors like DNA methylation raises the possibility of development of strategies to extend the period of normal nephrogenesis [19]. Methods to induce *de novo* nephrogenesis postnatally are also currently the focus of ongoing animal experiments [20].

The increasing survival rate of the preterm and SGA babies also puts them at the risk of development of various co-morbidities. It is, thus, imperative that a long-term surveillance plan for early detection of kidney diseases be implemented with appropriate preventive measures to check the progression to chronic kidney disease.

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## Nephrocalcinosis: Biochemical Evaluation and Genetic Analysis

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**N**ephrocalcinosis, characterized by the deposition of calcium salts in the renal parenchyma, is detected as diffuse renal calcifications on high-resolution ultrasonography or computed tomography. Patients usually do not have symptoms or have features related to the underlying etiology. Rarely, the disease may be severe enough to result in metabolic dysfunction and end-stage renal disease.

The condition may involve either cortical or medullary locations. Cortical nephrocalcinosis is uncommon and results from damage to the renal parenchyma, followed by dystrophic calcification [1]. It is described in chronic glomerulonephritis, cortical necrosis, sickle cell disease, malignancy and trauma. Medullary nephrocalcinosis is much more common and arises from disturbances in calcium homeostasis, mineral reabsorption in the thick ascending limb, or abnormal acid-base regulation in the collecting duct. Medullary nephrocalcinosis is diagnosed in 7-40% preterm neonates. Chief risk factors include gestation <32 weeks and birthweight <1500 g [2]. Hypercalciuria might result from acidosis, parenteral nutrition, medications (loop diuretics, vitamin D, corticosteroids, methylxanthines), and high calcium and low phosphorus intake. Nephrocalcinosis resolves by early childhood, while low glomerular filtration rate (GFR) and reduced concentrating capacity may persist [2].

Compared to adults, children often show an underlying metabolic disorder and higher risk of progression, with poor renal function on follow-up [3]. It is, therefore, necessary to identify the underlying cause, initiate therapy if possible, and provide appropriate counseling. Clinical evaluation includes information on prematurity, concomitant diseases, prior therapies, diet, fluid intake, and family history. Careful biochemical evaluation of urine (on two or more occasions) and blood is done to screen for common metabolic disorders [4].

Distal renal tubular acidosis (RTA), varied causes of hypercalciuria, and primary hyperoxaluria (PH) account

for most patients; 12.5% failed to show an etiology [5]. Another retrospective series on 152 German patients showed that the chief causes were idiopathic hypercalciuria (34%), primary tubular disorders (32%) and vitamin D toxicity (8%) [6]. Similar findings were reported from other European countries, showing distal RTA, Bartter syndrome, vitamin D toxicity and idiopathic hypercalciuria in the majority [7].

In the current issue, Ramya, *et al.* [8] report the etiology in 54 children with nephrocalcinosis managed at a single tertiary care center. Following biochemical studies, the authors report dRTA in 18 (33.3%) and PH in 9 (16.7%) children. There was high frequency of consanguinity (50%), and more than a quarter of the patients had positive family history of a similar illness. Standard biochemistry-based definitions were used to define the etiologies; genetic confirmation was sought in only 8 children. A significant proportion had hypercalciuria secondary to RTA, Dent syndrome, Bartter syndrome, and hypomagnesemia. A cause was not found in a minority, suggesting that systematic metabolic evaluation helps in diagnosing the underlying illness in most patients with nephrocalcinosis.

The report has some limitations [8]. First, while the diagnosis of PH (based on oxalate excretion >40 mg/1.73 m<sup>2</sup>/d) was made in 9 patients, genetic studies were done in only four. In the absence of genetic confirmation, the possibility of enteric or dietary hyperoxaluria cannot be excluded [9]. Secondly, the phenotype of PH associated with mutations in *AGXT*, *GRHPR* and *HOGAI* is variable, and has reasonable implications for management. Therefore, the diagnosis of PH must be confirmed by enzyme studies or genetic analysis. Patients with specific *AGXT* mutations, p.Gly170Arg or p.Phe152Ile, respond well to oral pyridoxine [10]. A precise diagnosis is always necessary for patients to be enrolled in clinical trials using silencing RNA [11].

Disorders like distal RTA, Bartter syndrome, Lowe syndrome, Dent disease, and cystinosis have characteristic phenotypes, enabling relatively secure diagnosis. Our

understanding of the genetic basis of these disorders has considerably improved. Three new genes have been described for distal RTA: *WDR72*, *FOXI1* and *ATP6V1C2*. Mutations in these genes produce a phenotype similar to that for previously known genes (*ATP6V0A4*, *ATP6V1B1* and *SLC4A1*) for this disease. Similarly, mutations in multiple genes may result in Bartter syndrome with nephrocalcinosis (*SLC12A1*, *KCNJ1*, *CLCNKB*, *CaSR*, *MAGED2*), hypomagnesemia with hypercalciuria (*CLDN16*, *CLDN19*), Dent disease (*CLCN5*, *OCRL1*) and hypophosphatemia with hypercalciuria (*SLC34A1*, *SLC34A3*) [3]. A clinical diagnosis is also possible for other diseases, e.g., Fanconi-Bickel syndrome (*SLC2A2*), 24-hydroxylase deficiency (*CYP24A1*) and hypercalcemia with hypocalciuria (*CaSR*, *GNA11*, *AP2S1*). However, confirmation of diagnoses by appropriate genetic studies is recommended, before embarking in many instances for specific therapy. A number of conditions including variants in *ADCY10*, *SCL34A1* and *CYP24A1* might present with hypercalciuria alone, and misclassified as idiopathic hypercalciuria unless genetic diagnosis is obtained, as might have occurred in the current or previous studies.

Recently, the Hildebrandt group showed that high-throughput screening for 30 genes enables diagnosis in ~15% patients with unresolved nephrolithiasis/nephrocalcinosis [12]. The group also reported that in a larger cohort, whole-exome sequencing helped diagnose ~45% patients with nephrocalcinosis [12]. Higher diagnostic yield was present in the young (58% in those <3 years), positive family history (41%) and consanguinity (75%). Given the proportion of subjects with positive family history and consanguinity, the study by Ramya, *et al.* [8] would have benefited from detailed genetic studies.

Children with nephrocalcinosis should be referred to clinical units experienced in managing such patients. Systematic biochemical screening is recommended for evaluating the underlying cause [4]. Additional genetic diagnosis is useful for confirming the etiology, and counseling parents regarding the likely course of disease and future extrarenal manifestations. It also provides an opportunity for prenatal diagnosis in future pregnancies. While targeted therapies are available for many monogenic disorders, phenotype-genotype correlation

will allow patient stratification for future studies. Given the need in most patients to screen for multiple genes, we advise high-throughput genetic testing using the clinical exome approach.

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## **Acute Peritoneal Dialysis in Neonates with Acute Kidney Injury**

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**A**cute kidney injury (AKI) is defined as sudden decrease in glomerular filtration rate leading to fluid and electrolyte imbalance, disturbed acid-base homeostasis and retention of nitrogenous waste products. It affects about 5% of patients admitted to hospitals and 30% of cases in intensive care units [1]. In the recent past, two large cohort studies, Assessment of worldwide acute kidney epidemiology in neonates (AWAKEN) [2] and Assessment of worldwide acute kidney injury, renal angina, and epidemiology (AWARE) [3] have provided an in depth spectrum of AKI in neonates, children and young adults. In neonates, the incidence of AKI was found to be 30%, which varied according to gestational age such as 47.9% in gestation of  $\geq 22$  to  $< 29$  weeks, 18.3% between  $\geq 29$  to  $< 36$  weeks and 36.7% in  $\geq 36$  weeks [2]. The overall incidence of AKI in children has been reported to be 27%; with severe AKI in 11.6% of children in intensive care settings [3]. As such there are several definitions to define AKI based on rise in the serum creatinine level, decrease in urine output and estimated glomerular filtration rate. However, serum creatinine varies with age, muscle mass, nutritional and hydration status. It has major limitations in newborns because of reflection of maternal creatinine in initial 48-72 h after birth, varying degree of reabsorption from proximal tubules, lower glomerular filtration rates and maturation differences based on gestational age. Modified kidney diseases: Improving global outcomes (KDIGO) criteria can be applied to define AKI in neonates [4]. This classification defines AKI in different stages based on absolute rise in serum creatinine from a previous trough level and decrease in urine output or anuria over time.

Regarding etiologies of AKI, hypovolemia following acute gastroenteritis, sepsis, hemolytic uremic syndrome and malaria are common in older children in developing countries [5], while ischemic/hypoxic and nephrotoxic injury to preterm/term neonates, sepsis and post-cardiac surgery are predominant etiologies in developed countries [6].

The neonates may present with lethargy, fever/ low body temperature, decreased urine output/ anuria, vomiting, hypotension, seizures, and palpable kidneys and bladder, if there is obstructive uropathy. Initial investigations include hemogram, complete blood count, blood culture, C-reactive protein, renal function test, arterial blood gas analysis, urine microscopy and culture study, and ultrasonography kidney, ureter and bladder to detect underlying congenital malformations. Voiding cystourethrogram can be performed earlier (within 24-72 h of life) in patients with suspected lower urinary tract obstruction.

Supportive therapy is in the form of maintenance of fluid and electrolyte balance, antibiotics in modified doses for treatment of sepsis, use of vasopressor agents for hypotension, and ventilatory support, if required. Oliguria and fluid balance are important parameters in critically ill patients. Cases of oliguric AKI have a three-fold increased risk of undergoing renal replacement therapy as compared to non-oliguric AKI. The renal replacement therapies available for neonatal AKI are peritoneal dialysis (PD), hemodialysis and continuous renal replacement therapy. Choice of therapy depends upon the technical expertise, vascular access and availability of machines. The option of PD is often the only modality available in developing countries, which can be instituted at the earliest. The type of catheter can be flexible (Tenckhoff double cuffed straight/swan neck or Cook PD soft catheter) or rigid straight with stylet or improvised PD catheters (pig-tail, angiocath, intercostal drainage tube). However, flexible catheter is preferred because of better inflow, outflow and lesser chances of leakage, peritonitis and perforation.

The article by Okan, *et al.* [7] in this issue of *Indian Pediatrics* reports on the use of acute PD with multifunctional flexible catheter in the treatment of very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates. In this small observational study, the etiologies of AKI were patent ductus arteriosus, necrotizing enterocolitis, sepsis, asphyxia and hydrops

fetalis. About 2.8% of neonates required PD and the mortality was high (81%), which could be because of lower gestation and birthweight. Kara, *et al.* [8] also found high mortality of 77% in their study on acute PD in neonatal AKI. The contributors for mortality in AKI patients are multiorgan failure, sepsis, AKI stage 2 and 3, presence of fluid overload and need for ventilatory support [3,8,9,10]. Fluid balance has been found to be closely associated with outcome and negative fluid balance at post-natal day seven in the hospital setting was associated with a lesser risk of need for mechanical ventilation in near-term/term neonates [9]. In a large cohort of AWAKEN study, significant contributors for mortality were AKI, and longer duration of hospital stay [2]. As such, AKI is an independent risk factor for mortality during hospitalization.

The initiation of PD in VLBW and ELBW is the preferred dialysis modality to treat AKI. Since mortality in neonatal AKI is still very high, early institution of PD should be undertaken as a life-saving procedure.

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## Management of Lupus Nephritis in Children

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Lupus nephritis affects 50-75% of all children with systemic lupus erythematosus with a higher prevalence in Asians. It remains a major contributor to morbidity and mortality in childhood onset lupus. Proliferative lupus nephritis (class III and class IV) warrants aggressive treatment to prevent progression to end stage renal disease. Newer immunosuppressive agents available in the last decade offer more options to treat lupus nephritis. Despite guidelines from professional bodies, there remains a lack of consensus on the treatment of refractory disease and duration of maintenance therapy. We review the treatment options for pediatric patients with lupus nephritis based on studies and published guidelines in the last decade, and highlight opportunities for continued improvement in care.

**Keywords:** Glomerulonephritis, Induction, Immunosuppression, Maintenance.

Childhood-onset systemic lupus erythematosus (cSLE) has an incidence of 0.3 to 0.9 per 100,000 children-years and a prevalence of 3.3-8.8 per 100,000 children with higher prevalence rates in non-white populations including Asians [1]. About 10-20% of cases of SLE are diagnosed during childhood with a median age of onset of 11-12 years, and these patients have increased disease severity and lower survival rates [2]. Renal disease occurs in 50-75% of all cSLE patients, mostly within the first two years of diagnosis [2,3]. As per the American College of Rheumatology (ACR) criteria, lupus nephritis is defined as persistent proteinuria ( $>0.5$  g/day or  $>3+$  by dipstick) and/or cellular casts in the urine. A spot urine protein/creatinine ratio of  $>0.5$  can be substituted for the 24-hour urine protein measurement and an 'active urinary sediment' ( $>5$  RBC/high power field (hpf),  $>5$  WBC/hpf in the absence of infection, or cellular casts limited to red blood cells or white blood cell casts) can be substituted for cellular casts [4]. Initial manifestations of renal disease range from minimal proteinuria and hematuria to nephrotic-range, rapidly progressive glomerulonephritis, severe hypertension, and acute kidney injury. The frequency of nephritis in patients with SLE is significantly higher in African Americans, Asians (40-82%) and Hispanics than in whites (29%) and is higher in men [5]. Nephritis is a major risk factor for morbidity and mortality in SLE and 10% of patients with lupus nephritis will develop end stage renal disease (ESRD) with a higher risk in patients with more severe histological classification (44% over 15 years) [5].

As there may be a lack of clinico-pathologic correlation, a renal biopsy is the gold standard for diagnosis. Histopathology is valuable in guiding treatment and a renal biopsy is strongly recommended for all patients with clinical evidence of lupus nephritis for classification of nephritis and evaluation of activity and chronicity [6,7]. The recommendations of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) revised in 2018 are currently used as the basis for the classification of lupus nephritis [8,9]. In general, class I (minimal mesangial) and class II (mesangial proliferative) nephritis are mild lesions and require little to no targeted immunosuppressive treatment due to a favorable natural history. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that treatment for class I/II lupus nephritis be dictated by extra renal manifestations; except that patients with nephrotic range proteinuria receive steroid or calcineurin inhibitor (CNI) therapy [10]. Class III (focal proliferative) and class IV (diffuse proliferative) lesions are the most frequent and severe findings in childhood lupus nephritis [2,11]. Patients with proliferative lesions have the highest risk of ESRD and, thus, are treated with aggressive immunosuppression [2]. Combination of class III or IV with class V (membranous) lupus nephritis is prevalent and treatment strategies used for proliferative nephritis should be followed [10]. With current treatment regimens, the incidence of ESRD in patients with proliferative lupus nephritis has improved and the 5-year renal survival of children ranges from 77-93% [12].

## Goals of Therapy

Therapeutic goals for the treatment of lupus nephritis include achieving prompt renal remission, avoiding flares, preventing chronic renal impairment, improving survival and quality of life, and minimizing iatrogenic effects. As short-term outcomes improve, more attention is needed on balancing the risks of long-term immunosuppressive exposure. However, it is important to remember that failure to achieve and maintain remission of nephritis reduces the rates of renal survival and overall survival.

The treatment of proliferative lupus nephritis is commonly divided into two distinct phases: induction and maintenance. The induction phase is composed of intense immunosuppression aimed at achieving remission with resolution of active inflammatory changes. Consensus renal response definitions in pediatric LN define substantial response (complete remission) as normalization of renal function, inactive urine sediment (<5 WBC/hpf, <5 RBC/hpf, and no casts), plus spot protein/creatinine ratio <0.2 [13]. Induction is followed by a longer maintenance phase, during which less intense immunosuppressive regimens are used to sustain remission while attempting to minimize side effects associated with medications. The widely used KDIGO practice guidelines are based on adult data, but suggest that pediatric providers follow the same treatment algorithms [10]. In the absence of robust clinical trial data in pediatric patients with proliferative LN, consensus treatment plans have been developed by CARRA (Childhood Arthritis and Rheumatology Research Alliance) for induction therapy based on available scientific evidence and pediatric rheumatology group experience with the goal of improving prognosis by standardizing treatment plans [13].

## INDUCTION THERAPY

The consensus treatment plans for induction therapy recommend either intravenous cyclophosphamide (IV-CYC) or mycophenolate mofetil (MMF) along with steroids for a duration of 6 months (**Table I**). Consensus was reached to administer a total of 6 monthly IV-CYC dosages (starting with 500 mg/m<sup>2</sup> and increasing based on tolerance and WBC nadir to a maximum dosage of 1,500 mg). In the adult literature, this standard dosing regimen (designated the NIH regimen) has been compared to a low dose (or Euro-lupus) regimen which consists of 500 mg IV-CYC every 2 weeks for 6 treatments followed by initiation of maintenance therapy. These regimens have shown a similar efficacy in the populations studied and the ACR recommends this regimen for IV-CYC induction in patients who are white with European background [7]. The KDIGO guidelines

also include option for oral cyclophosphamide (1.0-1.5 mg/kg/day, maximum 150 mg/day) for 2-4 months [10]. MMF is recommended at a dose of 600 mg/m<sup>2</sup>/dose (maximum 1,500 mg) twice daily. This is similar to European pediatric consensus dosing regimens (1200 mg/m<sup>2</sup>/day, maximum 2000 mg/day; when poor response option to increase to maximum of 1800 mg/m<sup>2</sup>/day, maximum dose 3000 mg/day) [11]. African-Americans and Hispanics with lupus nephritis may respond less well to IV-CYC than patients of white or Asian races; thus, MMF is the preferred agent for these populations [7]. Observational studies and a recent single center trial from India suggest a comparable rate of response with either IV-CYC (both dosing regimens studied) or oral MMF [14–16]. However, one pediatric study in the Indian population detected better efficacy of MMF compared with IV-CYC induction [17].

Despite dramatic variability of glucocorticoid prescribing practices, CARRA consensus guidelines for induction provided three regimens (primarily oral, primarily IV, and mixed oral/IV) with the goal to achieve a daily dosage of oral glucocorticoids between 10 and 20 mg upon completion of induction therapy at 24 weeks [13]. High dose IV methylprednisolone pulses (30 mg/kg/dose IV for three consecutive days, maximum 1000 mg/dose), but not oral glucocorticoids, have the potential to eliminate the interferon- $\alpha$  gene expression signature in cSLE, by reducing the number of plasmacytoid dendritic cells and hence all regimen allow the use of this therapy, which is invariably used for severe disease [13]. Most studies in cSLE report the use of oral prednisone 1-2 mg/kg/day (maximum 60 mg/day) with tapering schedule by 10-20% at one- or two-week intervals based on clinical improvement [11].

Other immunosuppressive agents with some evidence for efficacy include azathioprine, abatacept (in conjunction with CYC), calcineurin inhibitors (CNI), (cyclosporine, tacrolimus), and rituximab. CNI-based regimens have been studied in Asia, and often combine MMF and steroids with a CNI ('multitarget therapy'). A large Chinese randomized trial reported improved rates of complete and partial renal remission at 24-weeks in patients treated with low-dose MMF, tacrolimus, and steroids compared to monthly IV-CYC and steroids for induction of proliferative LN [18].

Rituximab has generally been reserved as an adjunctive therapy in patients with relapsed or refractory disease. To date, prospective randomized controlled trials have failed to show a significant benefit in clinical outcomes with the addition of rituximab to standard of care induction therapy [19]. However, one study in pediatric

**Table I Summary of Common Treatment Regimens for Proliferative Lupus Nephritis**

<i>Induction therapy (choose one)</i>		
Cyclophosphamide (CYC) IV (high dose, NIH regimen)	6 doses, given monthly Initial dose 500 mg/m <sup>2</sup> , increase as tolerated to 1000 mg/m <sup>2</sup> (maximum dose 1500 mg)	Adjust dose for renal insufficiency and low WBC nadir (7-10 d after dose)
Cyclophosphamide (CYC) IV (low dose, Euro-Lupus regimen)	6 doses of 500 mg/dose, given every 2 wks	
Mycophenolate mofetil (MMF)	600 mg/m <sup>2</sup> /dose twice daily for 6 mo (maximum dose of 1500 mg twice daily)	May start lower dose and escalate to target dose within 4 wk. Consider maximum dose to 1000 mg twice daily in Asian population
<i>Maintenance therapy (choose one)</i>		
Mycophenolate mofetil (MMF)	600 mg/m <sup>2</sup> /dose (maximum dose of 1,000 mg twice daily)	
Azathioprine (AZA)	2-3 mg/kg/day (maximum 150 mg/d)	
<i>Glucocorticoids*</i>		
Induction		
3 consensus regimens for induction from CARRA are summarized below – common goal is to achieve a daily dosage of oral glucocorticoids of 10-20 mg upon completion of induction therapy after 24 wks; all allow for the use of up to 3 high-dose methylprednisolone pulses (30 mg/kg/dose up to 1000 mg/dose) at the start of induction		
	>30 kg ( <i>oral regimen</i> )	<30 kg ( <i>oral regimen</i> )
Primarily oral		
Pulse 3× in wk 1 ( <i>optional</i> )	60-80 mg daily for wks 1-4, decrease by ~10 mg daily every 2-4 wk	2 mg/kg/d for wk 1-6, decrease by ~5 mg daily every 2-4 wk
Primarily IV		
Pulse 3× in wk 1, 1-3×/wk in wk 2-7, 1×/month in wk 8-24	20 mg daily for wk 1-11, 15 mg daily for wk 12-18, 10 mg daily for wk 19-24	10 mg daily for wk 1-11, 7.5 mg daily for wk 12-18, 5 mg daily for wk 19-24
Mixed oral/IV		
Pulse 3× in wks 1, 1×/mo in wk 2-24	60 mg daily for wk 1-2, 50 mg daily for wk 3, 40 mg daily for wk 4, Decrease by 5 mg daily every 4 wks	1.5 mg/kg daily for wk 1-2, 1.2 mg/kg daily for wk 3, 1 mg/kg daily for wk 4, Decrease by 0.1 mg/kg daily every 4 wks
Maintenance <sup>#</sup>		
Continue to taper to 5-10 mg daily. Trials evaluating efficacy of maintenance therapies allowed up to 10 mg daily of steroid therapy.		

\*Used throughout therapy in conjunction with above medication regimens, Often escalated for extra-renal causes or concern for LN flare, Wide variation in practice patterns. #If disease remains well-controlled, slowly decrease dose until steroid therapy is discontinued, No clear guidelines for timeline of taper or discontinuation.

population demonstrated significantly improved flare-free survival in patients who received rituximab as induction therapy, as compared to patients treated with CYC or MMF [17]. Furthermore, a systematic review of studies that documented outcomes for patients with refractory lupus nephritis suggests that rituximab effectively induced remission in patients who had not achieved remission with standard therapies [20]. There are clinical trials underway which include children using rituximab as an induction agent. Additionally, there are several other B cell directed therapies which have recently shown promise in the treatment of LN including other B cell depletion agents targeting CD-20 (obinutuzumab, ocrelizumab), proteasome inhibitors (bortezomib, ixazomib) which particularly affect plasma cells, and B-cell activating factor

(BAFF, also known as B-lymphocyte stimulator (BLyS)) antagonists (belimumab, tabalumab) [21].

#### ADJUNCTIVE THERAPY

The ACR and EULAR/ERA-EDTA recommend that all SLE patients with nephritis be treated with a background of hydroxychloroquine to improve outcomes by reducing renal flares and limiting the accrual of renal and cardiovascular damage [6,7]. Additionally, all patients with proteinuria >0.5 g/day (or >0.5 urine protein/creatinine ratio) should have blockade of the renin-angiotensin system to reduce intraglomerular pressure unless otherwise contraindicated [7,11]. Up to 80% of patients with SLE are treated with non-steroidal anti-inflammatory drugs (NSAIDs) for extra renal

manifestations, mainly arthritis and serositis. These medications can induce sodium retention and reduction in GFR, and lupus nephritis is a risk factor for hemodynamically mediated, NSAID-induced acute renal failure [22]. However, while a safe dosing and duration of NSAID use for extra renal manifestations in patients with lupus nephritis has not been established, it is reasonable for most patients to receive these medications if needed with close monitoring of renal function and re-evaluation for ongoing therapy on a regular basis.

## MAINTENANCE THERAPY

The goal of maintenance therapy is to prevent relapse and control the disease by limiting inflammation and damage. Up to 50% of patients with proliferative lupus nephritis relapse following reduction/cessation of immunosuppressive therapy. In the adult population, the relapse rates range from 5 to 15 per 100 patient-years for the first five years of follow up [22]. Incidence of flares in the Indian pediatric population has been reported to be about 0.16 episodes/person/year with median duration to onset of first flare of 29 months [23]. The ACR recommends either MMF (1-2 g/day) or azathioprine (AZA) (2 mg/kg/day) and low dose steroid for the maintenance phase of treatment [7]. European evidence-based recommendations for treatment of childhood-onset lupus nephritis also advise use of MMF or AZA as maintenance therapy [11]. The KDIGO guidelines additionally suggest that a CNI be used for maintenance therapy in a patient intolerant of MMF or AZA [10]. Low dose oral prednisone is continued to attain the minimum dose required for control of extrarenal symptoms. Across different trials, the maintenance prednisone dose ranged from 0 to 0.2 mg/kg/day [24-26]. Two recent meta-analyses evaluating treatment for proliferative lupus nephritis found that MMF was the best therapy for maintaining remission and preventing kidney failure during maintenance treatment [27,28]. AZA should be used when MMF is contraindicated or following failure of MMF therapy. Additionally, patients maintained on multitarget therapy (tacrolimus and MMF) had similar rates of relapse to the group that had received IV-CYC who were then maintained on AZA therapy [29].

The ideal length of this therapy phase is unknown, and regimens reported in the literature vary from one to five years. In older literature, stopping cyclophosphamide abruptly was associated with a rapid deterioration of renal function [30], but evidence supporting timeline and withdrawal of currently accepted maintenance regimens remains limited. The majority of patients in trials were adults and the duration of the maintenance phase varied widely, with a mean follow-up time ranging from 18-36 months. The usual extended

therapy dose of MMF in adult patients is 1000 mg twice daily (or 1200 mg/m<sup>2</sup>/day with a maximum dose of 1000 mg twice daily) [6,7,11]. The dose may be tapered in stable patients, but there are no specific guidelines on the timeline of this taper.

Common end points of trials evaluating maintenance therapy include time to disease flare, doubling of serum creatinine, or development of ESRD, and these studies are designed to compare medication regimens. There are no published randomized controlled trials designed to prospectively evaluate duration of maintenance therapy; however, a randomized clinical trial is underway to address this specific question (Clinicaltrials.gov identifier NCT01946880). Relatively small retrospective studies have shown that some patients with proliferative lupus nephritis who enter stable remission can be maintained without immunosuppressive treatment for years [22,25]. One of the larger studies to date evaluating duration of maintenance therapy included 32 patients in whom therapy was successfully withdrawn with a subsequent median follow up period of 203 months. This study found that longer median duration of treatment (57 months vs 30 months) and longer duration of remission before withdrawal of therapy (median 24 months vs 12 months) were associated with decreased risk of disease flare [25]. Thus, these authors recommended at least five years of treatment prior to withdrawal of therapy. However, when the decision to stop therapy was made, four patients were receiving only low dose AZA (25-50 mg/day) and the other 28 were taking only low dose prednisone, which is less therapy than the standard maintenance regimens at this time.

In the most recent ACR guidelines, the task force panel did not vote on the rate of medication taper during the maintenance phase given the lack of adequate data [7]. Consensus documents have indicated a minimum duration of three years [6,11]. Beyond this time period, there is little data to guide treatment and consensus statements suggest that continuing treatment for longer should be individualized with an effort first to withdrawal glucocorticoids [6]. A re-biopsy has been suggested in those patients with sustained remission to verify histologic remission prior to discontinuing immunosuppression [5]. Most of the published studies in which immunosuppression was either minimized or stopped originated in Europe, therefore these findings cannot necessarily be extrapolated to patient groups with different ethnic backgrounds [22].

## CONCLUSION

Advances in immunosuppressive medications have resulted in improved renal survival and quality of life in

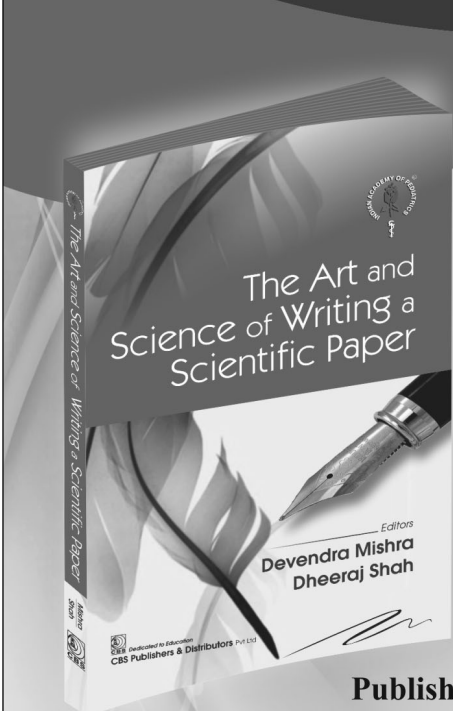
pediatric patients with lupus nephritis. Newer agents such as MMF are effective as induction therapy, though with variation amongst different ethnic groups. The duration of maintenance therapy is a particularly important question in pediatric onset lupus nephritis given the potential for cumulative immunosuppressive medication exposure over time. Currently, there is little data to guide duration of treatment beyond three years in patients with well-controlled disease. Consensus statements support tapering medication around this time point with the initial goal of withdrawal of glucocorticoids. Although reducing rates of renal flares is important in preventing disease-related morbidity and mortality in patients with cSLE and lupus nephritis, a period without corticosteroids and immunosuppressive therapy could be particularly useful for preventing iatrogenic morbidity.

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## Coronavirus Vaccine: Light at the End of the Tunnel

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The world is currently facing an unprecedented global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Predicting the next source of the pandemic can be very challenging. As vaccination is the best way to prevent an infectious disease, the development of an effective vaccine against SARS-CoV-2 can not only reduce the morbidity and mortality associated with it, but can also lessen the economic impact. As the traditional method of vaccine development takes many years for a vaccine to be available to the society, the vaccine development for SARS-CoV-2 should be speeded up using a pandemic approach with fast-track approvals from the regulatory authorities. Various challenges associated with developing a vaccine during the pandemic such as technological hurdles, clinical development pathways, regulatory issues, and support from global funding agencies are expressed here.

**Keywords:** COVID-19, Immunization, Pandemic, Prevention, SARS-CoV-2.

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Many cases of respiratory illness started appearing in the month of December, 2019 in Hubei Province, China [1]. The microorganism responsible for this illness was subsequently discovered as coronavirus, and later categorized as genetically related to coronavirus (SARS-CoV) that was responsible for the severe acute respiratory syndrome (SARS) which occurred in 2003. This new virus was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the disease was designated as Coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) [2,3].

Structural analyses have shown that this novel virus uses host cell receptor known as Angiotensin-Converting Enzyme-2 for its binding [4]. Transmission dynamics confirmed that reproductive number ( $R_0$ , which signifies the number of people who can get infected from one contagious person) of SARS-CoV-2 can be in the range of 2–3, and thus has the potential to spread rapidly [5]. Based on the clinical and epidemiological data from the Chinese health authorities, clinical manifestations of the disease by severity have shown that mild cases occur in 81% of cases, severe disease is seen in 14% of cases and critical disease has occurred in 5% of cases [6]. Considering the infectivity and the severity of COVID-19, vaccines and therapeutics to tackle this deadly disease are the greatest need of the hour.

### CAN WE PREDICT THE NEXT PANDEMIC?

Global pandemic is a major public health concern. Modern

means of travel and the volume of travel make it easier for any virus to rapidly spread across the world. Pandemic is a once-in-a-lifetime low-probability event but a high-cost problem that should not be ignored. The next pandemic was anticipated to be a more virulent form of influenza but the world is currently in the midst of a novel coronavirus pandemic.

Though Middle East Respiratory Syndrome (MERS) and SARS were featured in the WHO's list of critical infectious diseases in 2018, it was not anticipated to cause a global disease within a short span of time [7]. Such is the unpredictability of a global pandemic that the world is currently facing.

### THE NEED FOR A COVID-19 VACCINE

As the infectivity of the SARS-CoV-2 virus is very high compared to other corona viruses reported so far, an effective vaccine is the best way to contain the rapidly escalating proliferation of this infection. Although the mortality rate is lower compared to other similar viral respiratory diseases such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the magnitude of the infection caused by SARS-CoV-2 is severe and higher, to a large extent, leading to increased number of deaths worldwide.

SARS-CoV-2 infection has the potential to become a seasonal disease like influenza and persist with humanity in the future [8]. An effective vaccine can help in reducing the rate of infection, and can significantly reduce the morbidity and mortality of COVID-19. Vaccine can also

decrease the probability of resurgence of the disease and its future impact. The implementation of an effective vaccination is the only way to moderate the economic burden of this unprecedented pandemic.

### **SPEEDING-UP VACCINE DEVELOPMENT DURING PANDEMIC**

There is an urgent need to expedite the development of COVID-19 vaccine. The vaccine industry was able to develop H1N1 vaccine fairly rapidly because the technology and regulations were already in place to develop influenza vaccine. Global experiences with influenza vaccines have outlined the urgency for investing in modern technologies for faster vaccine development as well as increasing the scale of production. Customizing these technologies to various other viruses can speed up vaccine development during a pandemic.

Organizations such as Coalition for Epidemic Preparedness Innovation (CEPI), an innovative global partnership between public and private organizations are striving to quicken vaccine development for various potential and critical diseases, as well as facilitate uniform availability of these life-saving vaccines. CEPI aims to develop vaccines for various pathogens till phase 2a stage, which can be expedited to full-scale development during future outbreaks [9].

CEPI and the World Bank organized a conference on the three main imperatives for COVID-19 vaccine effort: speed, manufacture and deployment at scale, and global access, which has ultimately led to the formulation of COVID-19 Vaccine Development Taskforce [10].

### **Multiple Technology Platforms Under Evaluation**

The wide ranges of technologies that are being developed for SARS-CoV-2 include nucleic acids, protein subunit, replicating viral vector, non-replicating viral vector, and inactivated virus approaches. Newer approaches based on nucleic acids such as DNA or mRNA can facilitate potentially rapid production, as they do not need fermentation [9]. For some platforms, adjuvants could improve the immune responses with lower doses thus ensuring vaccination of larger populations without any reduction in efficacy [11]. Currently, several platforms are being developed and the list of SARS-CoV-2 vaccine candidates in development is given in *Web Table 1*.

### **CHALLENGES IN COVID-19 VACCINE DEVELOPMENT**

The development of a vaccine for SARS-CoV-2 can cause distinct challenges.

- Developing a viable immunogen using the various proteins of SARS-CoV-2 such as S protein, N protein, M protein is the initial challenge.
- Development of successful animal model for COVID-19 may be challenging although two animal models; one hACE2 transgenic mice model and another, primate macaques model have been successfully developed. This may be due to the highly infectious and pathogenic nature of the virus [12].
- Vaccine development is a lengthy process, starting from product development to the completion of the phase III clinical trial before marketing the vaccine, which can take several years, usually 10 to 20 years.
- Preclinical experience with other SARS vaccine candidates has created red flags about worsening of the disease, which may be attributed to antibody-dependent enhancement.
- Correlates of protection are not known.
- Planning and coordinating clinical trials in these emergency-like situations can be difficult, both for predicting the trial sites for outbreak as well as ensuring the site's preparedness.
- In a high-mortality situation such as COVID-19 pandemic, regulators may not accept conventionally designed clinical trials such as comparison with a placebo arm.
- Viral mutation may lead to different subtypes thus causing difficulty in vaccine design.
- Vaccines are generally manufactured using Good Manufacturing Practices (GMP) to ensure that quality is controlled and consistency is maintained. For many vaccine candidates in the current pipeline for SARS-CoV-2, these GMP processes need to be developed, which can be time consuming.
- For vaccines that will be developed with novel technologies, GMP needs to be developed from the beginning, thus adding to the financial burden and delaying the production of vaccines.
- Issues related to vaccine ownership, funding, pricing and supply chain, and the coordinated administration strategy can pose significant barriers.

### **Role of Regulatory Bodies**

The traditional vaccine development process follows various phases such as product development, pre-clinical, clinical trial phases (phase I, II, and III) before the vaccine gets regulatory approval for marketing although phase IV and post-marketing surveillance studies are



conducted after marketing the product. This traditional approach is time consuming and not feasible to follow during the pandemic.

Keeping greater benefit of the vaccine for the societal need, vaccine development using pandemic approach will be the best approach for rapid development of vaccines as shown in **Fig. 1**. This type of innovative approach can save the time spent in pre-clinical and clinical trial phases. The regulators should consider this approach for faster approval of vaccines.

**Funding for Vaccine Development During Pandemics**

Vaccine development during a pandemic should be considered as a global health emergency and not as any specific disease related issue, which is a prerogative of vaccine manufacturers. Public funding for vaccine development should be the top priority as any vaccine development, particularly during a pandemic can be a very risky investment, and public funding can reduce the potential risk for vaccine manufacturers, especially in the low and middle income countries.

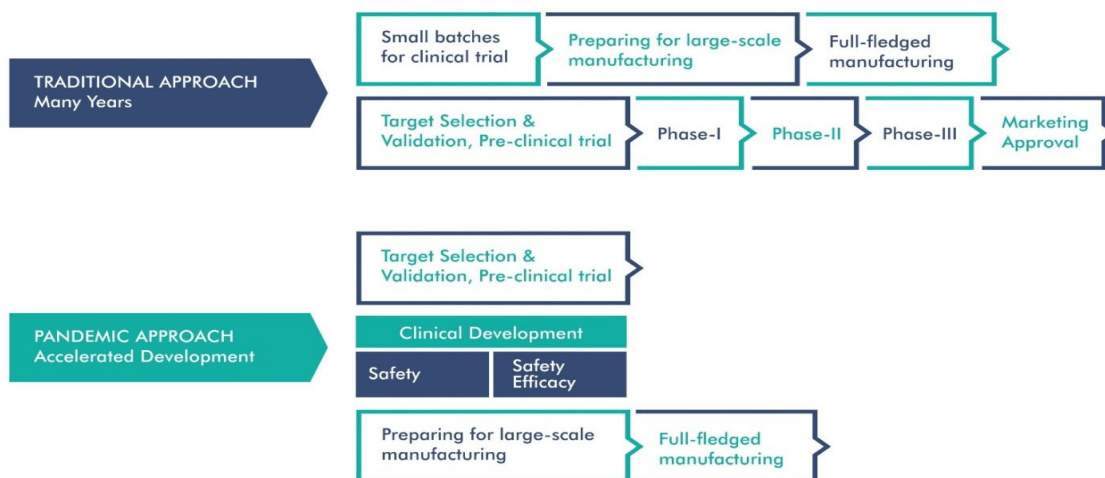
Pioneering finance mechanisms such as the International Finance Facility for Immunization (IFFIm) that have been successful in the past should be used to fund the development of COVID-19 vaccines [10]. Global Alliance for Vaccines and Immunizations (GAVI) board members also expressed support for the use of GAVI’s innovative financing instruments, such as its IFFIm and GAVI’s Advance Market Commitment to accelerate

vaccine development and access where needed [13].

There should be a global consensus and urgency for the development of a pandemic vaccine, at both national and international level to ensure that the vaccines are available and affordable to those who need them the most [14].

**Challenges After the Vaccine is Developed**

- For novel platform technologies, large-scale manufacturing can pose a significant financial risk as these facilities necessitate huge investments.
- High-income countries can procure large doses of vaccine for their own population, creating disparities in the global supply and demand.
- High risk populations should be identified through epidemiological and serological studies and vaccine delivery should be prioritized. This can halt the spread of the disease.
- As SARS-CoV-2 is a newer disease without adequate exposure in the population, any new vaccine may probably necessitate more than one dose of the vaccine and protective immunity is usually achieved after the second dose. Massive effort will be needed to ensure vaccine distribution and administration.
- There can be a scenario, albeit low-probability, where the pandemic threat has been abruptly curtailed. In such cases, vaccine development should be continued for potential vaccine candidates to restrict future threats.



**Fig. 1** Traditional approach vs. pandemic approach of vaccine development.

## FUTURE OUTLOOK

The global vaccine development efforts for COVID-19 pandemic are unparalleled. In the current scenario, there is an indication that vaccine could be available as early as 2021. This would be an extraordinary shift from the usual vaccine development timeframe which can range between 10-20 years. A new virus target and newer technologies can multiply the vaccine development risks, and dictates meticulous evaluation of safety and efficacy at every stage of vaccine development.

Robust coordination between vaccine manufacturers, regulatory authorities, public health authorities and governments is essential to make sure that potential vaccine candidates are fast-tracked for approval, manufactured and distributed seamlessly, particularly for low-income countries.

Considering the economic impact that COVID-19 has already caused in the initial 3-4 months of this global calamity, it is worthwhile to start investing in vaccines against emerging viruses, including neglected diseases, which can potentially cause significant human deaths and also impact the global economy. Global pandemics are inevitable. There should be strategically prepared protocols and emergency plans to develop vaccines in months rather than years. Lessons learned in managing the COVID-19 pandemic should pave the way for creating better roadmaps to face the next pandemic.

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**WebTable 1 List of SARS-CoV-2 Vaccine Candidates Under Development**

<i>Type of candidate vaccine</i>	<i>Developer</i>
<i>Platform: DNA</i>	
DNA with electroporation	Karolinska Institute/ Cobra Biologics (OPENCORONAProject)
DNA plasmid vaccine	Osaka University/ AnGes/ Takara Bio
DNA	Takis/Applied DNA Sciences/Evvivax
Plasmid DNA, Needle- Free Delivery	Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet, Inc.
DNA plasmid vaccine	Inovio Pharmaceuticals/Beijing AdvaccineBiotechnology
DNA plasmid vaccine	ZyduScadila
<i>Platform: Inactivated</i>	
Inactivated + alum	Sinovac
Inactivated	Beijing Institute of Biological Products/Wuhan Institute of Biological Products
TBD	Osaka University/ BIKEN/ NIBIOHN
Rabies vector platform	ThomasJeffersonUniversity/BharatBiotech
<i>Platform: M2SR</i>	
CoroFlu, self-limiting influenza virus	University of Wisconsin-Madison/ FluGen/ Bharat Biotech
<i>Platform: Non- replicating viral vector</i>	
ChAdOx1	University of Oxford
MVA encoded VLP	GeoVax/BravoVax
Ad26 (alone or with MVA boost)	Janssen Pharmaceutical Companies
MVA-S encoded	DZIF – German Center for Infection Research
Adenovirus- based NasoVAX expressing SARS2-CoV spike protein	Altimmune
Ad5 S (Grevax platform)	Greffex
Oral Vaccine platform	Vaxart
MVA expressing structural proteins	Centro Nacional Biotecnología (CNB-CSIC), Spain
<i>Platform: Live attenuated virus</i>	
Deoptimized live attenuated vaccines	Codagenix/Serum Institute of India
Measles Virus (S, N targets)	DZIF – German Center for Infection Research
<i>Platform: Protein subunit</i>	
Drosophila S2 insect cell expression system VLPs	ExpreS2ion
Peptide antigens formulated in lipid nanoparticle formulation	IMV Inc
S protein + Adjuvant	WRAIR/USAMRIID
S protein	National Institute of Infectious Disease, Japan
VLP-recombinant protein+ Adjuvant	Osaka University/ BIKEN/ National Institutes of Biomedical Innovation, Japan
Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax
Microneedle arrays S1 subunit	Univ. of Pittsburgh
Peptide	Vaxil Bio
Adjuvanted protein subunit (RBD)	Biological E Ltd
Peptide	Flow Pharma Inc
S protein	AJ Vaccines
Ii-Key peptide	Generex/EpiVax
S protein	EpiVax/Univ. of Georgia

*Contd....*

**WebTable I** *continued*

<i>Type of candidate vaccine</i>	<i>Developer</i>
S protein (baculovirus production)	Sanofi Pasteur
VLP-recombinant protein nanoparticle vaccine + Matrix M gp-96 backbone	Novavax
Molecular clamp stabilized Spike protein	Heat Biologics/Univ. of Miami
S1 or RBD Protein	University of Queensland/GSK/Dynavax
Subunit protein, plant produced	Baylor College of Medicine
Recombinant protein, nanoparticles (based on S- protein and other epitopes)	iBio/CC-Pharming
COVID-19 XWG-03 truncated S (spike) proteins	Saint-Petersburg scientific research institute of vaccines and serums
Adjuvanted microsphere peptide	Innovax/Xiamen Univ./GSK
Synthetic Long Peptide Vaccine candidate for Sand M proteins	VIDO-InterVac, University of Saskatchewan
<i>Platform: Replicating viral vector</i>	
Measles vector	OncoGen
Measles vector	ZyduS Cadila
Horsepox vector expressing S protein	Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research
Live viral vectored vaccine based on attenuated influenza virus backbone (intranasal)	Tonix Pharma/Southern Research
Influenza vector expressing RBD	BiOCAD and IEM
VSV vector expressing S protein	University of Hong Kong
<i>Platform: RNA</i>	
LNP-encapsulated mRNA cocktail encoding VLP, and LNP-encapsulated mRNA encoding RBD	IAVI/Batavia
Replicating Defective SARS- CoV-2 derived RNAs	Fudan University/Shanghai Jiao Tong University/RNA Cure Biopharma
LNP-encapsulated mRNA	Centro Nacional Biotecnología (CNB-CSIC), Spain
Liposome- encapsulated mRNA	University of Tokyo/ Daiichi -Sankyo
mRNA	BIOCAD
mRNA	China CDC/Tongji University/Stermina
mRNA	Arcturus/Duke-NUSB College London
mRNA	Curevac
<i>Platform: Virus-like particle (VLP)</i>	
Based on RBD displayed on VLPs	Saiba GmbH
Plant-derived VLP	Medicago Inc.
ADDomermulti epitope display	Imphoron Ltd and Bristol University's Max Planck Centre
<i>Platform: Unknown</i>	
Unknown	ReiThera
Unknown	BioNet Asia
Unknown	ImmunoPrecise
Unknown	MIGAL Galilee Research Institute
Unknown	Doherty Institute
Unknown	Tulane University
Unknown	SK Biosciences
Unknown	Vir Biotechnology/GSK
Unknown	Precision Vaccines Program at Boston Children's Hospital
Unknown	Kentucky BioProcessing (British American Tobacco)

## Assessment of Renal Growth and Function in Preterm Infants at Corrected Age of 12-18 Month

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**Objective:** To assess the kidney growth and function in appropriate for date and small for date (SGA) preterm neonates.

**Methods:** Appropriate for date and SGA preterm neonates with gestation <35 weeks, at 12-18 months of corrected age, attending the follow-up outpatient clinic of a Tertiary care level III neonatal unit. Renal function was assessed by measuring the serum creatinine level and estimated Glomerular Filtration Rate (eGFR) was calculated by using modified Schwartz formula. Kidney size was determined by ultrasonography using a 5 MHz sector probe with an accuracy of 1.0 mm.

**Results:** The mean (SD) serum creatinine and eGFR in the 120 children enrolled were 0.39 (0.16) mg/dL and 109.05 (44.66) mL/

min/1.73 m<sup>2</sup>, respectively. The mean (SD) lengths of right and left kidney were 54.3 (4.9) mm and 55.2 (4.77) mm, respectively. The kidney length, serum creatinine and eGFR were significantly lower in preterm SGA infants as compared to preterm AGA infants.

**Conclusion:** Preterm infants, especially SGA infants, at 12 to 18 months of corrected age have impaired renal growth with small kidney size.

**Keywords:** Chronic kidney disease, Outcome, Prematurity, Sequelae.

Neonates born preterm are at risk for multiple morbidities because of the organ immaturity. With improved survival of these premature infants, focus is now on short term and long-term morbidities. Prematurity is consistently associated with reduction in number of nephrons. Coupled with prematurity, multiple intrauterine and extra uterine insults may result in developmental maladaptation resulting in immediate, short-term and long-term renal complications. Effect of immaturity of organ systems on post-natal renal function is less well appreciated when compared to pulmonary and neurodevelopmental consequences [1,2]. Preterm infants are reported to have 1.73 times higher odds of developing chronic kidney disease [3].

The kidney length has been previously reported to be lower in preterm small for gestational age (SGA) infants compared with preterm appropriate for gestational age (AGA) infants [4,5]. As there are limited studies evaluating the post-natal kidney function and growth in preterm infants, we designed this study to assess the renal growth and function at 12-18 months of corrected age in preterm neonates with gestation less than 35 weeks at birth. We also compared the kidney growth and function between AGA and SGA infants

### METHODS

We conducted this cross-sectional observational study in a tertiary care level III neonatal unit over a period of 2 years from May, 2016 to May, 2018.

*Accompanying Editorial: Pages 395-96.*

All inborn preterm infants with gestational age <35 weeks at birth (with a minimum gestation of 25 weeks) born after May, 2015 and attending the follow-up clinic up to at least 12 to 18 months of corrected age were enrolled after obtaining a written consent from one of the parents. Infants with major malformations (including renal malformations) were excluded from the study.

The antenatal, perinatal and neonatal details of enrolled infants were collected in a predesigned proforma from the discharge summary, computerized database and case files. This data included maternal details (age, medical and pregnancy related illnesses, medication details, antenatal steroid administration and mode of delivery) and neonatal details (birth weight, sex, the need for resuscitation at birth and Apgar scores at 1 and 5 minutes, incidence of respiratory distress syndrome, patent ductus arteriosus (PDA) – clinical or

echocardiography proven, culture positive sepsis, necrotizing enterocolitis stage II and above, use of nephrotoxic medications like aminoglycosides, metabolic derangements like hypoglycemia, electrolyte disturbances, apnea, jaundice, presence of intra ventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, acute kidney injury (AKI) [6] and anthropometry at discharge). Feeding details such as duration of exclusive breastfeeding, type of feeding in the first 6 months, time of initiation of complementary feeding, and illnesses requiring admission in the hospital were also documented.

Renal function was assessed by measuring the serum creatinine levels based on the modified Jaffe method [7] (Alkaline Picrate no deproteinization—Siemens Dimension RXL). Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine and length of the infants using the modified Schwartz formula ( $eGFR = k \times \text{length in cm} / \text{creatinine in mg/dL}$  with  $k$  value taken as 0.413) [8]. Kidney size was assessed by ultrasonography using a 5 MHz sector probe (Philips CX50 – Philips Ultrasound, Andover, MA, USA). The probe was placed on the back of the child in a supported sitting position. The kidney was identified in the sagittal plane along its longitudinal axis. Both length and breadth were measured to nearest 0.1 cm in both kidneys. All the measurements were done by a single radiologist who was blinded to antenatal and postnatal details including birth weight group. The expected length of the kidneys for that age and length of the child was estimated from the published normative data of Indian children [9]. Deficit in the length was calculated from the observed and the expected lengths of the kidneys and compared between SGA and AGA infants. With 95% confidence level and 80% power we needed a sample size of 119 to identify a difference in kidney of 1 mm compared to previous normative data [9].

**Statistical analysis:** Group comparisons for baseline data and outcomes was done using chi-square test or student  $t$  test for categorical and continuous variables, respectively. To know the independent effect of variables which are significant on univariate analysis, separate linear regression models were created using SPSS version 23 with kidney length (right and left), estimated GFR, serum creatinine as dependent variable and gestation, growth restriction at birth, sepsis, PDA, use of amikacin, antenatal steroids, singleton, mode of delivery, gender, neonatal AKI as independent variables.  $P$  value  $<0.05$  was considered as significant.

## RESULTS

During the study period, 178 eligible infants attended the follow up clinic at 12 to 18 months of corrected age and

among them data for kidney size and function was available for 120 infants (58 parents refused consent). The mean birth weight and the mean gestation of study population was 1242.33 (340.36) grams and 30.32 (2.08) weeks, respectively. Baseline variables including neo-natal morbidities were comparable for AGA and SGA infants except for proportion of infants from multiple pregnancy and preterm pre-labor rupture of membranes (PPROM) in the mother was higher in AGA group and maternal pregnancy induced hypertension (PIH) and antenatal doppler abnormalities were higher in SGA group (**Table I**).

The mean lengths of the right and left kidneys in the study population were 54.3 (4.9) mm and 55.2 (4.77) mm, respectively. The mean breadths of the right and left kidneys in the study population were 24.6 (2.14) mm and 25.8 (2.26) mm, respectively. The mean creatinine level and mean eGFR in the study cohort were 0.39 (0.16) mg/dL and 109.05 (44.66) mL/min/1.73m<sup>2</sup>, respectively. Infants in

**Table I Baseline Details of Preterm Infants Enrolled in the Study (N=120)**

Variable	AGA group (n=90)	SGA group (n=30)
‡*Gestation (wk)	29.98 (2.1)	31.37 (1.67)
‡*Birthweight (g)	1306.56 (344.12)	1049.67 (246.44)
Male sex	53 (59)	16 (53.3)
ANS coverage	78 (86.7)	26 (86.7)
#Multiple pregnancy	27 (30)	3 (10)
*PIH	28 (31.1)	21 (70)
*Abnormal doppler	20 (22.2)	21 (70)
*PPROM (%) <sup>§</sup>	44 (49)	3 (10)
#LSCS (%) <sup>§</sup>	77 (85.6)	30 (100)
APGAR (5min)	8 (5,9)	8 (7,9)
Culture positive sepsis	20 (22.2)	8 (26.7)
HSPDA	17 (19)	7 (23.3)
HIE	2 (2.2)	0 (0)
AKI	5 (5.6)	1 (3.3)
BPD (%) <sup>§</sup>	8 (9)	4 (13.3)
‡*Reached full feeds (d)	7.14 (5.06)	10.47 (5.84)
‡#Regained birth weight (d)	13.94 (4.41)	11.5 (5.19)
‡CGA at discharge (wk) <sup>#</sup>	34.65 (2.15)	34.65 (2.15)
‡#Discharge weight (kg) <sup>#</sup>	1563.11 (201.07)	1484.33 (96)

Values in no.(%) except ‡mean (SD). \* $P < 0.0001$ ; # $P < 0.05$ ; ANS – PIH; – Pregnancy induced hypertension; PPRM – preterm premature rupture of membrane; LSCS – lower segment cesarean section; HSPDA – hemodynamically significant; NEC – necrotizing enterocolitis; HIE – Hypoxic ischemic encephalopathy; AKI – acute kidney injury; BPD – bronchopulmonary dysplasia; CGA – corrected gestational age.

SGA group had higher mean creatinine levels and lower eGFR values and smaller kidneys when compared to AGA group infants (**Table II**).

On regression analysis with kidney length as the dependent variable, birthweight Z score independently predicted the renal growth. With every one-point increase in Z score for birthweight, length of right kidney and left kidney improved by 1.52 mm (0.46-2.58 mm) and 1.54 mm (0.51-2.57 mm), respectively. On regression analysis with serum creatinine or GFR as dependent variable, gestation at birth and birthweight Z score independently predicted the renal function (serum creatinine levels and estimated GFR levels). With every week increase in gestation at birth and increase in birthweight Z score by 1 point, eGFR increased by 5.48 mL/min/1.73m<sup>2</sup> (0.27-10.69) and 14.34 mL/min/1.73m<sup>2</sup> (2.66-26.02), respectively. With every week increase in gestation at birth and increase in birth weight z score by 1 point, serum creatinine levels decreased by 0.01 mg/dL and 0.035mg/dL, respectively.

## DISCUSSION

In this cross-sectional observational study, we evaluated the renal function and growth at 12 to 18 months of corrected age in preterm infants with gestation <35 weeks at birth. At 12 months age, the average reported kidney size is 57 mm [9] and the reported serum creatinine values vary from 0.17 to 0.36 mg/dL [10]. In comparison to published norms for the age, preterm infants of this study had lower kidney growth and function and it was significantly compromised in preterm SGA infants in comparison with

**Table II Renal Growth and Function in Preterm Infants at Corrected Age of 12-18 Month (N=120)**

Variable	AGA group (n=90)	SGA group (n=30)	P- value
Serum creatinine, mg/dL	0.4 (0.18)	0.5 (0.09)	0.005
eGFR, mL/min/1.73m <sup>2</sup>	115.6 (48.41)	89.4 (21.37)	0.005
Kidney length, mm			
Right	55.4 (4.0)	51 (6.0)	<0.001
Left	56.2 (3.88)	52.3 (5.97)	<0.001
Kidney breadth, mm			
Right	24.7 (2.16)	24.3 (2.08)	0.36
Left	25.7 (2.45)	25.9 (1.60)	0.71
Growth deficit, mm			
Right	-2.7 (4.4)	-6.0 (6.37)	0.002
Left	-1.9 (4.06)	-4.7 (6.0)	0.005
*Expected kidney length, mm	57.9 (2.3)	57.8 (2.24)	0.93

All values in mean (SD); AGA – appropriate for gestational age; SGA – small for gestational age; eGFR – estimated glomerular filtration rate; \*for corresponding body length.

preterm AGA infants. The reason for this reduced renal growth and function in our preterm infants may be due to intrauterine growth restriction, preterm birth and postnatal factors like hyperoxia, exposure to toxic medications (aminoglycosides, non-steroidal anti-inflammatory drugs, etc.) and extra uterine growth restriction. The extra uterine insults in the neonatal period on the immature kidney may result in reduced nephron number, glomerular and tubular injury and may further predispose these children to long-term complications in later life. In the studies that evaluated preterm SGA infants [4,5], prematurity and weight for gestational age had significant effect on kidney growth at 12 and 18 months of corrected age. Our conclusions are similar but the parameters used for measuring the renal growth are different – kidney volume in Schimdt, *et al.* [5] and relative kidney length in Drougia, *et al.*, [4]. Contrary to these findings, Hotoura, *et al.* [11] did not find any difference in mean kidney length between SGA and AGA infants at 12 months of chronological age. Differences in the baseline characteristics and differences in time points of assessment may be reasons for these differences in renal outcomes.

In our study, we have measured the renal function by calculating estimated GFR from serum creatinine levels using modified Schwartz formula. No previous study has evaluated the renal function at 12 to 18 months of corrected age or during infancy among preterm infants. Similar to our study, a study by Rodriguez-Soriano, *et al.* [12] reported significantly reduced GFR in preterm children compared to term controls. Other studies did not find any difference in renal function in terms of GFR in preterm infants compared to term infants in childhood [13-15]. Some authors have evaluated renal function using Cystatin c levels and have found that extremely low birthweight infants have higher levels when compared to term infants at a mean chronological age of 6.7 years, and ages 7 - 11 years, respectively [16,17].

Evaluation of both renal growth and function, and availability of renal data in 70% of infants approached for the study are the main strengths of this study. Cross-sectional design and estimation of renal function by creatinine levels renal growth only by renal length (unlike renal volume), and lack of data on blood pressures are the main limitations.

Preterm infants at 12 to 18 months of corrected age have reduced renal growth and lower kidney function. Compared with AGA preterm infants, SGA preterm infants are at an increased risk for impaired renal function and poor renal growth. All preterm infants and more so the SGA preterm infants should be tracked for development of chronic kidney disease in adolescence and adult life.

### WHAT THIS STUDY ADDS?

- Preterm infants, especially preterm small-for-gestational age infants, are at an increased risk of poor renal growth and impaired renal function.

*Ethical approval:* Institutional Ethics Committee of Fernandez Hospital; No. 19/20016 dated June 27, 2016.

*Contributors:* KVR: concept, study design, data collection, written the manuscript; DP: data collection; DM: performed Renal ultrasound for all children; MS, SM: reviewed the manuscript.

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## Etiological Profile of Nephrocalcinosis in Children from Southern India

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**Objective:** To study the etiological profile and patterns of clinical presentation of nephrocalcinosis. **Methods:** In this observational study, patients 18 years or younger, referred to the pediatric nephrology clinic with nephrocalcinosis were evaluated for etiology. Symptoms/signs at presentation, estimated glomerular filtration rate (eGFR) at presentation and follow-up, and growth parameters were recorded. **Results:** The etiology of nephrocalcinosis ( $n=54$ ) included distal renal tubular acidosis ( $n=18$ ; 33.3%), primary hyperoxaluria ( $n=9$ ; 16.7%), Bartter syndrome ( $n=7$ ; 13%), Dent disease ( $n=4$ ; 7.4%), cystinosis, familial hypomagnesemia with hypercalciuria and idiopathic hypercalcemia of infancy (2 each). Idiopathic nephrocalcinosis was seen in 5 (9.3%) children. Clinical features included failure to thrive (53.7%), polyuria (44.4%), bony deformities (31.5%) and hypokalemic paralysis (11.1%). At a median (IQR) follow-up of 24 (8, 56) months, the mean (SD) eGFR had improved from 59 (25.5) to 77 (31.48) mL/min/1.73m<sup>2</sup> ( $P<0.01$ ). Consanguinity was present in 50% (27/54). Genetic analysis in 5 primary hyperoxaluria cases confirmed AGXT mutations in 4; and GRHPR mutation in 1 child. **Conclusion:** Distal RTA, primary hyperoxaluria and Bartter syndrome were the common etiologies of nephrocalcinosis in our patient population.

**Keywords:** Distal RTA, Calculi, Outcome, Tubular disorders.

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**N**ephrocalcinosis (NC) is defined as calcium deposition in the renal parenchyma as detected by renal ultrasonogram. Pediatric NC is a rare entity and might occur secondary to inherited renal tubular disorders, vitamin D excess, etc [1-4]. A comprehensive metabolic evaluation of NC would help in specific therapies, prevent progression to end-stage renal disease and enable optimal prenatal counseling.

Most published information on NC is from developed nations [1,5] and there is paucity of information regarding pediatric NC from India [6]. Since NC often has an underlying genetic or metabolic etiology, it can be speculated that its etiological profile is likely to vary with ethnicity. We studied the etiological profile of NC among children from Southern India.

### METHODS

This cross-sectional study was conducted at the pediatric nephrology clinic of a referral hospital in Southern India from July, 2017 through July, 2019, after obtaining approval from the institutional ethics committee. Prior written informed consent was obtained from the parents. The primary objective of the study was to evaluate the

underlying etiology of NC, while the secondary objectives were to record the patterns of clinical presentation, complications and outcomes (estimated glomerular filtration rate (eGFR) on follow-up) in these children.

Accompanying Editorial: Pages 397-98.

All patients  $\leq 18$  years with NC who were referred for diagnostic evaluation were included. NC was defined as calcium deposition in the renal parenchyma as detected and graded by ultrasound. Medullary NC was graded as: grade 1, mild increase in echogenicity of medullary pyramids; grade 2, mild diffuse increase in echogenicity of medullary pyramids without acoustic shadowing; and grade 3, greater homogenous increase in echogenicity of medullary pyramids with acoustic shadowing [1]. Cortical nephrocalcinosis was diagnosed by the presence of calcifications in the renal cortex.

This was an observational study, supplemented by analysis of hospital records. For the prospective component of the study, consecutively presenting children who were referred for evaluation of NC were evaluated. For the retrospective component of the study,

data were collected from the records of children 18 years or younger with NC, who had presented to the pediatric nephrology clinic over the last 10 years and were under follow-up at the pediatric nephrology clinic.

We have been using the following protocol for investigating NC for the last 10 years: (i) First-line investigations- Blood pH, blood urea, creatinine, sodium, potassium, magnesium, chloride, serum bicarbonate, calcium, phosphorous, alkaline phosphatase, uric acid; urinalysis for urine pH, crystals, urine culture (if clinically indicated), spot calcium: creatinine ratio and 24-hour urine excretion of calcium, oxalate, uric acid and creatinine, were recorded. Estimated glomerular filtration rate (eGFR) was determined using modified Schwartz formula [7]. (ii) Second-line investigations- Urine sodium nitroprusside test was restricted to patients where a cause of NC was not found on first-line investigations. Blood parathyroid hormone (PTH) and 25 hydroxycholecalciferol was evaluated in patients with hypercalcemia (serum calcium >11mg/dL on >2 occasions). Urine  $\beta_2$  microglobulin levels were performed in males with suspected Dent disease.

Following definitions were used for defining the etiology of nephrocalcinosis [6, 8-10]: Distal renal tubular acidosis (RTA) was diagnosed in patients with suggestive clinical features (failure to thrive, polyuria, rickets, hypokalemic paralysis, etc) and hyperchloremic metabolic acidosis (serum bicarbonate <18 mEq/L), normal anion gap (8-12 mEq/L), normal fractional excretion of bicarbonate (<5%), urine pH >5.5 and hypercalciuria (elevated urinary calcium >4 mg/kg per day in a 24 hour urine sample). Idiopathic hypercalciuria was defined as hypercalciuria with absence of other tubular defects and normocalcemia (9-11 mg/dL). Bartter syndrome was diagnosed in children with suggestive clinical features (failure to thrive, polyuria, etc), metabolic alkalosis (serum bicarbonate >25 mEq/L), hypokalemia (potassium <3.5 mEq/L), normal blood pressure, increased urinary potassium (>20 mEq/L) and chloride (>30 mEq/L), with high plasma renin activity. Primary hyperoxaluria was defined as elevated urinary oxalate excretion (>40 mg/1.73 m<sup>2</sup> per day on a 24-hour urinary specimen) and no history of malabsorption, steatorrhea or intestinal surgical resection. Hyperparathyroidism was diagnosed in those with high serum calcium (>11 mg/dL) and PTH (>50 pg/mL) with or without hypercalciuria. Hyperuricosuria was diagnosed if uric acid excretion was >815 mg/1.73m<sup>2</sup> on a 24-hour urine specimen. Dent disease was diagnosed as per standard definitions [10]. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) was diagnosed in those with low serum magnesium

(<1.5 mg/dL), urinary magnesium wasting (fractional excretion  $\geq$ 5%), hypercalciuria, NC with/without family history of hypomagnesemia with hypercalciuria. Idiopathic hypercalcemia of infancy was diagnosed when hypercalcemia (>11 mg/dL) was noted in the absence of vitamin D toxicity, hyper-parathyroidism, absence of calcium supplement intake or subcutaneous fat necrosis.

Determination of the cause of NC was followed by specific therapy. Patients were advised to consume plenty of fluids and to restrict intake of added salts. Long term outcome was assessed in terms of clinical improvement, weight Z score, height Z score and renal functions.

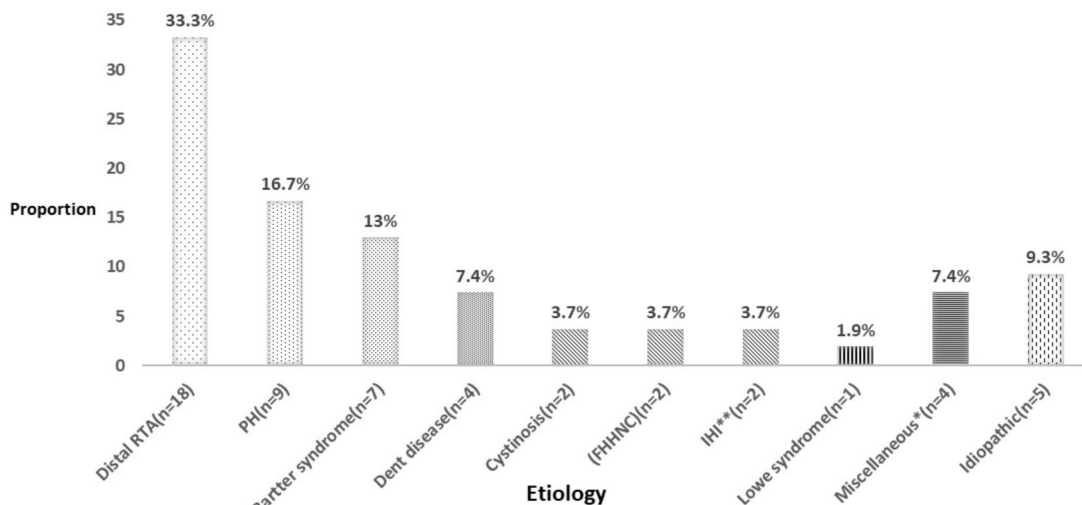
*Statistical analyses:* The data were analyzed by SPSS 23.0. Normality of data was analyzed by Kolmogorov-Smirnov test. Paired t test was used to compare means of two dependent sample groups. Median and IQR of two dependent sample groups were compared using Wilcoxon-signed rank sum test.

## RESULTS

Of the 54 children with NC (29 males), 18 were recruited prospectively. Fifty-two children had medullary NC. One child with primary hyperoxaluria had both cortical and medullary NC, while 1 child with autosomal recessive polycystic kidney disease (ARPKD) had cortical NC. **Fig. 1** shows the etiological profile of NC in our study. Distal RTA, primary hyperoxaluria, Bartter syndrome and Dent disease were the most common causes of NC.

Dent disease was diagnosed in 4 cases, of which 2 cases had type 1 phenotype (with no metabolic acidosis), while the other 2 cases had a phenotype consistent with type 2 Dent disease (with metabolic acidosis). Out of two children with FHHNC, one had positive family history of hypomagnesemia and urolithiasis in a maternal uncle. Cystinosis was diagnosed in two cases of NC, who had Fanconi syndrome and cystine crystals in cornea. They were treated with potassium citrate, phosphorus supplements and oral cysteamine (in one case). Another child with medullary NC had global developmental delay, bilateral cataracts, hypotonia and Fanconi syndrome; and was diagnosed as Lowe syndrome. Two infants were diagnosed as idiopathic hypercalcemia of infancy (serum calcium 12.5 mg/dL and 12 mg/dL, respectively) and were treated with bisphosphonates, on which the serum calcium levels normalized.

**Table 1** provides the baseline clinical and biochemical features of the enrolled children. Grade 1, 2 and 3 nephrocalcinosis were noted in 45 (83.3%), 8



RTA-Renal tubular acidosis; PH- Primary hyperoxaluria; FHHNC-Familial hypomagnesemia with hypercalciuria and nephrocalcinosis; ARPKD- Autosomal recessive polycystic kidney disease; IHI- Idiopathic hypercalcemia of infancy

\*Includes 1 case each of Rabson-Mendenhall syndrome, ARPKD, Familial isolated hypoparathyroidism and Hyperuricosuria

**Fig. 1** Etiology of nephrocalcinosis in the enrolled children (N=54).

**Table I** Baseline Clinical and Biochemical Characteristics of Children with Nephrocalcinosis (N=54)

Parameters	Value
Age at symptom onset, mo	24 (6, 48)
#Age at diagnosis, mo	36 (11.5, 84)
#Symptom-diagnosis interval, mo	24 (7.6, 59)
<i>†Clinical features</i>	
Failure to thrive (WFA<-2 Z score)	29 (53.7)
Polyuria	24 (44.4)
Polydipsia	17 (31.5)
Rickets	19 (35.2)
Hypokalemic paralysis	6 (11.1)
Short stature	5 (9.3)
Carpopedal spasm	5 (9.3)
Pathological fractures	4 (7.4)
Acute kidney injury	3 (5.6)
Hematuria	4 (7.4)
<i>‡Biochemical features</i>	
*eGFR at presentation, mL/min/1.73m <sup>2</sup>	59 (25.5)
Metabolic acidosis	26 (48.1)
#Serum creatinine at presentation, mg/dL	0.59 (0.49, 0.70)
eGFR <60 mL/min/1.73 m <sup>2</sup> at diagnosis	24 (44.4)
eGFR <60 mL/min/1.73 m <sup>2</sup> at last follow up	15 (27.8)
^Associated urolithiasis	3 (5.55)

Values in no. (%) except \*mean (SD) or #median (IQR); †Recurrent vomiting, salt craving, and antenatal detection in 2 each; eGFR-Estimated Glomerular filtration rate, WFA- Weight for age; ^One child each with primary hyperoxaluria, familial hypomagnesemia and hypercalciuria with nephrocalcinosis (FHHNC), and Rabson-Mendenhall syndrome.

(14.8%) and 1 (1.9%) of cases, respectively. All the NC cases (except the 5 idiopathic cases) had hypercalciuria. There was history of consanguinity in 27 (50%) of cases, while there was a family history of nephrocalcinosis in 14 (25.9%) of cases. The mean (SD) 24-hour urinary oxalate in 9 children with primary hyperoxaluria was 85 (31.8) mg/1.73 m<sup>2</sup>/day. Four children presented with persistently low eGFR for more than 3 months. During the median (IQR) duration of follow up of 24 (8, 56) months in children with NC, there was improvement in the weight Z scores and eGFR (**Table II**).

Genetic studies were performed in 8 children. Out of these, in five children with primary hyper-oxaluria, AGXT mutation was detected in four cases; and GRHPR mutation in one. One child with distal RTA had ATP6V0A4 mutation, and two children with Bartter syndrome had ROMK and CLCN-KB mutations, respectively.

**Table II** Growth and Biochemical Features at Presentation and at Follow-up in Children with Nephrocalcinosis (N=54)

Parameter	At presentation	At last follow up <sup>†</sup>
*Age, mo	36 (11.5, 84)	78 (38, 144)
*Weight (Z score)	-3.4 (-2.0, -4.98)	-2.95 (-3.75, -1.68)
#Height (Z score)	-3.20 (2.04)	-2.96 (2.02)
#eGFR*, mL/min/1.73m <sup>2</sup>	59.04 (25.5)	77 (31.48)

<sup>†</sup>Median (follow up) of 24 (8,56) mo; eGFR-estimated Glomerular filtration rate using modified Schwartz formula; values in \*median (IQR) or #mean (SD); P<0.01 for all comparisons except age.

### WHAT THIS STUDY ADDS?

- Distal renal tubular acidosis, primary hyperoxaluria, Bartter syndrome and Dent disease were the commonest etiologies of nephrocalcinosis at a referral hospital in Southern India.

## DISCUSSION

This study is one of the largest single-centre studies on the etiological profile of NC. The study showed that the most common etiologies of NC were distal RTA, primary hyperoxaluria, Bartter syndrome and Dent disease, together accounting for more than two-thirds of cases. Common clinical presentations included failure to thrive, polyuria and bony deformities. At a median (IQR) follow up of 24 (18, 56) months, the estimated glomerular filtration rate (GFR) had significantly increased, possibly due to resolution of AKI (resulting from a polyuric state).

There have been few studies evaluating the clinico-etiological profile of pediatric NC [1,4-6, 11]. Mantan, *et al.* [6] retrospectively evaluated the etiology of NC in 40 children from northern India, which included d-RTA (50%), idiopathic hypercalciuria (7.5%) and primary hyperoxaluria (7.5%). At a median (range) follow up of 35 (14,240) months, the eGFR had declined from 82.0 (42,114) to 70.8 (21.3, 126.5) mL/min/1.73 m<sup>2</sup>. Ronnefarth, *et al.*, [1] retrospectively evaluated 152 children with NC from Germany, which included idiopathic hypercalciuria (34%), hereditary tubular disorders (32%) and vitamin D toxicity (8%). The eGFR had increased from 96 to 103 mL/min/1.73m<sup>2</sup>. Dogan, *et al.*, [4] in 36 Turkish children with NC, reported distal RTA (30.5%), Bartter syndrome (13.8%), Vitamin D toxicity (8.3%), idiopathic hypercalciuria (5.5%) and primary hyperoxaluria (5.5%). Among 41 children from Italy, hereditary tubulopathies was the single largest etiology (41.4%), of which distal RTA was seen in 17% [5]. During a mean follow up of 4.4 years, eGFR remained stable in 89% [5].

There appear to be some differences in our results when compared to those of the aforementioned studies [1,4,6]. The etiological profile of our enrolled cases is notable for the absence of idiopathic hypercalciuria, which in previous studies ranged from 7.5%-34% [1,4,6]. The hypercalciuria in our enrolled cases was secondary in nature. Furthermore, a cause for NC was not identifiable in 9.3% of enrolled cases in our study. This is comparable to the results of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) survey (6%) [1]. Consanguinity was noted in 50% of our cases; and this, along with ethnic variations could have accounted for high percentage of inherited tubulopathies.

Hypercalciuria was commonly noted in our study, highlighting its importance as a major pathogenic factor [12,13]. Primary hyperoxaluria was another important cause, similar to those reported in developed countries [14,15]. We did not encounter any cases of vitamin D excess among the enrolled cases.

Owing to resource constraints, genetic studies could not be performed in all cases. Moreover, we could not perform urine citrate estimation due to logistic reasons. Finally, the etiological profile of patients enrolled in this study might be affected by a referral bias.

To summarize, distal RTA, primary hyperoxaluria, Bartter syndrome and Dent disease were the most common etiologies of NC in our study. Failure to thrive, polyuria, polydipsia and bony deformities were the common presenting features in our patients. With a systematic approach, etiologies of NC could be identified in most of the cases.

*Contributors:* KR, SK, PS: management of the patients; KR: collected the data, reviewed the literature and drafted the first version of the manuscript; SK: conceptualized the study, collected the data, reviewed the literature, revised the manuscript and critically reviewed the manuscript. All authors contributed to drafting of the manuscript and approved the final version of the manuscript; SK: shall act as guarantor of the paper.

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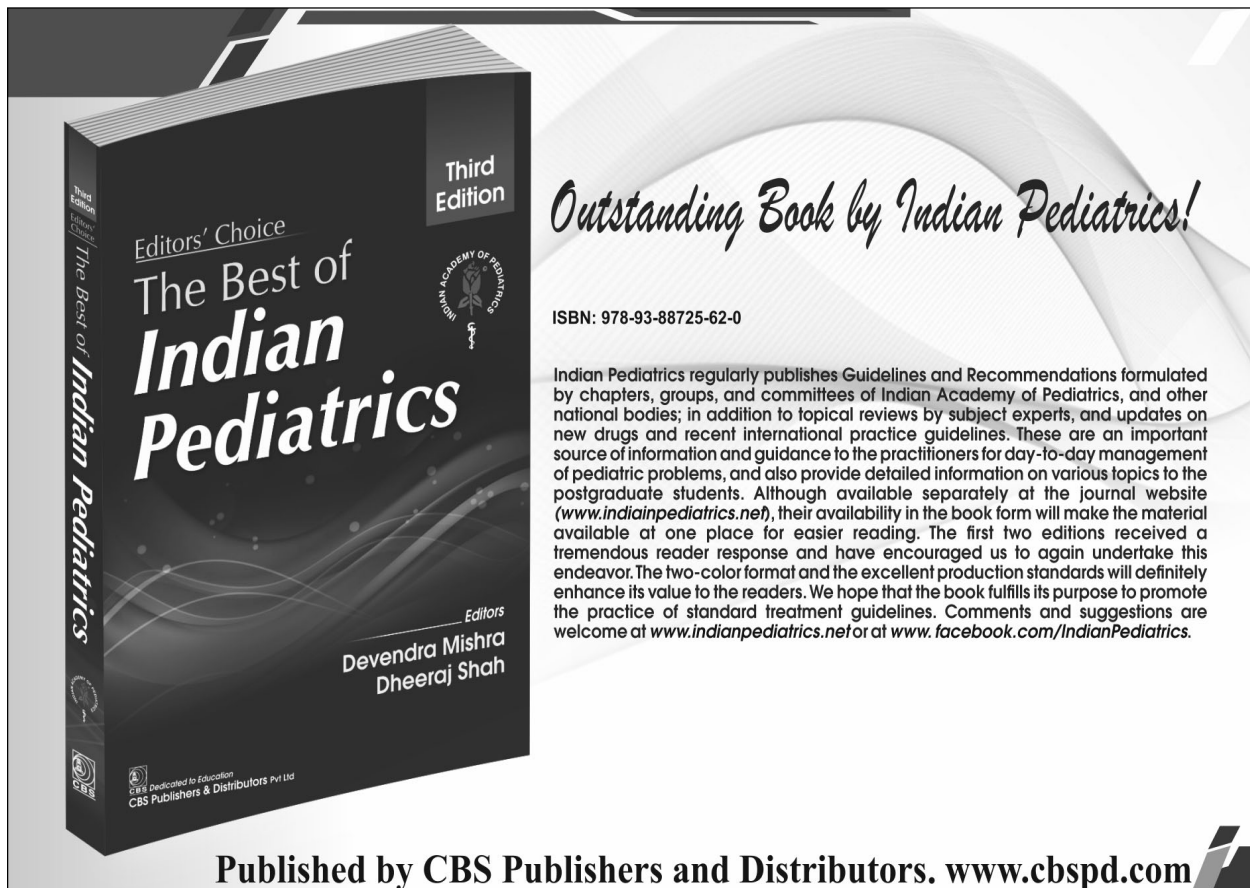
*Competing interests:* None stated.

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## Acute Peritoneal Dialysis in Premature Infants

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**Objectives:** This study aimed to investigate the underlying causes and outcomes of less than 1500 g birth weight infants who underwent acute peritoneal dialysis (PD). **Methods:** Case records of infants with birthweight less than 1500 g from January 2015 to June 2018 were reviewed. **Results:** The median (range) birth weight and gestational age of the patients were 720 g (555-1055) and 26 weeks (23-27.5), respectively. Underlying factors for the development of acute kidney injury (AKI) were patent ductus arteriosus (PDA) (15 patients), necrotizing enterocolitis (NEC) (10 patients), sepsis (7 patients), asphyxia (2 patients) and hydrops fetalis (2 patients). Multifunctional 10 F flexible catheter was used for the procedure. Median PD onset time was 7 days (4.5-13.5) and median PD duration was 3 days (1.5-3.5). Overall mortality rate was 81 % (n=17). **Conclusions:** Despite high overall mortality, PD is technically feasible in very low birthweight (VLBW) and extremely low birthweight (ELBW) neonates using a multifunctional catheter.

**Keywords:** Acute kidney injury, Low birth weight infant, Peritoneal dialysis.

Peritoneal dialysis (PD), hemodialysis, continuous hemodialysis, hemofiltration-hemodiafiltration or slow continuous ultrafiltration are therapeutic options for renal replacement therapy (RRT) for acute kidney injury (AKI) [1]. PD is the preferred modality than hemodialysis because it is more physiological, results in less pro-inflammatory effects than hemodialysis, simplicity of the method, minimal requirement of equipment and avoidance of the morbidity of vascular access [2-4]. However, the morbidity and mortality rates of PD in premature infants may be high because of concomitant systemic problems that contribute to the development of AKI. There are limited studies demonstrating the experience of PD in very low birthweight (VLBW) and extremely low birthweight (ELBW) neonates. We report experience of PD in preterm neonates with AKI and risk factors of AKI, complications of PD and causes of deaths.

### METHODS

This retrospective study was conducted in the Department of Neonatology, Zeynep Kamil Maternity and Children's Training and Research Hospital, University of Health Sciences, Istanbul. Data on VLBW and ELBW premature neonates who underwent PD for AKI between January 2015 and June 2018 were collected. Medical

information for demographic data, laboratory parameters, post-treatment recovery and mortality rates were extracted.

*Accompanying Editorial: Pages 399-400.*

PD was indicated for AKI (urine output of <0.7 mL/kg/h for 24 h or anuric for 12 h) [5] and failure of conservative treatment (furosemide or water restriction in cases without hypovolemia) or signs of uremia (impaired cardiac and respiratory function or seizures), refractory hyperkalemia, and metabolic acidosis or fluid overload. PD catheters were inserted by a pediatric surgeon under sterile conditions with local anesthesia at the bedside. The multifunctional catheter is polyethylene, disposable, non-traumatic, rounded with distal two-hole, and can also be used for aspiration or discharging (10 F, Bicakcilar, Turkey). A single-headed multifunctional flexible catheter was placed percutaneously in the left lower quadrant following a 0.5-1 cm horizontal incision below the umbilicus in the supine position. Approximately 4 h after the catheter placement, manual PD administration was started at 10 mL/kg/h and gradually increased up to 20-30 mL/kg/h with the standard dialysate solutions with glucose concentrations of 1.36%, 2.27%, or 3.86% (Dianeal,

#### WHAT THIS STUDY ADDS?

- Peritoneal dialysis is technically feasible in premature neonates weighing below 1500g using a multifunctional catheter.

Baxter Healthcare, Deerfield, USA). The catheter was connected to the peritoneal dialysate fluid and drain bags. The one hour-PD cycle comprised of three periods: filling (10 minutes), dwelling (30 minutes), and draining (20 minutes). Heparin and antibiotics were added to dialysis fluid at a dose of 40 U/L with 125 mg ampicillin and 125 mg cefazoline per liter.

Statistical analysis was performed using SPSS 16 for Windows. Continuous data was expressed as median and interquartile range (IQR). Categorical data was expressed as proportions and compared using Chi-square test. Nonnormally distributed numerical and ordinal variables were compared with the Mann Whitney U test. Student *t*-test was performed to compare parametric variables. Paired *t*-test was used to compare paired samples. A *P* value of less than 0.05 was considered statistically significant.

#### RESULTS

Twenty one (2.8%) (11 males) out of 714 neonates (birth weight <1500 g) required PD during the study period. The median (IQR) birth weight and gestational age of the neonates were 720 g (555,1055) and 26 weeks (23, 27.5), respectively. Fifteen (71.4%) neonates were ELBW and 12 (57%) were delivered by cesarean section. Underlying factors for the development of AKI were patent ductus arteriosus (PDA) (*n*=15), necrotizing enterocolitis (NEC) (*n*=10), sepsis (*n*=7), asphyxia (*n*=2) and hydrops fetalis (*n*=2). Median (IQR) PD onset time was 7 days, (4.5,13.5) and median (IQR) PD duration was 3 days (1.5, 3.5). Demographical data and biochemical parameters before and after PD are depicted in **Web Table I**. Significant difference was observed in pH levels (*P*=0.007), unlike other parameters. There was no improvement with PD for oliguria and hyperkalemia in ten neonates, serum urea levels in 15 neonates and acidosis in eight neonates.

Dialysis related complications were observed in nine patients (42.8%) neonates. Leakage developed in 6 (28.5%) neonates, but did not hamper working and catheter revision was performed in 3 (14.2%) neonates with catheter obstruction. Intestinal perforation or bladder injury was not observed. Color change was observed in the peritoneal fluid in 5 (23.8%) neonates with a history of perforated NEC but cultures were sterile. The mortality rate was 81% (*n*=17).

#### DISCUSSION

The present study reports etiology of AKI and experience with PD in ELBW and VLBW neonates. The retrospective nature and the small number of cases are the main limitations of this study. The main causes of AKI in VLBW and ELBW infants are sepsis, asphyxia, respiratory distress syndrome (RDS), PDA and NEC [6-9]. PD is the most preferred RRT strategy for AKI treatment in preterm infants in our clinic. Slow and controlled fluid removal provided by PD makes fluid elimination safer without hemodynamic instability [10]. However, inappropriate placement, occlusion or leakage of the catheter, peritonitis, and perforation are frequent factors that restrict its use [11]. Mortality with catheter related complications significantly decreased with the use of Tenckhoff catheters [12]. However, the limited availability of appropriately sized PD catheters for VLBW and ELBW infants is a common challenge. Yu, *et al.* [6] performed PD using vascular catheter in babies with birth weight <1000 g. Bed-side catheter insertion and ease of use of a multifunctional flexible 10F catheter makes it an accessible and inexpensive choice. Problems such as insufficient flow and high risk of leakage around the catheter may be seen. Leakage rates may vary from 5.8 – 29% [7,8,13], similar to our results.

The morbidity and mortality rates with PD are higher in neonates with multisystem problems [14], reported earlier 59.3-81.3% [7,8,15,16]. Mortality rate in the present study was higher, probably as the median gestational age and birth weight of were lower. Tetta, *et al.* [17] reported high (95%) mortality rate in premature babies with multiorgan failure and sepsis, which could be related to the underlying causes, rather than complications of PD.

To conclude, PD is technically feasible in VLBW and ELBW neonates using a flexible 10F catheter. Clinical and biochemical improvement in AKI is governed by underlying cause of AKI.

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**Web Table I Clinical and Laboratory Features of Premature Neonates Before and After Peritoneal Dialysis**

S.No.	Sex	Gest age (wk)	Weight (g)	Underlying causes	PD starting age (d)	PD duration (d)	Pre/post pH*	Pre/post sodium (mmol/L)	Pre/post potassium (mmol/L)	Pre/post urea (mg/dL)	Pre/post creatinine (mg/dL)	Outcome	Cause of death
1	M	27	1060	PDA	1	4	7.50/7.50	130/131	3.6/3.6	12/10	1.6/0.9	Survived	-
2	M	27	493	Sepsis/PDA	3	3	7.05/7.35	128/144	5.4/5.5	26/9	2.5/0.8	Died	Pulmonary hemorrhage
3	M	29	1130	NEC	18	11	7.20/7.35	141/142	5.3/5.3	62/63	1.9/1.9	Died	Gastric perforation
4	F	23	635	NEC/PDA	13	3	7.10/7.11	141/141	5.2/5.1	51/50	1.2/1.3	Died	NEC
5	F	27	770	PDA/NEC	5	3	7.11/7.35	144/143	3.5/3.4	26/25	1.9/1.9	Died	Twin-twin transfusion
6	M	22	480	PDA	5	1	7.11/7.11	144/144	6.7/6.7	50/53	1.1/1	Died	Metabolic disturbances
7	M	22	520	NEC/PDA	7	8	7.14/7.14	160/160	5.8/5.7	118/115	2.9/2.7	Died	Immaturity
8	F	23	1050	NEC/PDA	12	3	6.90/6.93	154/155	6.5/6.6	148/150	5.4/5.1	Died	Electrolyte disturbances
9	M	29	920	Asphyxia/PDA	3	2	7.11/7.11	138/138	8.3/8.1	24/22	1.9/2	Died	Asphyxia
10	F	26	640	NEC/PDA	6	18	7.17/7.35	148/143	7.6/3.5	124/120	2.8/3	Died	Pulmonary hypertension
11	M	23	590	Sepsis/PDA	24	3	7.03/7.40	130/132	6.1/6	64/70	1.8/1.6	Died	Broncho-pneumonia
12	M	28	650	Sepsis/NEC	83	2	7.20/7.38	141/140	5/5.3	67/9	1.5/0.8	Survived	-
13	F	27	1200	NEC/PDA	11	1	7.15/7.15	132/131	4.8/5	87/85	2.8/3	Died	Sepsis
14	M	22	470	PDA	10	3	7.19/7.40	140/140	7.8/8	122/120	2.2/2.2	Died	Immaturity
15	F	29	1235	Hydrops fetalis	4	1	6.90/6.90	122/125	10/9	83/87	3/3	Died	Hydrops
16	M	24	720	Sepsis/NEC/PDA	14	2	7.45/7.45	120/145	6.2/4	94/13	1.9/0.7	Survived	-
17	F	25	830	Sepsis/NEC	6	1	7.30/7.30	152/152	8/7	125/120	3.3/3.5	Died	Sepsis
18	M	26	1005	Hydrops fetalis	7	4	7.30/7.45	139/140	7/6.5	9/12	1.2/1.1	Died	Hydrops
19	F	29	1010	Asphyxia	11	6	6.92/7.30	135/132	3.9/4	10/10	1.3/1.5	Survived	-
20	F	24	480	Sepsis/PDA	5	2	7.15/7.35	140/141	6.3/6.1	130/100	5.7/5.5	Died	Sepsis
21	F	23	460	Sepsis/PDA	3	1	7.20/7.20	150/151	5/5	119/115	5.5/5	Died	Immaturity

Gest: gestational; NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, PD: peritoneal dialysis; \*P<0.05 before and after PD.

## Radiographic and Clinical Features of Children With Coronavirus Disease (COVID-19) Pneumonia

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**Objective:** The purpose of this study was to investigate chest computed tomography (CT) findings in children with coronavirus disease-19 (COVID-19) pneumonia in our hospital. **Methods:** This study included 22 pediatric patients with confirmed COVID-19 from January to March, 2020. The chest CT images and clinical data were reviewed. **Results:** The most prevalent presenting symptoms were fever (64%) and cough (59%), and a mildly elevated mean (SD) C-reactive protein (CRP) level of 11.22(11.06) and erythrocyte sedimentation rate of 18.8(15.17) were detected. The major CT abnormalities observed were mixed ground-glass opacity and consolidation lesions (36%), consolidations (32%), and ground-glass opacities (14%). Peripheral distribution (45%) of lung lesions was predominant. Most of the lesions were multilobar(68%), with an average of three lung segments involved. **Conclusion:** Children with COVID-19 had relatively milder symptoms and less severe lung inflammation than adults. Chest CT plays an important role in the management of children with COVID-19 pneumonia.

**Keywords:** Diagnosis, Evaluation, SARS-CoV-2, Management.

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The 2019 novel coronavirus (COVID-19) pneumonia, reported in Wuhan (Hubei Province, China) since late 2019, has garnered intense attention worldwide [1]. The World Health Organization has declared this outbreak as a pandemic. While COVID-19 is usually common in middle-aged or elderly people, the incidence of COVID-19 is rare in children, and children have mild clinical symptoms [2]. Chest computed tomography (CT) can identify infected lesions, indicating viral pneumonia, which plays an irreplaceable role in the screening of COVID-19. There are only limited data available regarding the typical chest CT imaging findings of COVID-19 in children [2]. In this study, we retrospectively evaluated radiographic features of chest CT and clinical features in children with confirmed COVID-19.

### METHODS

This study was approved by the Medical Research Ethics Committee of our institution. The requirement for patients' informed consent was waived due to the retrospective nature of the study. From January 16, 2020 to March 14, 2020, a search of the electronic system and Picture archiving and communication system (PACS) was

performed in our department. All pediatric patients with suspected/proven COVID-19 were being routinely subjected to CT chest at our center. The inclusion criteria were: (i) epidemiological history: either travel/residence history in Wuhan or exposure history to patients with fever from Wuhan suffering from respiratory symptoms within 14 days before the onset of illness; and (ii) laboratory diagnosis: positive detection of COVID-19 in throat swabs or lower respiratory tract by real-time fluorescence polymerase chain reaction (Shanghai ZJ Bio-Tech Co, Ltd, Shanghai, China).

The following clinical data of the patients were collected and assessed: sex, age, pharyngeal discomfort, cough, expectoration, chest congestion, myalgia and abdominal pain or diarrhea. Information regarding the physical examination at admission was evaluated, including the heart rate, body temperature, respiratory rate and blood pressure. Moreover, the laboratory data were also assessed, including total and differential leukocyte, erythrocyte sedimentation rate (ESR), procalcitonin, and C-reactive protein (CRP) levels.

*Imaging technique:* All patients completed non-contrast chest CT scans in a separate examination room while the

CT technician utilized secondary protection. Chest CT images were obtained using a 16-row multi-detector CT scanner (Siemens Somatom Sensation; Siemens, Erlangen, Germany). The CT examination parameters were as follows: 120 kVp, 140 mA, 5 mm collimation, 1.35:1 pitch, a pulmonary kernel (B70f) and a mediastinal kernel (B30f), reconstruction slice thickness of 1.0 mm, and high spatial resolution algorithm. All the patients over the age of three years were scanned in a supine position while holding their breath at full inspiration, while children under the age of three completed examinations while asleep (were not required to hold their breath).

All chest CT scans were reviewed independently by two senior radiologists, while they were blinded to the name and clinical data of the patients. The two radiologists reached a consensus about the lung abnormalities, and an agreement was reached by discussion if the conclusions were different. All CT images were viewed on both lung window (width, 1500 HU; level, 500 HU) and mediastinal window (width, 350 HU; level, 40 HU) settings. The major CT dimensions, including the presence of ground-glass opacities, 'crazy-paving sign', consolidation, and mixed ground-glass opacities and consolidation lesions, were fully evaluated. The detailed definitions of the above features were as per a previous publication [3,4]. The distribution of lung abnormalities was recorded as predominantly sub-pleural (involving mainly the peripheral one-third of the lung), central (involving mainly the central one-third of the lung), mixed (involving both sub-pleural and central regions), and diffuse (continuous involvement without respect to lung segments) according to a similar report [5]. The scattering patterns of lesions (focal, multifocal and diffuse) were also classified. The number of bilateral lung segments affected by pneumonia was recorded simultaneously.

*Statistical analyses:* All statistical analyses were conducted using Statistical Package for Social Sciences software version 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Records of 22 patients (12 males) were included in this study. The mean (SD) age was 8 (6) years. The most prevalent presenting symptoms were fever (14 cases, 64%) and cough (13 cases, 59%). Two patients had no clinical symptoms or chest CT abnormalities; however, they were in close contact with confirmed cases and had positive results on a COVID-19 nucleic acid test. Chest CT scans were obtained at mean (SD) 3 (3) days (range: 0-11) after the onset of symptoms. Laboratory investigations showed that the most frequent abnormalities were mildly elevated CRP [mean (SD)=11.2 (11.6)] and ESR values [mean (SD)=18.8 (15.17)] (**Web Table 1**).

Most patients showed bilateral lung involvement (15, 68%) (**Table 1**). Of the spatial distribution of all lesions, the right lower lobe (9, 41%) was most commonly involved. The average number of infected lung segments was three (range: 0-15) for all patients, with less than three lung segments involved in 55% patients. The major CT abnormalities observed were mixed ground glass opacities and consolidation lesions (8, 36%), or consolidations alone (7, 32%) (**Fig.1**). In addition, two children (9%) showed a 'crazy-paving sign' characterized by reticular interlobular septal thickening within patchy ground glass opacities [6]. Multifocal lesions (15 cases, 68%) were most common, and patients had lymph node enlargement.

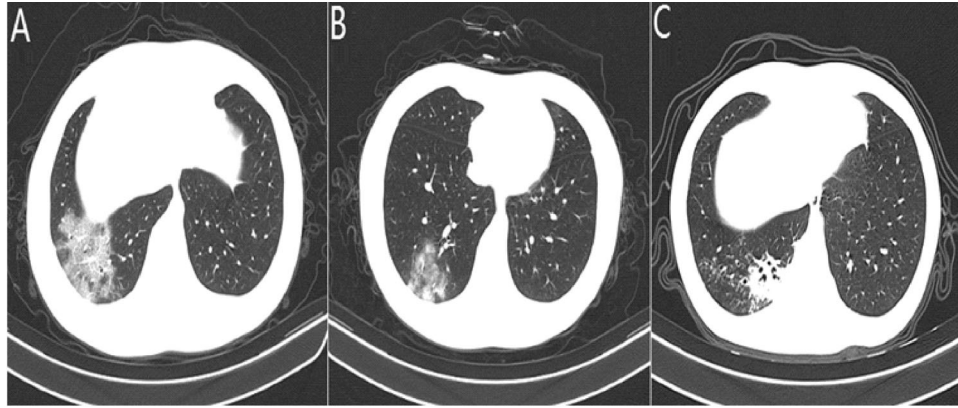
## DISCUSSION

The novel coronavirus related to the MERS and SARS coronaviruses [7,8] has now spread to become a pandemic, with wide-ranging effects. We found that typical clinical symptoms were similar to those of other types of coronavirus infections, such as SARS and MERS [9-11]. CT chest findings were noted to be characteristic and have been detailed.

**Table 1 Computed Tomography Chest findings in Pediatric Patients with COVID-19 (N=22)**

<i>Finding</i>	<i>No. (%)</i>
Ground glass opacities	3 (14)
Crazy-paving sign	2 (9)
Consolidation	7 (32)
Ground glass opacities and consolidation	8 (36)
<i>Lung region distribution</i>	
Unilateral	5 (23)
Bilateral	15 (68)
Subpleural	10 (45)
Central	1 (5)
Mixed	9 (41)
<i>Lung lobe involved</i>	
Right upper lobe	2 (9)
Right lower lobe	9 (41)
Left upper lobe	3 (14)
Left lower lobe	6 (27)
*Lung segments involved	3 (3)
<i>Distribution</i>	
Focal	3 (14)
Multifocal	15 (68)
Diffuse	2 (9)

*Data represented as no. (%) or \*mean (SD). Two patients had no chest CT abnormalities.*



**Fig. 1** Computed tomography findings in children with coronavirus-19 (COVID-19) pneumonia: (a) ground glass opacities; (b) consolidation; and (c) ground glass opacities and consolidation.

There is usually a certain time interval between the onset of symptoms and hospitalization of COVID-19 patients. In our study, the time interval between the first chest CT examination and the onset was 0 to 11 days. An initial negative result of chest CT examination may occur (2 cases, 9%), but lung abnormalities could be discovered among most of the patients. Most of the patients had mild symptoms as well as temperature elevation, but their lung manifestations were relatively obvious. In contrast to those in bacterial pneumonia [4], lung lesions showed similar imaging features to other viral pneumonias, mainly ground glass opacities, extensive interlobular septal thickening and patchy consolidation. In the early stage, COVID-19 reflects mainly interstitial lung damage, such as thickening of the interlobular septa and the presence of ground glass opacities. Alveolar edema, exudation and bleeding can be manifested in different degrees of ground glass opacities on CT images, as inflammation involves the alveoli. In more than one-third of cases, abnormal lung manifestations were presented as a mixture of GGOs and consolidations, implying a rapid progression of pneumonia, which is probably due to a lower immune response in children than in adults. In severe cases, owing to the collapse of alveoli or massive infiltration of inflammatory cells, lung parenchymal injury may occur, presenting as lung consolidation. Although more detailed pathological changes of COVID-19 need to be further studied, research has shown that angiotensin-converting enzyme 2 (ACE2) is an important receptor of the SARS-CoV-2 surface spike protein domain, which is similar to the case for SARS-CoV. Given that it is highly contagious, its affinity may be greater than that of SARS-CoV [12]. Human ACE2 receptors are abundantly expressed in type II alveolar epithelial cells. The outer bands of the lungs and the sub-pleural space are dense areas where terminal bronchi are dilated to form alveolar ducts, which can also

explain the characteristics of lesion distribution from an anatomical perspective. In addition, thickened small blood vessel shadows and faint shadows surrounding the nodules are also characteristic in some reports.

Globally, similar outbreaks of respiratory diseases have also been observed for SARS and MERS, and those causative pathogens belong to the beta-coronavirus family [13]. There is a certain similarity of chest CT imaging features between SARS and COVID-19 [14]. For instance, both GGOs and consolidations are dominant and concentrate mainly in bilateral sub-pleural areas; otherwise, cavities, pleural effusion and enlarged lymph nodes are rare. However, SARS had more severe interstitial fibrosis during the absorption phase of pneumonia. After discharge, CT images of SARS patients still showed thickening of the lobular septum, subpleural and distal bronchiolar dilatation, and honeycomb changes [15]. The lung lesions of SARS progressed more rapidly and were termed white out or 'white lung' because consolidation and coalescing infiltrates pervaded the lungs, leaving few recognized air spaces. The COVID-19 patients in this study did not show 'white lung', although we observed lesions involving 15 lung segments in one case, and the distribution of lesions was mainly sub-pleural. Furthermore, we note that 55% of cases involved less than three lung segments, which is different from previous reports of adult patients. This finding suggests that COVID-19 has a mild inflammatory infiltration in children, which indicates that they are more likely to recover than adults after symptomatic treatment, and the specific mechanism needs to be further studied.

This study has several limitations. First, the sample size of this study is small because the incidence of children with COVID-19 is not high. Including additional cases could have improved the recognition of image

### WHAT THIS STUDY ADDS?

- Chest computed tomography findings and clinical features of pediatric patients with COVID-19.

features of COVID-19 in children. Second, longitudinal studies on follow-up CT changes during treatment in children need to be carried out. These studies can reflect the course of disease development and pathological changes and may provide valuable experience for future treatment and rehabilitation.

In summary, we found that common chest CT findings in COVID-19 in children include multiple mixed ground glass opacities and consolidation lesions in both lungs, with mostly sub-pleural distribution. The ‘crazy-paving sign’ was found in a few cases, and the number of lung segments involved was small, with an average of three. More data on this aspect will assist clinicians in diagnosis and management of COVID-19 in children.

*Contributors:* All authors have contributed, designed and approved the study.

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*Ethical approval:* Medical Research Ethics Committee of Yichang Central People’s Hospital, Yichang, China.

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**Web Table I Examination Findings and Laboratory Abnormalities in Children with COVID-19 (N=22)**

<i>Variable</i>	<i>Mean (SD)</i>
Heart rate (bpm)	98.2 (17.62)
Respiratory rate (breaths/min)	24.7 (7.07)
#Systolic pressure (mm Hg)	112.4 (9.44)
#Diastolic pressure (mm Hg)	70.5 (6.97)
White blood cell count ( $\times 10^9/L$ )	6.5 (1.97)
Neutrophil count ( $\times 10^9/L$ )	3.9 (1.76)
Neutrophil proportion (%)	59.4 (19.34)
Lymphocyte count ( $\times 10^9/L$ )	2.0 (1.26)
Lymphocyte percentage (%)	31.1 (15.10)
C-reactive protein (mg/L)	11.2 (11.06)
Erythrocyte sedimentation rate (s)	18.8 (15.17)
Procalcitonin (ng/mL)	0.05 (0.02)

## Predictors of Renal Complications in Children With Hematotoxic Snakebite

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**Objective:** To study the predictors of renal complications following hematotoxic snakebite in children. **Methods:** This comparative study was conducted in the pediatric ward of a tertiary-care centre among 364 consecutively children admitted with hematotoxic snakebite between January 2016 and December 2017. Clinical and laboratory indicators were compared between children who developed acute kidney injury and those who did not. **Results:** Acute kidney injury was seen in 139 children (38.2%), majority being stage 2 (55, 39.5%). 59 children (16.2%) developed permanent renal damage and 16 (4.4%) died due to envenomation. Acute tubular necrosis was the most common (25, 39.1%) histopathological change. **Conclusion:** Receiving anti-snake venom more than one hour after bite was the most significant adverse prognostic indicator, both for renal complications and mortality.

**Keywords:** Acute kidney injury, Anti-snake venom, Envenomation.

Snakebite is a common problem in tropical countries, affecting nearly 6 million people every year, with nearly 10% of these fatalities occurring in India [1]. Russell's viper (RV) (*Daboia russelii*), the foremost cause of morbidity and mortality [2], and is responsible for both hemato-toxicity and neuro-toxicity. Local tissue damage, venom induced coagulopathy, platelet dysfunction, phospholipase A<sub>2</sub> induced rhabdomyolysis, hyperkalemia, acute kidney injury (AKI) and multi-organ dysfunction, all are effects of RV venom [3]. Direct toxic action of the venom may also be responsible for AKI [4].

Different studies have estimated that the incidence of AKI following hematotoxic bite ranges from 10-32% [4]. Recently, it was reported that there is a geographical variation in the venoms of snake and this variation is responsible for different efficacies of ASV in different parts of country [5]. There is scarcity of data regarding the factors responsible for AKI following hematotoxic envenomation, especially in children. Hence this study was conducted to find out the incidence of renal complications following hematotoxic snake bites and to identify the clinical and laboratory indicators which help in predicting AKI early.

### METHODS

A comparative study was conducted in the pediatric emergency ward of a tertiary care centre in between January, 2016 to December, 2017. Prior approval was

taken from the institutional ethics committee. Hematotoxic envenomation was identified by identification of snake by the victim/ relatives or witness, and features of intoxication characterized mainly by a positive 20 minute whole blood clotting test (WBCT).

On admission, all the children received 10 vials of ASV diluted with 100 mL/ 200 mL normal saline (0.9% NaCl). Depending on correction of coagulopathy and clinical indication, upto 30 vials of ASV were used. Serum urea and creatinine, electrolytes and an electrocardiogram were obtained at the time of admission. These were repeated once daily or when clinically indicated, till discharge or normalization of the value in three repeated tests. Acute kidney injury was defined according to KDIGO guidelines (Kidney disease: Improving global outcome) [6]. Dialysis (peritoneal dialysis in this institution and hemodialysis in a referral hospital) was used when the patient developed signs of fluid overload, developed oliguria/ anuria (defined as urine output <0.5 mL/kg/h for last 24 hours), hyperkalemia (defined as >5.5 mEq/L with ECG changes or >6 mEq/L). If these values were not normalized even after 6 months of discharge or there was persistent hypertension, it was assumed that there is permanent renal damage. The follow-up period was 6 months or till normalization of renal function, whichever was later.

*Statistical analysis:* Shapiro-Wilk test was used to check normal distribution. Chi-square test was used to find the

significance of difference between attributes in contingency tables, whereas one-way ANOVA was used to check the significance of difference between means. Kruskal Wallis H test was used for skewed data. Pearson's product moment correlation coefficient (r) was calculated to find the degree and direction of relationship of dependent and independent variables. Significantly correlated variables were considered for a binary logistic regression model taking AKI, permanent renal damage and mortality as dependent /outcome variable to calculate the adjusted odds ratio.  $P < 0.05$  was taken as statistically significant. Analysis was done by SPSS version 19.0 (Statistical Packages for Social Sciences Inc, Chicago, IL, US).

## RESULTS

During the study period, 371 children were admitted with hematotoxic envenomation. Children with known kidney disease, who were severely ill and died immediately, and those with parental refusal of consent were excluded from the study (7 children were excluded; 1 with end stage renal disease due to lupus nephritis, 2 were severely ill and died immediately, and 4 refused consent). Finally, 364 children (69% males) were included. Mean (SD) age of the study population was 8.9 (2.3) years. Majority of them belonged to lower socioeconomic status (60.7%). Out of the 364 children, 139 (38.2%) developed AKI following envenomation. Out of these 48 (34.5%), 55 (39.5%) and 36 (26.0%) children developed stage 1, 2 & 3 AKI, respectively. Sixteen children (4.4%) died and 59 (16.2%) children developed permanent renal damage. Different clinical and laboratory parameters of two groups of children (with AKI and without AKI) are presented in **Table I**.

Administration of ASV following 1 hour of bite emerged as the most significant predictor of AKI (adjusted OR=23.4, 95% CI=22.1-24.8), permanent renal injury (adjusted OR=19.7, 95% CI=18.9-20.5) and mortality (adjusted OR=15.2, 95% CI=14.7-15.7) (**Table II**). Our model can correctly predict 67.2%-78.9% variation of AKI, 62.1-70.3% variation of permanent renal injury and 53.1-61.7% variation of mortality. Renal histopathology was done in 48 (81.4%) children suffering from permanent renal damage and 16 children (100%) who died. Acute tubular necrosis (25, 39.1%) was the most common finding in histopathology, followed by renal cortical necrosis (12.5%).

## DISCUSSION

In this study conducted to detect the incidence and predictors of renal complications due to hematotoxic envenomation, we found that 38.2% children developed

**Table I Characteristics of the Study Population and Acute Kidney Injury (N=364)**

Variables	No AKI (n=225)	AKI (n=139)
Age <sup>#</sup> , y	9.1 (1.7)	5.8 (1.0)
Female sex	170 (67.7)	81 (32.3)
Rural residence	116 (53.5)	101 (36.5)
Bite on trunk	49 (46.2)	57 (53.8)
Single Bite	221 (73.7)	79 (26.3)
Time b/w bite and ASV <sup>#</sup> , min	36.4 (5.9)	74.5 (8.3)
Vials of ASV required*	10 (10-30)	20 (10-30)
<i>Local reaction</i>		
<5 cm	106 (84.1)	20 (15.9)
5-10 cm	72 (66.0)	37 (34.0)
>10 cm	47 (36.4)	82 (63.7)
<i>System involvement</i>		
No	203 (83.2)	41 (16.8)
One system	17 (26.6)	47 (73.4)
>1 system	5 (8.9)	51 (91.1)
Neurotoxicity	24 (20.5)	93 (79.5)
<i>Alteration of K<sup>+</sup></i>		
No	158 (89.8)	18 (11.2)
After 6 h	23 (43.4)	30 (56.6)
2-6 h	32 (42.1)	44 (57.9)
<2 h	12 (20.3)	47 (79.7)
K <sup>+</sup> level <sup>#</sup> (mEq/L)	3.9 (0.3)	5.7 (0.6)
<i>Altered WBCT</i>		
6 h	202 (96.2)	8 (3.8)
12 h	21 (25.3)	62 (74.7)
>12 h	2 (2.8)	69 (97.2)
Bleeding	48 (32.7)	99 (67.3)
Ventilation	7 (8.0)	81 (92.0)
Blood product	55 (34.8)	103 (65.2)
Inotropes	88 (42.5)	119 (57.5)

All values in no. (%) except <sup>#</sup>mean (SD) and \* median (IQR); WBCT -whole blood clotting test, K<sup>+</sup>- serum potassium; All comparisons  $P < 0.01$  except  $P < 0.001$  for rural residence and bite on trunk; b/w - between.

AKI following bite and 26% of them developed stage 3 AKI. Acute tubular necrosis was the most common finding in renal histopathology.

Measurement of serum venom level was not possible in our setting. Nearly 20%, 30% and 40% variation of AKI, permanent renal injury and mortality still remained unexplained. Renal histopathology could not be done in all the children due to invasive nature of the investigation and lack of consent.



### WHAT THIS STUDY ADDS?

- Administration of ASV following 1 hour of bite is the most significant predictor of acute kidney injury, permanent renal injury and mortality.

**Table II Acute Kidney Injury, Permanent Renal Injury and Mortality in Children with Hematotoxic Snakebite (N=364)**

Variables	AKI (n=139)	Permanent renal injury (n=59)	Mortality (n=16)
Anti-snake venom after 1 h	23.4 (22.1-24.8)	19.7 (18.9-20.5)	15.2 (14.7-15.7)
Need of mechanical ventilation	18.1 (17.4-18.9)	16.2 (15.8-16.6)	13.8 (12.6-15.0)
Bleeding	15.6 (15.3-15.9)	12.9 (12.1-13.7)	9.5 (8.5-10.6)
Blood products	13.2 (12.5-13.9)	8.7 (8.5-9.0)	1.8 (0.3-2.9)
Serum potassium level >6 mEq/L	9.9 (8.2-11.6)	7.5 (6.9-8.1)	1.7 (0.6-2.1)
Alteration of pH in first 2 h	8.7 (8.1-9.3)	5.7 (5.1-6.4)	1.2 (0.7-1.8)
Requirement of inotropes	5.5 (4.7-6.3)	1.1 (0.8-1.3)	1.1 (0.6-1.5)
Rural residence	5.1 (3.8-6.4)	1.2 (0.7-1.5)	0.9 (0.3-1.4)

Values in adjusted odds ratio (95% CI).

Previous studies report 14.6-45.9% children developing AKI after hematotoxic envenomation and 24.5% developing permanent renal injury [7-9]. Mortality was lower in the current study than previous Indian reports of 6.6-22.3% [7-9]. This variability may be due to local variation of venom, heterogeneity of population and availability of resources [5,9]. Similar to the finding of current study, other authors have also noted that the time between administration of ASV and the snakebite was the most significant predictor of AKI [8,9]. Howarth, *et al.* [10] determined that mean periphery to systemic circulation time of venom was 58 (7) minutes. Hence, administration of ASV after 1 hour was less effective in prevention renal impairments. However, Krishnamurthy, *et al.* [7] did not find any significant association between delayed administration of ASV and development of AKI. AKI was more common among the younger children may be due to their ambulatory nature leading to more circulation of toxin [11]. Similar to the findings of current study, multiple researchers have also reported pre-hospital factors, alteration of 20 WBCT for prolonged time, neurotoxic signs and severe illness (characterized by bleeding, requirement of mechanical ventilation, blood products and inotropes) predict adverse outcome [9, 12-15].

To conclude, delay in administration of ASV was the most significant predictor of renal complications and mortality following hematotoxic bite. Prompt hospitalization after bite leads to early initiation of treatment and lesser fatality. As the composition of venom varies according to geographic location [5] and present study includes children from part of Bengal, Bihar and

Jharkhand only, further multi-centric research should be undertaken before generalization of findings of this study.

*Ethical Clearance:* Institution Ethics Committee, Burdwan Medical College, BMC/PG/4456 dated 14/12/2015.

*Contributors:* KI: writing manuscript, collection of data, analysis of data; SS: collection of data, analysis of data, designing study; AR: collection of data, writing and revising manuscript. AKD: planning study, revising manuscript.

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## Enuresis, Lower Urinary Tract Dysfunction and Teachers' Perceptions: A School-based Survey

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**Objective:** To determine the prevalence of enuresis and lower urinary tract dysfunction among Indian schoolchildren, and describe teachers' perceptions regarding toilet requests. **Methods:** Anonymous survey of students of a secondary school in Visakhapatnam, India by a modified version of the Dysfunctional voiding and incontinence scoring system (DVISS) in 2518 parents. Two questionnaires – the Bathroom behaviour scale and Teachers' hassle scale for toilet requests were designed, validated and administered to 138 teachers. **Results:** We received 1911 (75.9%) modified DVISS questionnaires with response; 1790 (93.7%) were valid. History was compatible with enuresis in 85 (4.7%), non-monosymptomatic enuresis in 38 (2.1%), overactive bladder in 46 children (2.6%), dysfunctional voiding syndrome in 14 children (0.8%) and both overactive bladder as well as dysfunctional voiding syndrome in 4 (0.2%). Responses of 43 (31.2%) teachers indicated refusal of toilet requests; medical cause underlying frequent toilet requests was understood by 82 (59.4%) teachers. At least one aspect of toilet requests was a frequent or intense hassle in 43 (39.8%) and 29 (28.7%) teachers, respectively. **Conclusion:** Toilet requests are misunderstood by and present a stressor to a sizeable minority of teachers.

**Keywords:** Habits, Incontinence, School Children, Toilet break.

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Enuresis is a common childhood problem. However, it can cause significant distress to the affected individuals and is also associated with sleep disturbances and behavior problems [1-3], thus hampering the overall quality of life. The term 'lower urinary tract dysfunction (LUTD)' refers to conditions where children have symptoms related to voiding in the absence of any overt uropathy or neuropathy [4,5], and is a part of the group of conditions known as bladder-bowel dysfunction (BBD) [4]. LUTD is associated with psychological comorbidity, urinary tract infection (UTI), vesicoureteral reflux (VUR) and constipation. The exact prevalence of LUTD in the population is not known but is estimated to be between 2% and 21.8% [6].

Teachers' awareness of the voiding habits of normal children and decision-making when faced with toilet requests have significant implications in both the evolution and management of LUTD [7,8]. Toilet requests should ideally be honored by teachers [7] but can be a stressor because of interference with teaching schedules and administrative expectations. However, there is very little data on awareness and stress amongst teachers related to this aspect of childcare.

We planned this study to estimate the prevalence of LUTD and enuresis among student in a single school, and to assess the knowledge of teachers regarding voiding habits of children, record perceptions of teachers regarding toilet use, and measure stress experienced by teachers due to toilet requests.

### METHODS

This observational descriptive study was conducted in a secondary school in Visakhapatnam, India after clearance by Institutional ethics committee of the affiliated hospital of the authors, as well as permission from school authorities. The parents of the students in the school have stable employment with the Central Government but are relocated frequently. The school has adequate number of clean toilets. The participants of the study were students aged 5 to 17 years, and all teachers of the school.

Enuresis was defined as passage of urine while sleeping. Non-monosymptomatic enuresis was defined as enuresis and any one of the following (i) passage of urine in the clothes while awake (ii) and any of the following symptoms: straining while passing urine, pain while passing urine, interrupted stream of urine, need to

return to pass urine a second time immediately after passing urine, urgency, holding manoeuvres or passing urine in clothes before reaching the toilet. Overactive bladder was defined as presence of any two of the following symptoms: urgency, holding manoeuvres or passing urine in clothes while awake. Dysfunctional voiding syndrome was defined in the presence of any of the following (i) any two of the following symptoms; straining while passing urine, pain while passing urine, interrupted stream of urine and need to return to pass urine a second time immediately after passing urine (ii) passage of urine in clothes while awake and any one of the following symptoms: straining while passing urine, pain while passing urine, interrupted stream of urine, and need to return to pass urine a second time immediately after passing urine.

To assess the prevalence of LUTD, the Dysfunctional voiding and incontinence symptom score (DVISS) [9] was used as a community-based screening tool, after suitable adaptation with permission of the author. The modified questionnaire was translated into Hindi by forward and reverse translation by five healthcare professionals each of whom were fluent in Hindi and English, with final reconciliation by the authors. Face validation was performed by a team consisting of a psychologist, a pediatrician and a community medicine specialist. With an estimated prevalence of 9% for LUTD, as well as enuresis [10,11], the minimum number of participants was estimated to be 1721 at 1% absolute error of margin with a finite correction and 99% confidence interval.

To assess the knowledge of teachers regarding voiding habits of children and their perceptions regarding toilet use, a questionnaire known as Bathroom behavior scale (BBS) was prepared. To evaluate the stress experienced by teachers due by toilet requests in terms of frequency as well as intensity, a second questionnaire, *i.e.* the Teachers' hassle scale for toilet requests (THSTR) was prepared. Both questionnaires were prepared after inputs from 10 teachers from different schools. With an assumed prevalence of 20% regarding awareness of LUTD among teachers, the minimum number of participants required for assessing knowledge of teachers regarding voiding habits was estimated at 136 at 1% absolute error of margin with two finite correction and 99% CI.

Face-validity of the BBS as well as the THSTR was assessed by the expert opinion of three pediatricians and another ten teachers from other schools, with separate feedback forms. Content validity was assessed using feedback forms distributed to these experts.

Data collection for the study was performed in February - March, 2019.

Both Hindi and English versions of the modified DVISS were sent to parents of all students in grade 1-9 and grade 11, along with a letter of consent explaining the purpose of the survey and clarifying that response to the questionnaire was purely voluntary. Data regarding name, age, sex and class were not collected to ensure anonymity. In case the parents did not return the questionnaire within three days of distribution, a single reminder was sent to them by the teachers to allow collection up to seven days after distribution of the questionnaire. The BBS and THSTR were administered to all teachers of the school.

After collection, the filled modified DVISS questionnaires were interpreted question-wise to elicit history suggestive of enuresis, non-monosymptomatic enuresis, dysfunctional voiding syndrome and overactive bladder. Forms with incomplete information and conflicting responses were rejected.

*Statistical analysis:* Reliability scores of the Frequency and Intensity subscales of the THSTR were calculated by Cronbach alpha. All statistical analysis was performed using Microsoft Excel 2016.

## RESULTS

Of 2518 questionnaires of the modified DVISS distributed to parents, 1911 (75.9%) were returned. On scrutiny, 1790 (93.7%) were valid. The prevalence of individual symptoms is shown in **Table I**. Symptomatology compatible with enuresis was noted in 85 children (4.7%, 95% CI 3.7-5.8%), non-monosymptomatic enuresis in 38 children (2.1%, 95% CI 2.0-3.6%), overactive bladder alone in 46 children (2.6%, 95% CI 1.8-3.3%), dysfunctional voiding syndrome alone in 14 children (0.8%, 95% CI 0.4-1.2%). Thus, a total of 64 children (3.6%, 95% CI 2.7-4.5%) had at least one form of LUTD, *i.e.* overactive bladder or dysfunctional voiding syndrome.

A total of 138 questionnaires of the BBS and THSTR were distributed to teachers and all were returned. Sixty-eight teachers (49.3%) were unaware of the correct amount of water requirement of a child, 34 (24.6%) were unaware of the number of times that a child voids in a day 43 (31.2%) believed that toilet requests in the middle of a class should be denied, and 93 teachers (67.4%), believed that such requests lead to more requests from other children. A medical cause for frequent toilet requests by a child was considered a likely possibility by 82 teachers (59.4%).

**Table I** Prevalence of Symptoms

<i>Symptom</i>	<i>Prevalence</i>
Daytime incontinence	34, 1.9 (1.3-2.5)
Damp underwear	19, 55.9 (53.5-58.2)
Damp pants	10, 29.4 (27.3-31.6)
Pants soaking wet	5, 14.7 (13.0-16.4)
Bedwetting	85, 4.7 (3.7-5.8)
Damp bedsheets	52, 61.2 (58.9-63.5)
Bedsheets soaking wet	33, 38.8 (36.5-41.1)
Urine passed > 7 times/d	325, 18.2 (16.3-20.0)
Straining during micturition	35, 2.0 (1.3-2.6)
Pain during micturition	16, 0.9, (0.5-1.3)
Interrupted stream	26, 1.5 (0.9-2.0)
Need to return to void a second time	27, 1.5 (0.9-2.1)
Urgency	98, 5.5 (4.4-6.6)
Holding manuvres	106, 5.9 (4.8-7.0)
Passing urine in pants on the way to the toilet	19, 1.1 (0.6-1.6)
Stools passed less than daily	222, 12.4 (10.8-14.0)%

\*Values in number, % (95% confidence interval).

Reliability of the Frequency and Intensity subscales of the THSTR were 0.80 and 0.85, respectively. Of 138 questionnaires of the THSTR that were returned, 108 (78.3%) and 101 (73.2%) were valid on the frequency and intensity subscales, respectively. The results of the responses to the THSTR are shown in **Web Table I**. At least one aspect of toilet requests was a frequent hassle in 43/108 (39.8%) and an intense hassle for 29/101 (28.7%) teachers with valid responses. Significant overall stress due to toilet requests in terms of frequency and intensity was noted in six teachers (5.6%) and one teacher (0.7%), respectively.

## DISCUSSION

In this study, we report prevalence of enuresis in 4.7%, non-monosymptomatic enuresis in 2.1%, overactive bladder in 2.6% and dysfunctional voiding syndrome in 0.8% children, respectively. We also report that a significant minority of teachers are unaware of the physiological basis of the toileting behaviour of children and that a significant proportion of teachers feel that at least one aspect of toilet requests constitutes a stressor.

There is a wide variation in the estimated prevalence of enuresis in developing countries, Indian studies report values between 7-12%. [3,12,13]. A Nigerian study reported figures as high as 37.0% [1]. The estimated prevalence of enuresis in our study, is lower than these studies. This may be due to absence of traditionally reported risk factors such as crowded families, low

educational level of parents, jobless father, working mother and single parent [14], as well as inclusion of older children in our cohort, in whom enuresis has a tendency to resolve [15].

The exact prevalence of non-monosymptomatic enuresis and LUTD in the general population is not known, probably because of a lack of population-based studies. Hellström, *et al.* [16] in a survey of 7-year old Swedish school entrants reported a prevalence of 2.3% and 2.0% of non-monosymptomatic enuresis among boys and girls, respectively as compared to 2.1% overall prevalence in the present study. They also reported daytime incontinence in 6.0% girls and 3.8% boys as compared to overall prevalence of 1.9% in the present study [16]. Sampaio, *et al.* [11], in a population-based study based in Brazil, reported a 9.1% prevalence of LUTD as compared to 3.6% overall prevalence in the present study [11]. Lower prevalence in the present study may again have been due to inclusion of older children, a high representation of middle-class families with access to free medical care by the majority.

In our study, a sizeable proportion of teachers were unaware of fluid requirements and toilet requirements of children. Lack of awareness regarding elimination habits of children has been reported previously among schoolteachers [17], and among school nurses [18]. Resistance or conflicting rules regarding toilet requests have been reported as an area of concern for children and adolescents with bladder problems in qualitative studies by in Sweden [19] as well as in the UK [20]. In our study, we report that toilet requests are a stressor for a significant minority of teachers. Instructions to teachers regarding the toilet habits of children may help in mitigating these concerns. Healthcare providers and parents should also be encouraged to involve the school authorities while planning and prescribing urotherapy because individualized health plans with involvement of teachers are reported to improve continence [8].

Anonymous response from parents did not allow analysis of the age-or gender-wise distribution of symptoms. The study was conducted in a population from the middle- and upper-middle class with access to free medical care and its generalizability is therefore limited to such populations. We did not collect data related to presence of uropathies or urinary tract infection. We also did not collect data related to comorbidities of enuresis and LUTD such as screen-time, obesity, scholastic performance, sleep disturbances and behavior disorders.

To conclude, we report the prevalence of enuresis and LUTD in a sub-group of Indian schoolchildren from a

single center, and provide data on teachers' perceptions about toilet requests of school children. Incorporating information on these aspects during teacher-training may address related stress among teachers.

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*Contributors:* RWT: conceptualized the students' aspect of the study, designed the study, modified the DVISS questionnaire, analyzed data, and prepared the manuscript; NT: conceptualized the teachers' aspect of the study, prepared and performed validation of the BBS and THSTI questionnaires, analyzed questionnaires and was involved in preparing the manuscript; SKS: revised the study design, calculated sample size, conducted the survey, analysed the DVISS questionnaires, conducted, biostatistical analysis, revised the manuscript.

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**Web Table I Findings of the Survey Using Teachers' Hassles Due to Toilet Requests (THSTR)**

<i>Item</i>	<i>Problem area (frequency)</i> <i>(n=108)</i>			<i>Problem area (Intensity)</i> <i>(n=101)</i>		
	<i>No.</i>	<i>%</i>	<i>95% CI</i>	<i>No.</i>	<i>%</i>	<i>95% CI</i>
My class gets interrupted due to toilet requests	5	4.6	3.6-5.6	4	4.0	3.0-4.9
My chain of thoughts get interrupted due to these requests	11	10.2	8.8-11.6	7	6.9	5.7-8.1
If I allow one child, it will trigger more requests from other children	27	25.0	23.0-27.0	10	9.9	8.5-11.3
My lesson plan for the day gets interrupted due to these requests	2	1.9	1.2-2.5	3	3.0	2.2-3.8
Children misuse the permission to go to the toilet by distracting the class	7	6.5	5.3-7.6	4	4.0	3.0-4.9
Children misuse the permission to go to the toilet by absenting themselves from the class	3	2.8	2.0-3.6	3	3.0	2.2-3.8
I feel conflicted when I have to allow a child to go to the toilet	2	1.9	1.2-2.5	5	5.0	3.9-6.0
I worry that if I don't allow a child to go to the toilet, he will wet/soil in the class.	17	15.7	14.0-17.5	6	6.0	4.8-7.1
I am held responsible for absenteeism of my student from the class even for a toilet request	10	9.3	7.9-10.6	12	11.9	10.4-13.4
When I deny a toilet request, there is a complaint from the parent	4	3.7	2.8-4.6	5	5.0	3.9-6.0
Parents do not understand the reasons behind my refusal for toilet request	8	7.4	6.2-8.6	2	2.0	1.3-2.6
In my teaching experience, toilet request is a source of stress for me	0			3	3.0	2.2-3.8

## Coronavirus Disease 2019 (COVID-19) in Children - What We Know So Far and What We Do Not

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Pediatric coronavirus disease-19 (COVID-19) infection is relatively mild when compared to adults, and children are reported to have a better prognosis. Mortality in children appears rare. Clinical features of COVID-19 in children include fever and cough, but a large proportion of infected children appears to be asymptomatic and may contribute to transmission. It remains unclear why children and young adults are less severely affected than older individuals, but this might involve differences in immune system function in the elderly and/or differences in the expression/function of the cellular receptor for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)- Angiotensin converting enzyme 2 (ACE2). Laboratory findings and chest imaging may not be specific in children with COVID-19. Diagnosis is by Reverse transcriptase-Polymerase chain reaction (RT-PCR) testing of upper or lower respiratory tract secretions. This review additionally considers COVID-19 in immunosuppressed children, and also suggests a management algorithm for the few children who appear to present with life threatening infection, including the potential use of antiviral and immunomodulatory treatment. The most significant threat to global child health from SARS-CoV-2 is unlikely to be related to COVID 19 in children, but rather the socio-economic consequences of a prolonged pandemic.

**Keywords:** SARS-CoV-2, Pandemic, Management, Immunosuppressed.

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Coronavirus disease-2019 (COVID-19) is a global health crisis. The clinical characteristics, disease progression and outcome in children and young adults appear significantly milder compared to older individuals. Since first being reported in Wuhan, China in December 2019, COVID-19 has rapidly spread to affecting over 200 countries worldwide. Children account for 1-5% of diagnosed COVID-19 cases [1]; although, many infected children may be asymptomatic and therefore not diagnosed without population screening. At the time of writing, in India, the number of virologically confirmed COVID-19 positive cases is 5273 (149 deaths) as per the Ministry of Health and Family Welfare (MOHFW) [2].

### VIROLOGY AND EPIDEMIOLOGY

Coronaviruses are a family of enveloped, single stranded, zoonotic RNA viruses which can rapidly mutate and recombine, leading to novel viruses that can spread from animals to humans [3]. The precise events that led to the emergence of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causing COVID-19 remain

unknown. SARS-CoV-2 is transmitted through inhalation of respiratory droplets of an infected person and touching surfaces contaminated with the virus. In previous coronavirus epidemics, children globally accounted for 6.9% of SARS 2002-3 infections and 2% of Middle East Respiratory Syndrome (MERS) infections. It appears that SARS-CoV-2 has a higher transmission capability compared with the closely related viruses causing SARS 2002-3 and MERS [4]. The true case fatality rate (CFR) of COVID-19 infection is currently unknown due to lack of population-scale longitudinal data. Thus, estimates of CFR currently vary between 0.5-5% [1,5].

### PATHOGENESIS

The SARS-CoV-2 virus utilizes Angiotensin Converting Enzyme 2 (ACE2) receptors as its cell surface receptor, similar to the SARS 2002-3 virus. ACE2 is expressed in highly biciliated epithelial cells in the human lungs and this receptor allows the virus to attach to the cell [6]. The ACE2 receptor is also expressed in the intestines, potentially accounting for the gastrointestinal symptoms that commonly occur in the early stage of the illness.



Severe COVID-19 disease is characterized by three phases: the first being the viral phase; the second being the cytokine storm; and the third encompassing acute respiratory distress syndrome (ARDS), impaired cardiac function and death [7]. The cytokine storm appears to be driven by a dysregulated host immune response [8] and might contribute to mortality [9]. The profile of the cytokine storm associated with severe COVID-19 disease is similar to that of secondary hemophagocytic lymphohistiocytosis (HLH), which is a rare complication of other viral infections (3.7-4.3%) [8]. Secondary HLH is characterized by fulminant and fatal hypercytokinemia with multiorgan failure. In severe infection, lower peripheral lymphocyte counts (CD4 and CD8 T cells), higher interleukin (IL) levels (IL-6 and IL-10), decreased interferon-gamma expression in CD4+ T cells and higher D-dimer and fibrin degradation products (FDP) levels, leading to increased thrombosis and multiorgan injury has been described. Moreover, patients with severe infection may also have abnormal coagulation parameters, perhaps related to high expression of ACE2 receptors in vascular endothelial cells.

## TRANSMISSION

Most infected children are likely to be secondary cases and acquire the infection after exposure to a COVID-19 positive adult, although there are no longitudinal data to confirm this yet. Intra-family transmission may be important [10]. An as yet unquantified proportion of children with COVID-19 is asymptomatic and may contribute to transmission. It is unknown whether COVID-19 is acquired by contact with infected feces [10,11]. In a report of 10 children admitted for COVID-19 with positive nasopharyngeal swabs, 8 of 10 children demonstrated persistently positive real time reverse transcriptase-polymerase chain reaction (RT-PCR) of rectal swabs after their nasopharyngeal testing had become negative [12]. It remains unclear whether the detection of virus by RT-PCR in fecal matter represents active viral replication or residual viral genomic material; however, it appears that viral shedding from the digestive tract might be greater and last longer than that from the respiratory tract [12].

## Why is Covid-19 Milder in Children?

Multiple reports have demonstrated that children and young adults have a milder form of the disease compared to adults [13]. Asymptomatic, mild and moderate infections comprise over 90% of all children who have tested positive for COVID-19 with fewer severe and critical cases (5.9%) compared to adults (18.5%) [13]. The possible reasons for lower number and milder infections in children and young adults include lower

exposure to virions, being isolated at home and minimal exposure to pollution and cigarette smoke contributing to healthier respiratory tracts. The elderly may be susceptible to severe COVID-19 disease by their qualitatively different immune response, encompassed by the terms ‘immunosenescence’ and ‘inflammaging’ [14]. Viral co-infection may be important in potentially leading to limited replication of the SARS-CoV-2 by direct virus-to-virus interaction and competition [15]. Additionally, the distribution, maturation and functioning of viral receptors such as ACE2 may be important in age-dependent susceptibility to severe COVID-19 [13,16].

Due to smaller number of reported cases in children, it is at present challenging to delineate the clinical characteristics of children with severe COVID-19 infection, combined with the lack of a clear biomarker to indicate severity of infection [17]. Dong, *et al.* [13], in the largest pediatric review of 2143 children, described that 13% of virologically confirmed children were asymptomatic. This makes epidemiological inference problematic since asymptomatic children are less likely to be tested and may still contribute to transmission. In addition, a significant proportion of children can also have co-infections with other viruses, and the detection of SARS-CoV-2 may therefore be clinically insignificant [11]. It has been proposed that the outcome for some children may be worse due to exposure to antenatal smoking and obesity [17].

Another theory that has been postulated is the protective role of Bacillus Calmette-Guérin (BCG) vaccine in COVID-19. BCG vaccination has been associated with heterologous immunity to other pathogens, potentially by a phenomenon called ‘trained immunity’ involving innate cells such as macrophages, monocytes and epithelia [18]. Trials are underway to understand if BCG vaccination may offer protection against COVID-19.

## CLINICAL FEATURES

Children of all ages can be infected with COVID-19, with more cases reported in younger children and infants [13]. Acknowledging the possible reporting biases discussed above, there is no age or sex preponderance [13] and the median age of infection is 6.7 years (range-newborn to 15 years) [19]. The incubation period of COVID-19 in children has been reported as 2 days (range-2 to 10 days) [1]. At the time of diagnosis, 13-15% of virologically positive children may be asymptomatic [13,19]. The most common symptoms described at onset in children are fever (50%) and mild cough (38%) [10]. Fever is present in about 40% of

children [19]. Other clinical features include sore throat, rhinorrhea, sneezing, myalgia, fatigue, diarrhea and vomiting. Children may have more upper respiratory symptoms than lower respiratory symptoms [13], and appear to recover in 1-2 weeks [20].

### Risk Stratification and Severity Classification

In the largest pediatric cohort to date, Dong, *et al.* [13] describe suspected and confirmed cases based on symptoms, laboratory abnormalities, chest imaging, and RT-PCR/genomic analysis. The severity of COVID-19 was divided into asymptomatic, mild, moderate, severe and critical. Severe COVID-19 accounted for 18 (2.5%) of virologically confirmed cases, and furthermore the definition of severe included children with only mild hypoxia. Critical COVID-19 was observed in 3 (0.4%) of virologically confirmed cases, defined by the presence of ARDS or organ failure. Though data on chronology of complications and predictors of mortality is available in adults, there is insufficient data on predictors of mortality in children.

### DIAGNOSTIC TECHNIQUES

The Ministry of Health and Family Welfare (MOHFW) [2] in their updated guidelines (as of 7 April, 2020) has categorized patients into three groups – those with mild, moderate and severe illness, and have designated COVID dedicated facilities for their treatment.

RT-PCR testing of nose and throat swab for detection of SARS-CoV-2 nucleic acid has been recommended as the confirmatory test for COVID-19 [21]. Other alternative samples for RT-PCR include bronchoalveolar lavage or endotracheal aspirate. The Government of India has now advised the use of antibody tests in patients with symptomatic influenza-like illness (ILI) in 25 districts across the country, or ‘COVID hotspots’ [22]. Based on the results of the antibody test, confirmatory RT-PCR and clinical assessment, hospital treatment or home isolation measures are instituted, with contact tracing measures as per protocol.

The limited data in children describes relatively lower rates of lymphopenia and elevated inflammatory markers compared to adults [1]. Henry, *et al.* [23] summarized the findings from 12 studies on 66 children and reported normal leucocyte counts (69.2%), neutropenia (6.0%), neutrophilia (4.6%) and lymphopenia (3.0%). C-reactive protein (CRP) and procalcitonin were high only in 13.6% and 10.6% of cases, respectively. Slight elevation of liver transaminases is common [23]. It is recommended to monitor the lymphocyte count and CRP as signs for severe infection, while using procalcitonin levels to

detect potential bacterial co-infection [23].

Chest X-ray findings in children appear to be non-specific. Children with mild disease should not routinely need computed tomography (CT) chest imaging in view of the high radiation exposure [24]. When CT is performed, ground glass opacities is seen in one third of patients [19]. Peripheral distribution of lung lesions has been noted, with multilobar involvement [25]. Consolidation with surrounding halo sign is considered typical of pediatric patients [26]. However, chest CT alone cannot accurately diagnose COVID-19 due to similar radiological presentations with other infections.

Patients admitted with severe infection are known to have elevated plasma levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor (GCSF), interferon-gamma-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1-alpha (MIP1A) and tumor necrosis factor (TNF) alpha [9]. In a study comprising of 150 confirmed COVID-19 cases in Wuhan, China, elevated ferritin (mean 1298 ng/mL vs 614 ng/mL;  $P < 0.001$ ) and IL-6 levels ( $P < 0.0001$ ) were found in survivors compared to non-survivors [7]. These cytokines are produced by inflammatory macrophages which have been implicated in the cytokine storm. This is similar to previous outbreaks of MERS and SARS 2002-3 in terms of having high proinflammatory cytokines in patients with severe disease [27].

### MANAGEMENT OF PEDIATRIC COVID-19

Upon suspicion of COVID-19 infection, immediate Infection prevention control (IPC) measures must be instituted. Standard precautions such as hand hygiene, use of personal protective equipment (PPE), safe waste management and cleaning and disinfection of equipment must be followed as per the guidelines issued by the MOHFW [2].

For the few children who will require admission to a healthcare facility, the cornerstone of management is supportive therapy including adequate nutrition and calorie intake, fluid and electrolyte management and oxygen supplementation. Communication with parents and alleviating anxiety is an important part of management. In adults with severe COVID-19, early intubation and mechanical ventilation with lung protective strategies and prone positioning has been recommended [20]. Antibiotics may be indicated if bacterial super-infection is suspected.

There are no randomized clinical trial data to guide treatment of the very few children that present with life-threatening COVID-19 including severe pneumonia,

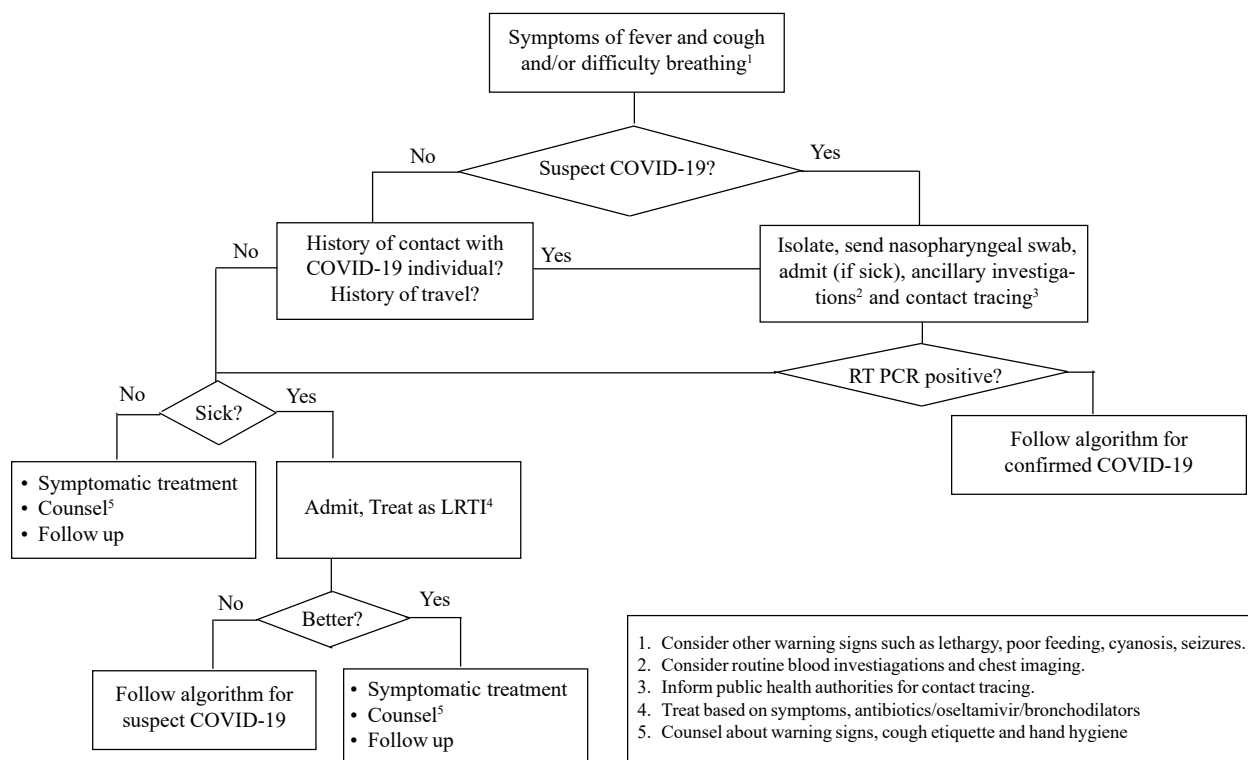
ARDS, sepsis and septic shock. Hence, the World Health Organization has not recommended any specific treatment for children until the results of ongoing clinical trials are available. We strongly believe that clinical trials of all therapeutic agents for COVID-19 are needed in children as well. It is important that when such clinical trials are open, children are treated only in the context of clinical trials and not outside these. In the absence of data from these trials, clinicians may be left in the difficult scenario of deciding whether to pursue treatment with antiviral drugs and immunomodulatory therapies for children with severe COVID-19. A relatively new antiviral drug being tested in adults with COVID-19 is remdesivir, which in combination with chloroquine has been found to inhibit SARS-CoV-2 growth *in vitro* [28]. Interferon alpha-2b and oral lopinavir/ritonavir together with corticosteroids for complications and intravenous immunoglobulin for severe cases has been recommended in one report in China [29]. A HIV test should be performed before commencing antiviral treatment, in particular lopinavir/ritonavir.

The MOHFW has allowed off label use of hydroxychloroquine in combination with azithromycin in adults with severe disease and requiring intensive care [2].

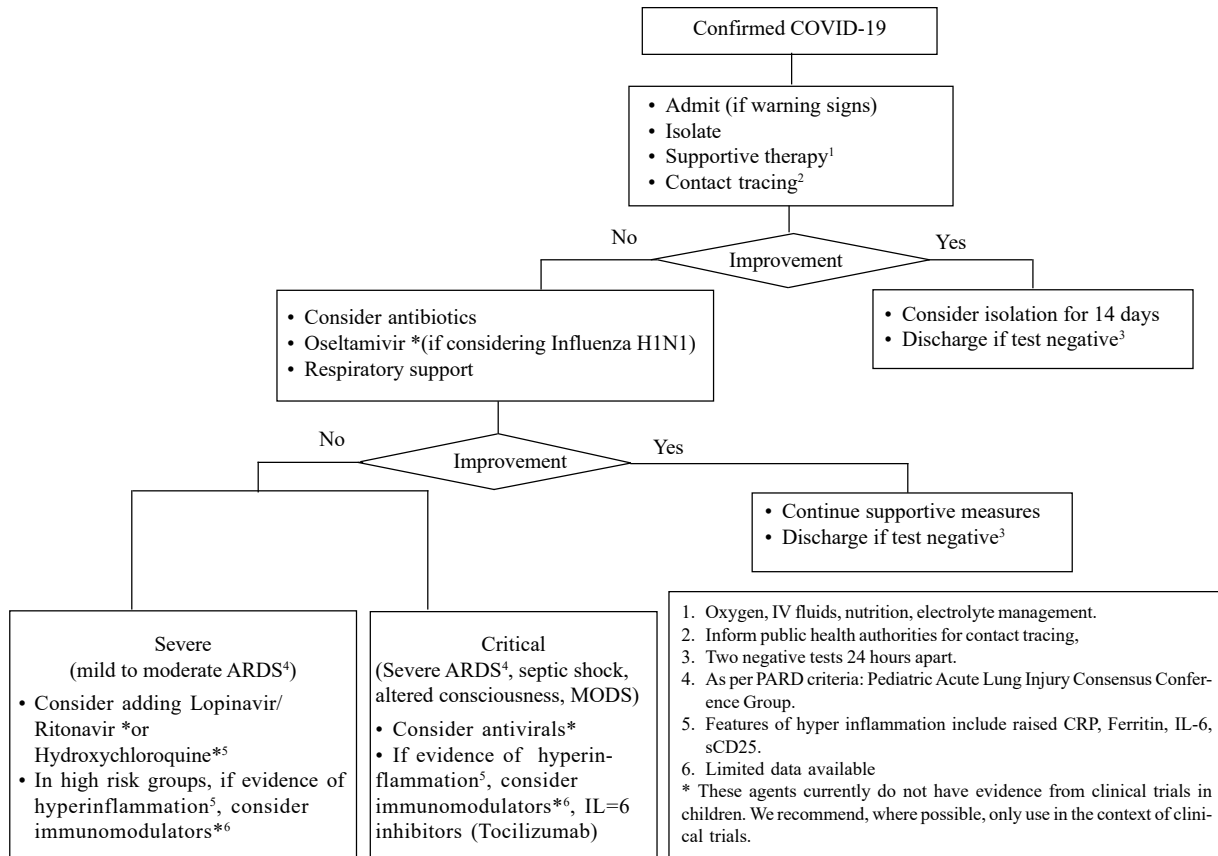
However, these treatments are not currently recommended in children below the age of 12 years. Corticosteroids are not routinely recommended and might exacerbate COVID-19 associated lung injury [30]. Ivermectin, the broad spectrum anti-parasitic agent, has *in vitro* antiviral action against SARS-CoV-2 [31].

Owing to the cytokine storm syndrome in COVID-19, there may potentially be a role of immunomodulators in treating patients with severe infections to ameliorate pulmonary inflammation and hopefully improve mortality. There is an established role of anakinra (IL-1 blockade) in survival benefit of patients with hyperinflammation, without increased adverse events [8]. A multicenter randomized control trial (RCT) of the IL-6 receptor blocker, tocilizumab is in progress in China for adults with COVID-19 pneumonia and raised IL-6 levels (ChiCTR2000029765) [32]. There may also potentially be a role of janus kinase inhibitors (JIKI), since these drugs block downstream inflammatory pathways and may alter cellular viral entry [33].

A suggested management algorithm based on the limited observational data from adults is depicted in **Figs. 1** and **2**. The common drugs used in COVID-19 are detailed in **Table I**. It is important to note that very few



**Fig.1** Suggested algorithm for case management of children with COVID-19 symptoms.



**Fig. 2** Suggested algorithm for case management of confirmed COVID-19 (Adapted from the BPAIIG Position Statement: SARS CoV2 Treatment Guidance version 1.2) [37].

**Table I Medications for Coronavirus Disease 2019 (Covid-19)**

Drug	Indication/Limitation
Paracetamol	<ul style="list-style-type: none"> <li>Recommended antipyretic (Avoid ibuprofen)</li> </ul>
Oseltamivir	<ul style="list-style-type: none"> <li>To be considered in influenza H<sub>1</sub>N<sub>1</sub> is differential</li> </ul>
Lopinavir /Ritonavir	<ul style="list-style-type: none"> <li>Can be considered if no improvement/severe infection</li> <li>Do not co-administer with hydroxychloroquine</li> <li>Limited data available on benefit in children</li> </ul>
Remdesivir	<ul style="list-style-type: none"> <li>Used as experimental drug in adults, limited data available on benefit in children.</li> </ul>
Hydroxychloroquine	<ul style="list-style-type: none"> <li>Can be used if no improvement/severe infection in children &gt;12 years</li> <li>Do not co-administer with azithromycin</li> <li>Limited data available on benefit in children</li> </ul>
Azithromycin	<ul style="list-style-type: none"> <li>Can be considered if no improvment/severe infection</li> <li>Limited data available on benefit in children</li> </ul>
Ivermectin	<ul style="list-style-type: none"> <li>Has shown <i>in vitro</i> anti-viral activity</li> </ul>
Immunomodulators	<ul style="list-style-type: none"> <li>Can be considered in suspected hemophagocytic syndrome</li> </ul>
<ul style="list-style-type: none"> <li>IL 1 inhibitor (Anakinra)</li> <li>IL 6 inhibitor (Tocilizumab)</li> </ul>	Not available in India Limited data available on benefit in children

children with COVID-19 are likely to need any specific therapy other than supportive treatment, and the decision to start antiviral or immunomodulatory treatment should therefore be made carefully in consultation with experts in pediatric infectious disease and immunology. Given that severe COVID-19 appears very rare in children, an important part of this assessment is ascertaining whether a positive RT-PCR for SARS-CoV-2 is a clinically important factor in explaining the child's condition, or whether more occult pathology may be responsible.

For neonatal management of COVID-19 infected mothers, it is recommended to have a separate room adjacent to the delivery room for neonatal resuscitation or for resuscitation staff to maintain at least a 2 meter gap between the infected mother and newborn [34]. Only essential personnel should attend the delivery with full PPE, with the mother following meticulous hand hygiene and wearing a mask. Standard neonatal resuscitation measures are to be followed and positive pressure ventilation if needed should be provided by a self-inflating bag and mask rather than a T-piece resuscitator. If the baby requires intensive care, a single patient room is ideal preferably with negative pressure. The baby should be tested at 24 hours of life and repeat testing should be performed at 48 hours. Antivirals/hydroxychloroquine/steroids or intravenous immunoglobulin (IVIG) should not be administered to the newborn. The baby should then be tested every 48-72 hours until two consecutive negative tests. It is critical that breastfeeding should be encouraged with the mother wearing a mask. The baby should be vaccinated prior to discharge from the hospital.

### IMPACT ON IMMUNOSUPPRESSED CHILDREN

Data on children with immunocompromised conditions and COVID-19 are scarce, but severe disease may be more common in adults with cancer [35]. Despite concerns that immunocompromised children may have severe infection analogous to infection with adenovirus, rhinovirus, influenza, respiratory syncytial virus, and experience from previous pandemics (such as influenza H1N1), Antiga, *et al.* [36] described that children who were immunocompromised were not at greater risk of severe COVID-19, probably owing to the fact that a functional host innate immune response is the main driver for lung damage. In Bergamo, among 200 transplant recipients including 10 inpatients, 100 with autoimmune liver disease and three undergoing chemotherapy for hepatoblastoma (inpatients), none had clinical pulmonary disease, despite the fact that 3 patients tested positive for SARS-CoV-2, suggesting that the immunocompromised may be protected by their

weaker immune response. No data is available on severity of COVID-19 infection in children with malnutrition, rheumatic heart disease or Human Immunodeficiency Virus (HIV) positive children.

### THE FUTURE

Several vaccines against SARS-CoV-2 are in development; however, it remains unclear when a successful vaccine might be rolled out. Studies on factors responsible for immune dysregulation may provide insights into developing vaccines capable of inducing durable protective immunity and avoiding vaccine-related adverse events.

This unprecedented pandemic should prompt improved global surveillance of infectious diseases, as well as cooperation and communication so that the global society remains interconnected and limits the spread of this outbreak.

Lastly, we fear the greatest impact on children from COVID-19 is likely to be delayed presentation of other childhood illnesses due to fear and ignorance amongst parents/families. This coupled with the impact of economic uncertainty on those in the low socio-economic strata, is likely to have a greater adverse impact on child health in India in these uncertain times.

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## Pediatric Renovascular Hypertension: Manifestations and Management

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Renovascular hypertension (RVHTN) is an important contributor to secondary etiologies of hypertension in the pediatric population. A delay in diagnosis can be associated with adverse outcomes. The etiologies of renal artery stenosis (RAS) vary from anatomical, inflammatory, genetic syndromes, intra-luminal, external compression and idiopathic. It is a silent disease with isolated hypertension as its primary clinical manifestation. Laboratory values can be notable for electrolyte derangements and renal dysfunction, but are not universally present. The diagnosis requires a high index of clinical suspicion and entails ruling out other secondary causes of hypertension while monitoring for target organ damage. Imaging of individuals with suspected RAS includes: renal ultrasound, computed tomography angiography, magnetic resonance angiography and renal scintigraphy, but angiography continues to be the gold standard. Various factors are used to determine the most appropriate method for ongoing care: anti-hypertensive therapy, with or without radiological or surgical intervention. In all instances, a multi-disciplinary team approach should be used to provide optimal care to these children and adolescents.

**Keywords:** Blood pressure, Fibromuscular dysplasia, Renal artery stenosis, Renal imaging.

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In children and adolescents, renal artery stenosis (RAS) accounts for up to 10% of the secondary causes of hypertension. Glomerular disease and renal parenchymal scarring are responsible for an additional sixty percent [1-3]. RAS is a heterogeneous disease process that includes intrinsic lesions of the renal arteries, extrinsic compressive masses, and intraluminal thrombosis that impede renal blood flow [4]. There is an increased risk of developing cardiac and neurologic complications in adulthood (*i.e.* myocardial infarction, stroke) when childhood onset renovascular hypertension (RVHTN) is not adequately managed [5]. There needs to be a high index of clinical suspicion to appropriately diagnose and manage RVHTN in children. Unlike adults where 70-80% of patients have largely non-correctable atherosclerotic lesions, children with RAS often have lesions that are amenable to therapeutic intervention [1]. The protean clinical and laboratory manifestations of RVHTN in children creates a significant challenge in diagnosis that may contribute to chronic kidney disease and target organ damage [5]. Given these difficulties, there is a need for a standardized approach to the diagnosis and management of RVHTN in children and adolescents [6]. In this review, we will examine the clinical findings, diagnostic studies, management, and intervention for pediatric RAS-associated hypertension. This information will hopefully contribute to future standardized recommendations to the approach and management of RVHTN in children and adolescents.

### ETIOLOGY

In contrast to adults where the main cause of RAS is from atherosclerosis, the etiologies in the pediatric population vary by disease process and by geography. The major contributor to pediatric RAS in North America and Europe is fibromuscular dysplasia (FMD), as opposed to Takayasu arteritis (TA) in Asia and South Africa [7,8]. The etiologies of RAS in children and adolescents are all summarized in **Box I** [7,9].

### CLINICAL CLUES

RAS is often a 'silent' diagnosis with many non-specific symptoms. We aim to summarize the most recent findings acknowledging the paucity of clinical features while understanding the concern for complications from long-standing renovascular-associated HTN.

*History:* The age of the child can be crucial in directing the differential of pediatric RAS. As an infant, there is a higher pre-test probability of having a thrombosis or emboli from a catheter site as opposed to the young child where syndromes and inflammation play a larger role [10]. The odds of detecting a secondary cause of hypertension are inversely proportional to the age of the child, creating an emphasis on early diagnosis [11]. In FMD, the mean age of diagnosis was 8.4 years with a range from 16 days to 17 years [12]. Most children often report non-specific symptoms including headache, and abdominal, and flank pain [12]. In contrast to adults,



### Box I Causes of Renal Artery Stenosis in Children and Adolescents

#### Non-inflammatory

Fibromuscular dysplasia  
Mid-aortic syndrome

#### Inflammatory

Takayasu arteritis  
Kawasaki disease  
Polyarteritis nodosa

#### Syndromes

Neurofibromatosis type 1  
Tuberous Sclerosis  
Williams' syndrome  
Marfan's syndrome  
Alagille syndrome  
Turner syndrome  
Congenital rubella

#### Localized tissue damage

Trauma  
Radiation

#### Extra-luminal

Compression by mass  
Wilms' tumor, Neuroblastoma, Other

#### Intra-luminal

Catheter-related thromboembolic disease  
Hypercoagulable states – nephrotic syndrome

#### Surgical

Transplant renal artery stenosis

#### Idiopathic

children may find it difficult to characterize common symptoms associated with hypertension, such as tinnitus or blurry vision [12]. A retrospective study in Israel noted behavioral changes within the 3-12 months prior to diagnosis of RVHTN that included hyperactivity, restlessness, and attention deficits [13]. This creates a conundrum for physicians that are evaluating these patients, as increased blood pressure can be missed or incorrectly diagnosed.

**Family history and genetics:** When referring to the etiologies of RAS, one of the largest categories include RAS-associated syndromes (**Web Table I**). Although the discovery of new genes continue to grow, data has shown that approximately 11%-60% of RAS cases are familial [7]. In a cohort of 93 children with RAS and mid-aortic syndrome (MAS) in Canada, 26% had an underlying genetic disease, 24% had an inflammatory process, and 50% were idiopathic [10]. Of the children with genetic conditions, about 40% had neurofibromatosis type 1 (NF-1) and the remaining had William syndrome or Alagille syndrome [10]. Within the FMD registry, there are a significant number of pediatric patients with a

family history of FMD in comparison to the adults, supporting a stronger familial genetic inheritance in pediatric FMD-related vascular disease [12,14]. In addition, children and adolescents with underlying genetic or inflammatory syndromes are more likely to have extrarenal vascular involvement including visceral and proximal aortic branches [10].

**Blood pressure measurements:** The physical examination in children and adolescents with RAS is most often unrevealing, which can cause a delay in diagnosis. The most common finding is of isolated hypertension. It is estimated that 26-70% of renovascular disease presents with hypertension in an otherwise asymptomatic child [15,16]. A report from the Midwest pediatric nephrology consortium in 2010 found no difference in age, weight distribution, or stage of hypertension when trying to differentiate between primary and secondary hypertension [17]. However, children with RAS typically present with stage 2 hypertension [18]. The likelihood of identifying a secondary cause of hypertension such as RAS has been found to be directly related to the degree of blood pressure elevation [11,19].

Other factors that must be taken into consideration include when and how the blood pressure measurements are taken in the clinical setting. Children in the United States start getting blood pressure measurements at the age of three unless they fall into a high-risk category. Unfortunately, some children may be referred with a history of elevated blood pressures after several clinic visits without intervention or evaluation due to the concern of inaccurate readings in an asymptomatic child [7]. Appropriate blood pressure readings are essential, which include the following: (i) appropriate cuff size; (ii) sitting position; (iii) right upper extremity; (iv) calm environment; and (v) after 3-5 minutes of rest. When the blood pressure is found to be elevated for the first time, four extremity blood pressures are obtained to evaluate for coarctation of the aorta and MAS [9].

**Physical examination:** Physical findings of RAS-associated syndromes are detailed in **Web Table I**. Children with Takayasu arteritis typically have constitutional symptoms and signs secondary to inflammation. This includes arthralgia, skin rashes, abdominal bruits, and absence of pulses [20]. In FMD, bruits can sometimes be heard overlying the epigastrium (7.4%), carotid arteries (7.4%), and flank (7.7%) [12]. For patients with MAS, a mid-abdominal murmur is a classic finding [4].

There is a subset of pediatric patients that present with secondary signs of target organ damage related to hypertension, including neurological (10-15%) and cardiac findings (7%) [4,15]. The neurological symptoms

can range from headache, seizures, stroke, to cranial nerve palsies [7,21]. Bell palsy is the most commonly identified cranial nerve palsy [15]. One study showed that older children are more likely to have cardiac findings of palpitations, murmur, or signs of congestive heart failure, with 10% of them having an underlying syndrome [3,12]. Ocular findings are specific to syndromes such as Alagille, but can be present as a non-specific sign of hypertensive retinopathy [3].

### LABORATORY EVALUATION

To evaluate for RVHTN, laboratory and imaging diagnostic tests need to be ordered in a step-wise fashion. An initial basic metabolic panel is appropriate to determine if there are signs of renal dysfunction (azotemia, elevated creatinine) or electrolyte derangements defined by hyponatremia, hypokalemia, and alkalosis suggestive of RAS.

*Sodium:* There have been a few pediatric cases of unilateral renal artery stenosis that presented with marked hyponatremia. This is termed hypertensive hyponatremic syndrome (HHS) [22]. The hyponatremia is postulated to occur from hyperactivation of the renin-angiotensin-aldosterone system (RAAS) with substantial increase in angiotensin II production directly causing arterial vasoconstriction. This results in a pressure natriuresis from the contralateral kidney that has normal function. The severity of the hyponatremia can be compounded by a reactive secretion of anti-diuretic hormone from the transient volume depletion [22,23].

*Potassium:* The presence of hypokalemia is rare, but is seen in the setting of unilateral RAS. With decreased perfusion to the affected kidney there is activation of the RAAS system with secondary hyperaldosteronism resulting in hypokalemia due to excessive urinary potassium loss [24]. Ultimately, this can be corrected with either improvement of the renal ischemic state or with blockade of the RAAS.

*Creatinine:* In unilateral disease, the serum creatinine concentration remains normal through compensation of the healthy kidney. However, monitoring is essential. Bilateral disease can have decreased renal function in the setting of hypoperfusion and can be exacerbated if angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) are initiated [24]. After anti-hypertensive medication is started for BP control in children with RAS, a metabolic panel including creatinine should be checked within 1-2 weeks to ensure that there is no evolving kidney injury.

*Urinalysis:* With unilateral RAS and prolonged ischemia to a single kidney, there may be compensatory

hypertrophy of the contralateral kidney, resulting in glomerular hyperfiltration. This phenomenon combined with chronic activation of the RAAS can lead to proteinuria and glycosuria, biomarkers of sub-clinical damage to an otherwise normal kidney.

*Plasma renin activity (PRA):* The PRA level is dependent on age, sodium intake, posture, and oscillates in a diurnal pattern. All these factors make a PRA value difficult to interpret. It can also be suppressed in primary essential hypertension in African Americans and various forms of monogenetic hypertension (e.g., Liddle syndrome). Studies have shown normal PRA values in 20%-37% of patients with unilateral RAS [25]. With bilateral RAS, the child is likely to have normal renin and aldosterone levels [1]. This is due to volume-dependent hypertension, after initial RAAS activation and volume retention there is subsequent suppression of renin release [26,27]. Given the low predictive value of PRA, further investigations need to be performed if there is a high index of clinical suspicion for RAS [27].

### RADIOLOGICAL IMAGING

There is no single screening, radiological study that can effectively exclude all the causes of RAS in children. There is an ongoing evaluation to identify modalities that are more sensitive and specific in diagnosing RAS (**Table I**) [7,8,28,29]. This is important from the patient perspective given that the gold standard for the diagnosis of RAS in children and adolescents continues to be the percutaneous angiogram, which is an invasive procedure.

*Renal bladder ultrasound (RBUS) with doppler:* A RBUS is the appropriate first line of imaging given its advantages (**Table I**) and the ability to assess for other secondary causes of hypertension including a mass, venous thromboembolism, renal dysplasia, and scarring [30]. It can provide valuable assistance in monitoring progression of RAS after angioplasty by specifically measuring the peak systolic velocity (PSV) and resistive indices of the affected vessel [31]. The many limitations of the doppler US include the difficulty in assessing small vessels, age-dependent cooperation, body habitus and operator proficiency. In children, when compared to angiography, it has a 27% sensitivity as a diagnostic alternative. Although, there are reports of better specificity ranging from 70-100% in both adult and pediatric populations [12,14]. Contrast enhanced ultrasound, a relatively newer modality, has shown improved sensitivity ranging from 79-100% for diagnosis of RAS and may be a better initial screening study [32].

**Table I Imaging Modalities for Renal Artery Stenosis**

<i>Modalities of imaging</i>	<i>Advantages</i>	<i>Disadvantages</i>	<i>Sensitivity</i>	<i>Specificity</i>
Renal Bladder Ultrasound (RBUS) with Doppler	Easy availability, non-invasive, fast, no radiation, simple, low cost	Operator-dependent, age-dependent cooperation, body habitus, may miss small lesions high false positive and false negative	27-63%	70-100%
Magnetic resonance angiography (MRA)	No radiation, improved image quality	Limited intrarenal vessel visualization, longer study, may require anesthesia, compromised by respiration	62-98%	70-96%
CT angiography (CTA)	Fast, improved image quality, not compromised by respiration	Requires radiation, limited intrarenal vessel visualization	64-100%	62-97%
Renal scintigraphy	Non-invasive, inexpensive	Low predictive probability, reduced accuracy in renal failure, does not visualize the vessels; inconsistent data	59-73%	68-88%
Digital subtraction angiography (DSA)	Detailed imaging of aorta and all branches, can transition to a therapeutic intervention	Radiation, requires anesthesia	100%	100%

*Magnetic resonance angiography (MRA):* An MRA provides detailed renal size and blood flow without exposure to radiation [14]. This is an appropriate study to assess the aorta and main renal arteries with limited visualization of intrarenal vessels. In adult studies, MRA's has shown to have a sensitivity of 92-98% and specificity of 70-96% in diagnosis of renovascular disease, particularly for atherosclerotic-associated RAS [33]. Limitations of MRA include its inability to assess involvement of segmental renal vessels. It can exaggerate the degree of narrowing within the main renal artery given lack of adequate spatial resolution compared with a computed tomography angiography [34]. In a pediatric cohort comparing US, MRA, and CTA in 25 patients with FMD, the MRA imaging study demonstrated a sensitivity of 62.5% for RAS detection with 100% specificity [8].

*Computed tomography angiography (CTA):* A CTA exposes the patient to radiation; however, radiation minimization protocols can be used to reduce this unwanted effect. CTA can depict the renal arteries with its first branches, kidney size, parenchymal wall thinning/scarring, and is not compromised by respiration as opposed to an MRA [29]. The CTA has proven to be the best and fastest alternative to an angiography in detecting RAS and renal artery aneurysms. The sensitivity has been shown to be as high as 84.2% in a pediatric study [8]. It can specifically detect thin webs that can be present in FMD that may be missed on MRA [29]. Within the adult population, it rivals an MRA with a sensitivity range of 64-100% and specificity range of 62-

97% [33]. Recent studies show that reconstruction techniques of CTA can reduce noise and improve accuracy of vessel diameter measurements [35,36].

*Renal scintigraphy:* Renal scintigraphy is a nuclear medicine study that is non-invasive and safe. A radioactive tracer, 99m-technetium-dimercaptosuccinic acid (<sup>99m</sup>Tc-DMSA) or 99m-Tc-mercaptoacetyl-triglycine (<sup>99m</sup>Tc-MAG3), is used to assess renal function with administration of an angiotensin-converting-enzyme inhibitor (ACEi). The renogram curve can suggest vessel narrowing by demonstrating time to peak activity and delayed washout. It has a low predictive probability and is an image that does not directly visualize the vessels. The results have continued to be inconsistent and the test has fallen out of favor in comparison to the prior modalities [29].

*Renal vein renin sampling:* Renal vein renin sampling is an invasive test that entails taking a blood sample from the inferior vena cava and comparing it to samples taken from the main renal veins. This test requires an anesthesiologist, and can be performed in conjunction with a diagnostic angiography *via* a femoral approach. The data allows one to identify the ischemic focus, which can be localized to the specific kidney that is involved. Given that imaging has progressed over the years and that selective renal vein sampling has low sensitivity (74%) and specificity (59%), it is not as commonly used [37]. In adults, the American college of cardiology/American heart association guidelines no longer recommend using it for detection of RAS [38].

*Digital subtraction angiography (DSA):* Renal angiography continues to be the gold standard and provides detailed imaging of the aorta and all of its branches. This entails injection of contrast *via* a percutaneous catheter into the aorta and main renal arteries. It is the most invasive out of all the tests, requires radiation exposure, and anesthesia for children and adolescents. The benefit of the angiogram includes the detailed vasculature that highlights occlusion of renal vessels and collateral vessels. It can be transitioned to a therapeutic intervention (angioplasty) or used to provide exact information for next steps in the management of RAS. A retrospective study was performed to evaluate the accuracy of US, MRA, and CTA in comparison to a DSA in 127 children with suspected RAS. The study demonstrated low sensitivities for the former modalities: 63%, 88%, and 80%, respectively [33]. Thus, the DSA remains the cornerstone for accurate diagnosis or exclusion of RAS.

## MANAGEMENT OF RAS

### *Initial Blood Pressure Management*

Pre-intervention is directed at blood pressure management with an appropriate antihypertensive agent and controlled reduction. Until bilateral RAS or unilateral RAS to a single kidney is excluded, treatment should be initiated with a vasodilator and/or a beta blocker. Once the former is excluded, an ACEi or ARB can be started. RAAS blockers are relatively contraindicated in critical main RAS and bilateral RAS, but can be used with segmental stenotic lesions [18]. In addition to in-office blood pressure monitoring, 24-hour ambulatory blood pressure monitoring (ABPM) can provide valuable information about control. In a study of 10 children with RAS on antihypertensive treatment with normal in-clinic blood pressure readings only two had adequate control by 24-hour ABPM [39]. **Fig. 1** outlines the initial evaluation and management of children with suspected RAS.

### *Treatment Options*

Treatment of RAS includes continuation of medical therapy with no intervention, or intervention through percutaneous transluminal angioplasty (PTA) or surgery. The goal of invasive treatment is to preserve renal function with restoration of renal perfusion, and to aid with blood pressure control [40]. The therapeutic decision algorithm is influenced by the patient anatomy, disease etiology, and clinical expertise of the institution [1].

### **Continuation of Medical Therapy**

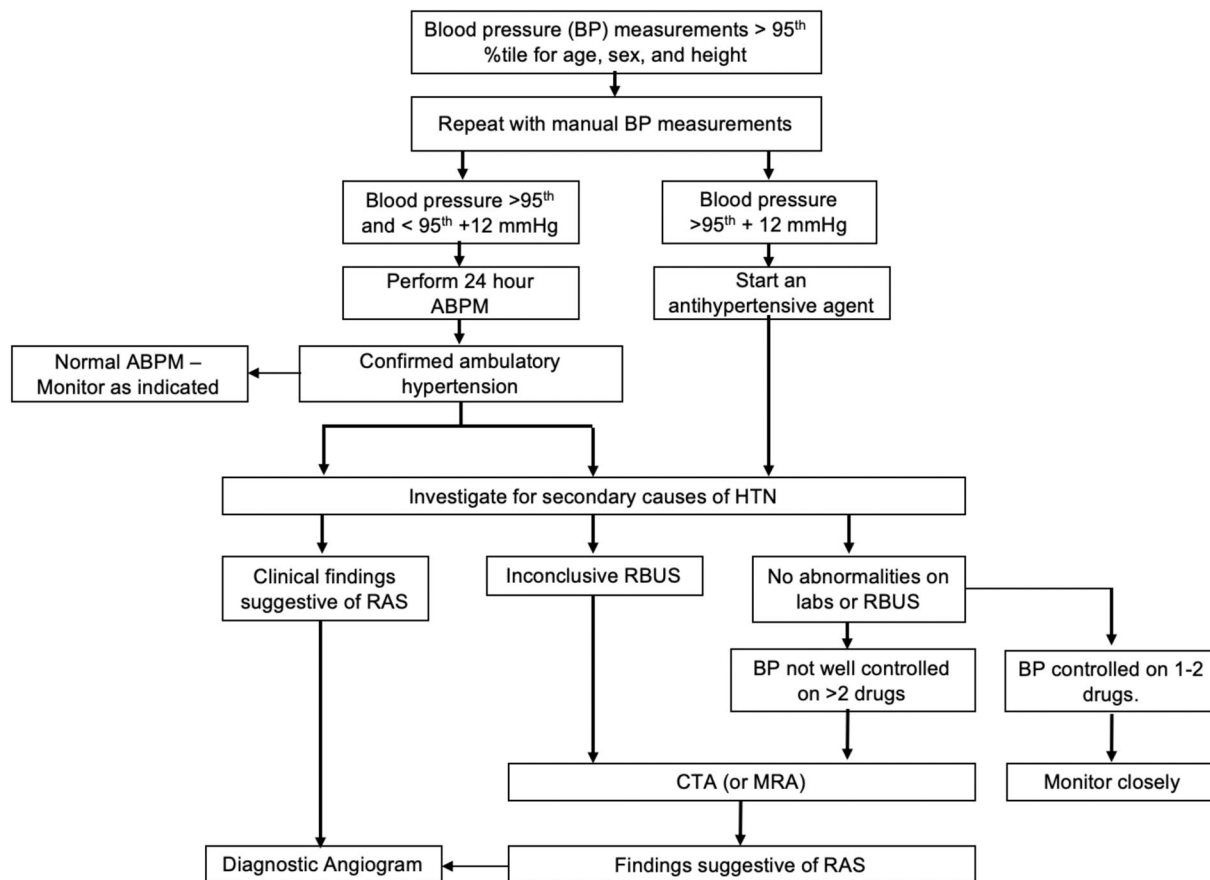
Continuation of medical therapy includes patients who

are still being evaluated for RAS and those who are not eligible for angioplasty or surgical intervention due to unacceptable risk or not technically feasible. In addition, at least half of the children that undergo an interventional radiology or surgical procedure will require continued medical therapy [8]. Patients who are not deemed eligible for intervention tend to have a poorer response to initial medical treatment and will require use of multiple antihypertensive agents from different classes to control their blood pressure. A trial of ACEi or ARB can be used in these patients with careful monitoring of renal function and after discussion about the risks and benefits with the family [7]. Taking a non-invasive approach to the management of blood pressure presents its own set of challenges related to medication adherence and drug side effects [1]. In small children, it may be prudent to wait for the child to complete puberty prior to attempting an intervention, this is particularly true for children with mid-aortic syndrome [41].

### **Interventional Radiology**

Many pediatric centers use PTA as first line therapy for RAS lesions of  $\leq 10$  mm, but a surgical approach is appropriate when the RAS is complicated by stenotic lesions  $>10$  mm, multiple stenosed large vessels, or bilateral RAS [42-44]. PTA is performed under general anesthesia with femoral or brachial artery access to introduce a long vascular sheath or a guide wire to the renal arteries. Intra-procedure anticoagulation is performed with heparin. The balloon diameter used for dilation varies with age and vessel size, which can be determined by measuring the adjacent, normal renal artery distal to the post-stenotic dilation or contra-lateral artery [44]. In resistant stenoses, use of the cutting balloon has been most successful in our center (**Fig. 2** and **3**). Renal artery stenting is another option when there are lesions that show elastic recoil or restenosis after conventional or cutting balloon angioplasty [44]. However, this is controversial, given that the long-term outcome is unknown including in-stent restenosis rates and limitation of future surgeries. In our institution, renal artery stent placement is avoided and is only used in emergent situations as a temporary bridge to surgical repair.

Adult studies have shown that the benefit from a primary angioplasty was as high as 93-98%, and in children cure or improvement is seen in over 50% of cases [3,43]. Complications associated with PTA include arterial spasm, dissection, and perforation of vessel [7]. Patients who have an inadequate response to PTA usually develop worsening hypertension within months post procedure [44].



ABPM: Ambulatory blood pressure monitoring, RBUS: Renal bladder ultrasound; RAS: Renal artery stenosis, MRA: Magnetic resonance angiography, CTA: CT angiography, HTN: Hypertension.

Fig. 1 An approach to the diagnosis of renal artery stenosis in children and adolescents.

## Surgery

Surgical approaches are primarily used when there is refractory hypertension after angioplasty, conservative medical therapy, or vascular lesions that are not amenable to angioplasty [7,44]. Patients with MAS, long segment stenosis, and aneurysms are best treated with a surgical approach. Surgical procedures include renal artery re-implantation onto an adjacent portion of normal aorta and aorto-renal bypass that uses a conduit of autogenous vessel or prosthetic material to connect the renal artery beyond the stenosis to the aorta. Patch aortoplasty and aortic bypass can be used for MAS [45].

In a published series of children and adolescents, surgical intervention has a cure rate of arterial hypertension in 70-82% and improved blood pressure measurements in 12-27% [41,46]. Cure rates in smaller case series are reported between 36-70% [44-46]. In

select cases with a poorly or nonfunctional kidney and unilateral disease, a nephrectomy can be performed that can result in long-term normotension [47].

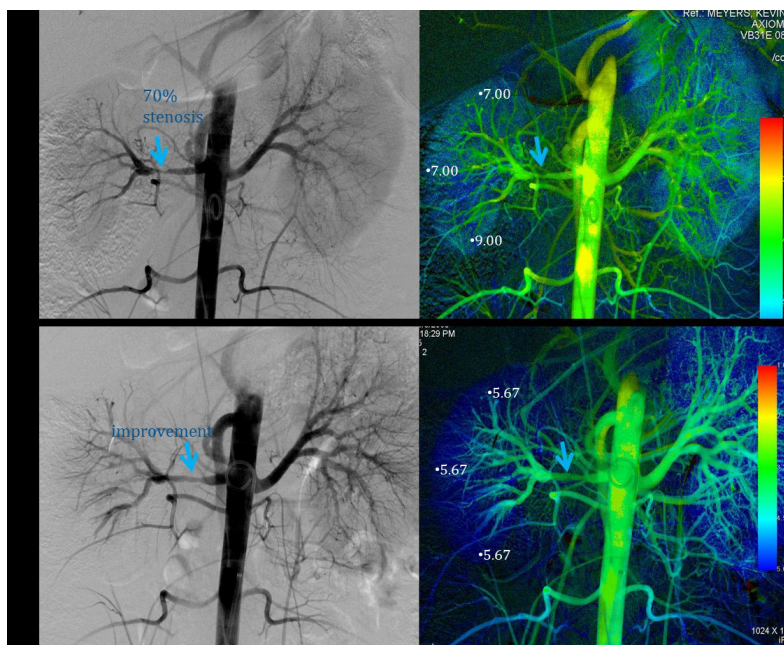
## CONCLUSIONS

RVHTN is an important cause of secondary hypertension in children and adolescents. A heightened clinical suspicion for RAS should be present when blood pressure control is refractory to multiple antihypertensive medications, an abdominal bruit is present, or in the setting of RAS associated syndromes. Medical management includes antihypertensive drug therapies for adequate blood pressure control. Meanwhile, a multidisciplinary team is essential in providing individualized care, and guidance on interventional radiology/surgical procedures.

*Contributors:* LV: corresponding author of the paper, coordination of the review article from planning,



**Fig. 2** (a) and (b): Marked stenosis near the origin of the right main renal artery (arrow) which supplies the upper and mid kidney with diminutive size and delayed perfusion of the right kidney (star) compared to the left; (c) and (d) Panel C and D: Successful, uncomplicated cutting balloon angioplasty of a tight right main renal artery stenosis in a 5-year-old girl with renovascular hypertension. Perfusion to the right kidney normalized on angiography following the angioplasty.



**Fig. 3** Sixteen-year-old female with hypertension and main right renal artery stenosis. Post angioplasty with 4 mm balloon significant improvement is noted in the >70% stenosis with improved time to parenchymal perfusion (TTP) noted on color parametric imaging with the patient now normotensive and off antihypertensive medications.

literature review, drafted the manuscript, designed tables, and finalized the submission; AMC: creation of figures, provided help with literature review and design of the paper, reviewed the manuscript; and KM: design and format of the paper, designed tables, reviewed the manuscript, and provided extensive input in finalized submission. All authors approved the final version of manuscript.

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**Web Table I Genetic Syndromes Associated with Renal Artery Stenosis in Children and Adolescents**

<i>Genetic condition</i>	<i>Mutation</i>	<i>Inheritance</i>	<i>Clinical association(s)</i>	<i>Renal vascular malformation</i>
Neurofibromatosis 1	<i>NFI</i> gene	AD	Neurofibromas - Café au lait macules, optic glioma, increased risk of tumors - pheochromocytoma, Lisch nodules	RAS, External compression - Wilm tumor
Tuberous sclerosis	TSC1, TSC2	AD	Tubers (glial nodules), seizures, adenoma sebaceum, myocardial rhabdomyomas, shagreen patch, ash-leaf macules	RAS, MAS, renal angiomyolipoma
Turner's syndrome	XO	Non-disjunction	Streak gonads, primary amenorrhea, short stature, webbed neck	Coarctation of aorta, MAS, RAS
Marfan's syndrome	Fibrillin	AD	Arachnodactyly, dissecting aortic aneurysm, ectopic lens, mitral valve prolapse	Aortic aneurysm, renal aneurysm, RAS
Loeys-Dietz syndrome	TGFBR1, TGFBR2, SMD3, TGRB2, TGFB3	AD, sporadic	Aortic aneurysm, aortic dissection, craniosynostosis, pes planus, scoliosis, hypertelorism, bifid uvula	RAS, renal artery aneurysm, coarctation of aorta
Alagille syndrome	JAG1, NOTCH2	AD	Xanthomas, cholestatic liver disease, pulmonic stenosis, broad forehead, deep-set eyes	Coarctation of aorta, RAS
Williams-Beuren syndrome	Deletion of genes in chromosome 7	AD, sporadic	Broad forehead, wide mouth, supra-aortic stenosis, developmental delay	MAS, RAS, coarctation of aorta, hypoplasia of the aortic arch
Hereditary Nephropathy, Aneurysms, and Muscle Cramps	COL4A1	AD	Intracranial aneurysms, arterial retinal tortuosity, cataracts, muscle cramps	Cystic compression of renal vessels
Alport syndrome	COL4A3, COL4A4, COL4A5	X-linked (common), AD, AR	Sensorineural hearing loss, anterior lenticonus, renal dysfunction	RAS
Idiopathic infantile arterial calcification	ENPP1, ABCC6	AR	Heart failure, respiratory distress, cyanosis	Vaso-occlusive RAS
Autosomal dominant polycystic kidney disease	PKD1, PKD2	AD	Recurrent UTI, kidney stones, heart valve abnormalities, aneurysms	Cystic compression of renal vessels, RAS
Autosomal recessive polycystic kidney disease	PKHD1	AR	Failure to thrive, respiratory failure, enlarged kidneys, oligohydramnios	Cystic compression of renal vessels, RAS

*AD: Autosomal Dominant; AR: Autosomal Recessive; RAS: Renal artery stenosis; MAS: Mid-aortic syndrome.*

## Renal Biopsy in Children

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Renal biopsy is an important investigation to make the diagnosis of an underlying glomerular or tubular disease, and is commonly done by trained pediatricians. In this review, we discuss the procedure and also detail important points in interpretation of renal biopsy in children.

**Keywords:** *Diagnosis, Glomerular disease, Management, Nephrotic syndrome, Steroid-resistant, Tubular disease.*

**R**enal biopsy is an important diagnostic tool in the hands of a pediatric nephrologist. While the first biopsy was done more than 100 years ago in United States, its utility in diagnostics has increased in the last few decades [1]. Since its regular introduction in 1951 by Iverson and Brun, renal biopsy has made a revolution in the study of renal diseases [2]. Renal pathology can be better delineated with the advent of newer stains, immunofluorescence and electron microscopy. While a renal biopsy is more useful in diagnosing glomerular diseases, it often provides information on tubular conditions as well.

### PRE-PROCEDURE CARE

The parents/ caregivers should be counseled and explained the procedural details and a written consent should be taken. The prerequisites for a biopsy are hemoglobin above 8 gm/dL, platelet count above 1 lakhs/mm<sup>3</sup>, normal INR and normal blood pressure. In the pre-biopsy checklist, it is important to take history of bleeding tendencies, allergies to povidone/iodine, ketamine, midazolam and lidocaine. Drugs like aspirin should be discontinued seven days before, warfarin 48 hr before and any other NSAIDs should also be stopped 48 hours prior to the procedure. The biopsy site should be inspected for any superficial infection. If the child is on hemodialysis, the procedure should be done after at least 24 hours of last dialysis session as heparin during the dialysis procedure may lead to excessive bleeding. For patients with prolonged BT (>8-10 minutes, e.g., in SLE, azotemia), 0.3 µg/kg IV desmopressin can be administered 30 min prior, or 2-4 µg/kg DDAVP intranasal 2 hours before the procedure. Desmopressin reduces the bleeding by improving the platelet functions.

### PROCEDURE

The renal biopsy is done under sedation and local anesthesia in prone position for native kidneys and in supine position for transplanted kidneys. Preferably the procedure should be done under real-time ultrasound guidance by a pediatric nephrologist/trainee in pediatric nephrology.

In conditions like abdominal distension and ascites the biopsy can be done in lateral decubitus or sitting position. A sandbag/rolled sheet or blanket is used under the abdomen to decrease the mobility of the kidney. An IV access is established and heart rate, saturation and blood pressure are monitored during the procedure. For procedural sedation the most preferred drugs are 1-2 doses of midazolam (0.1 mg/kg) and ketamine 0.5-1.0 mg/kg. Intravenous atropine 0.01 mg/kg is administered 1-2 minutes after midazolam. The left renal angle is the most preferred site for the renal biopsy. The lower pole of the kidney is located at this position. Local anesthesia is given at the site by infiltration of lignocaine injection after draping and cleaning (with spirit and povidone iodine). In the real time procedure under ultrasound guidance the automated biopsy gun should be introduced at the site in such a manner that its tip reaches the renal cortex.

### Technique

The sample is usually obtained from the lower pole of the left kidney located between the erector spinae muscle and the lower border of the 12th rib. A 16 or 18 gauge biopsy gun/automated needle is used for taking the percutaneous renal sample. Use of an 18 gauge needle is preferred in infants and young children while thicker bore should be used in all other age groups. The yield of

glomeruli is better with 16 gauge needle [3]. The use of an 18 gauge needle resulted in a significantly smaller sample size (9 vs 11 and 15 glomeruli) and less diagnostic success (53% vs 76% and 85%), with no significant differences in complication rates [3]. The sample should be taken from the renal cortex which harbors the glomeruli. The cortical thickness in an adult kidney is about 10 mm.

A renal sample is considered adequate for opinion if the yield of glomeruli is between 10-20. Minimum sample size for diagnosis varies greatly with the specific diagnosis. For instance, membranous glomerulonephritis (MGN) can be diagnosed even from a single glomerulus while focal segmental glomerulosclerosis (FSGS) can be missed if less than 10 glomeruli are obtained. Two to three passes with the automated gun are sufficient to yield tissue for light microscopy, immunofluorescence (IF) study and electron microscopy (EM). The sample should be removed from the biopsy needle with gentleness, taking care not to stretch or crush the tissue. Forceps should be avoided. An 18-gauge needle or a thin, wooden stick, such as a toothpick can be used. It is advisable to confirm adequacy of cortical tissue on the table itself with the help of a pathologist using the stereoscopic microscope. Once it is determined that suitable cortical tissue is obtained, about 2 mm tissue are cut off from each cortical and medullary ends of the two cores (**Fig. 1**). One cortical tissue and one medullary tissue is placed for IF study in a vial containing Michel transport media. Antigens of interest in the renal biopsy are protected for as long as a week in this media and the sample is stable at room temperature. The cortical and medullary samples for EM are sent in 1-3% glutaraldehyde that acts as a fixative. This fixative must be refrigerated and has a short half life. Care must be taken that no cross contamination of fixative fluids occur while placing the biopsy pieces in their respective vials.

### Complications

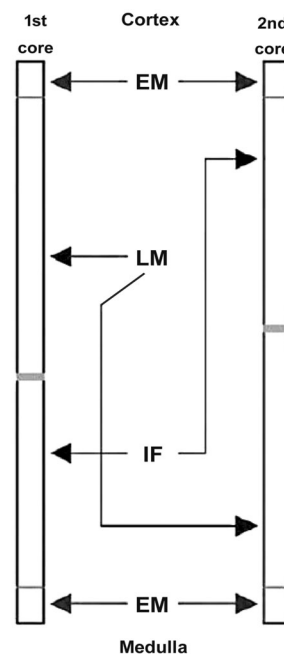
Complications of renal biopsy are few with the use of automated gun. Macroscopic hematuria following a biopsy has been reported to vary from 5-20% in different studies [4-6]. Rarely patients may develop colicky pain due to passage of clots in urine. Although clinically significant peri-nephric hematomas occur in less than 6% of the biopsies, peri-nephric hematomas have been demonstrated at 24-72 hours after biopsy in >90% of cases evaluated prospectively. Microscopic hematuria occurs in almost all patients and disappears over a 48-72 hours period. Serious complications like need for blood transfusion and development of an arteriovenous fistula are less frequent. A meta-analysis on complications

following renal biopsy in children reported the need for blood transfusion in 0.9% and need for another intervention due to the procedure in 0.7% of the biopsied children [7]. Absolute contraindications of the procedure are uncontrolled bleeding diathesis, uncontrolled severe hypertension, hydronephrotic kidneys while presence of a single kidney is a relative one.

### POST – BIOPSY CARE

Patient should stay in supine position for 4-6 hours and bed rest is recommended for 24 hours. The vitals should be monitored every 30 min for the first 2 hours and then hourly till 6 hours. Maintenance intravenous fluids (normal saline or N/2 saline or ringer lactate) are administered for the first 6 hours. Oral fluids are offered to the child when fully conscious and on demand. Paracetamol is used for pain relief if required. Most patients can be discharged after 24 hours of biopsy; however they should be instructed to avoid climbing of stairs, heavy work and play for one week following the procedure.

*Treatment of Complications:* (i) Gross hematuria: If coagulation is deranged it is recommended to use fresh frozen plasma or cryoprecipitate for reduction of bleeding. Also an extra dose of vitamin K should be administered. Blood transfusion may be necessary if 6 hour post biopsy hemoglobin falls by 10-15% of the baseline or the child clinically becomes pale. An urgent ultrasound abdomen should be done to visualize bleed,



**Fig. 1** Division of kidney biopsy cores for light microscopy, immunofluorescence and electron microscopy.

### Box I Common Indications for Renal Biopsy in Children

#### *Glomerular causes*

Steroid resistant nephrotic syndrome  
 Congenital nephrotic syndrome  
 Atypical nephrotic syndrome  
 Rapidly progressive glomerulonephritis  
 Non resolving post-infectious glomerulonephritis.  
 Recurrent gross hematuria  
 HBSAg/anti HCV positivity with proteinuria/hematuria

#### *Tubulo-interstitial nephritis*

Acute kidney injury >4 wks without cause

hematoma in such a situation. Rarely radiographic transcatheter embolization or surgical intervention may be required for continuous bleeding. (ii) Sedation related complications: Brief hypoxia, transient airway complications, vomiting or minor aspiration, laryngospasm are complications of sedation and might need repositioning of the child with suctioning of the airways, oxygen administration and rarely ventilation.

### INDICATIONS

The primary indication for renal biopsy in a child is steroid resistant nephrotic syndrome (SRNS) [8-9]. A recent retrospective review showed that 36.1% of the pediatric biopsies were for SRNS, 22.1% for steroid sensitive disease and 12% for acute kidney injury (AKI) [10]. Glomerular diseases (62.6%) predominated in the national Turkish registry review of all pediatric biopsies between 1991 and 2010 [11]. The most likely biopsy findings in patients with nephrotic syndrome are minimal change disease (MCD), FSGS and mesangioproliferative glomerulonephritis (Mes PGN) [12]. While MCD predominates in younger children, FSGS is more common in older children and adolescents [13]. Biopsy findings of membranoproliferative glomerulonephritis (MPGN) and MGN occur in less than 5% of patients with steroid resistant disease in children. Primary glomerular diseases accounted for almost 85% of all biopsies in older children in a recent study [13]. The indications for renal biopsy are listed in **Box I**.

All children with steroid sensitive or resistant nephrotic syndrome require a biopsy prior to starting calcineurin inhibitors (cyclosporine and tacrolimus) which are potentially nephrotoxic [9]. Besides children with nephrotic syndrome on calcineurin inhibitors for more than 2-3 years are often re-biopsied to look for features of nephrotoxicity before further continuation of these

agents. Other indications of biopsy are in patients with rapidly progressive renal failure where a suspicion of crescentic glomerulonephritis is kept. In patients with acute nephritic syndrome, renal biopsy is needed if the kidney functions are worsening or the investigations are not suggestive of a post streptococcal glomerulonephritis. Renal biopsy may be done in patients with AKI to identify the underlying cause where recovery is delayed beyond one month to differentiate acute tubular necrosis from other causes of AKI. Other conditions like acute and chronic interstitial nephritis can be identified on kidney biopsy. While kidney biopsy is not required for the diagnosis of chronic kidney disease (CKD) it may be done where the kidneys appear normal in size and corticomedullary differentiation on sonography and the cause of CKD is not explicable. In post transplant patients, the biopsy of the grafted kidney provides information on acute and chronic rejection. Biopsy of kidneys with structural anomalies should be done carefully under ultrasound guidance. In this article we would be discussing the biopsy interpretation of some common glomerular conditions occurring in native kidneys.

### INTERPRETATION

#### Light Microscopy

For light microscopic examination of renal biopsy specimen, stains used include hematoxylin-eosin stain (HE stain), periodic acid Schiff (PAS) stain, Masson trichrome and silver stains. Identification of cortex or medulla, number of glomeruli, and cells infiltrating the interstitium of the kidney like neutrophils and lymphocytes are best identified on the HE stain. For glomerular structure, PAS stain is better as it delineates mesangial cells and matrix. PAS and silver stains effectively stain the basement membrane while Masson's trichrome and silver stains are used for identification of fibrosis.

The number of glomeruli, size, presence of any sclerosis, focal or diffuse changes, and presence of any crescents or mesangial cell proliferation can be checked on light microscopy. Lesions involving <50% of glomeruli are called focal while more than that are called diffuse. If only a part of the glomerulus is involved it is termed segmental while involvement of the whole glomerulus is defined as global. Basement membrane thickening or splitting is seen in conditions like MGN and MPGN and is identified on PAS or silver stain. Vessel wall thickening, medial sclerosis or fibrinoid necrosis in case of vasculitis is better seen with PAS stain [14-16]. Stains like von Kossa for calcification and Congo red for identification of amyloidosis are used infrequently in specialized situations [14]. Chronic tubulointerstitial

damage can be identified on light microscopy as tubular atrophy and interstitial fibrosis. In acute interstitial nephritis, interstitial edema, infiltration by neutrophils, lymphocytes and plasma cells can be seen while in chronic interstitial nephritis; fibrosis instead of edema is a prominent feature [2].

### Immunofluorescence

IF study is done with labeled antisera and antibodies. Antisera or monoclonal antibodies against immunoglobulins (IgA, IgG and IgM), components of the classical or alternative complement pathway (C1q, C3c and C4d), protein light chains (kappa and lambda), albumin and fibrinogen are used for identification of different immunofluorescence patterns. The pattern of staining can be linear or granular; linear staining occurs in anti-GBM disease while granular in immune complex mediated injury. The location of deposits can be mesangial or in the peripheral capillary walls (PCW).

In conditions like MPGN and MGN, the immunoglobulin (IgG) deposits are primarily subendothelial and subepithelial respectively. Mesangial deposits of IgA are primarily seen in IgA nephropathy. Similarly granular C3 deposits in the PCW are consistent with a diagnosis of post infective glomerulonephritis (PIGN) while deposits of all immunoglobulins and complements (full house staining) are a hallmark of lupus nephritis.

Using immunohistochemistry procedures, antibodies against viruses like cytomegalovirus and polyoma virus can identify these in the biopsy specimens. Antibodies against hepatitis B and C antigens can be detected on renal tissue and nature of amyloid whether primary or secondary identified by AA Amyloid stain. Additional immunohistochemical study with antibodies, such as collagen IV alpha chains can be performed for identification of Alport's syndrome. In post transplant renal biopsies immunostaining for complement factor C4d can be done to identify humoral rejection.

### Electron Microscopy

It is not necessary, but helpful to do EM for all renal biopsies. The conditions in which electron microscopy will help confirm the light microscopy diagnosis are in the identification of podocyte structure alteration (effacement of foot processes) in MCD, changes of glomerular basement membrane especially thinning, thickening or splicing and the site of immune deposits (subendothelial or subepithelial). EM is essential for diagnosis of basement membrane abnormalities like thinning in thin basement membrane disease and irregular thickening with basket weave pattern in Alport's syndrome. EM is also essential in sub defining

the nature of deposits in immune complex deposition diseases like immunotactoid glomerulonephritis (GN) and fibrillary GN. Metabolic disease like Fabry disease also require EM for diagnosis. **Box II** gives in a nutshell what to look for in a renal biopsy specimen.

### BIOPSY PICTURE IN GLOMERULAR DISORDERS

Some salient biopsy characteristics of renal disorders are given in **Table I**; the biopsy picture in different conditions is discussed briefly below.

**MCD:** The glomeruli in MCD look almost unremarkable. There is no significant increase in mesangial matrix and cellularity and no thickening of basement membrane is identified. Tubules may show hyaline droplets representative of resorbed proteins following the heavy proteinuria. Immunofluorescence studies are generally negative for all immunoglobulins (**Fig. 2 a, b**). MCD is part of set of diseases called as podocytopathies characterized by abnormalities in the podocytes or visceral epithelial cells lining the glomerular capillary loops. There is simplification of foot processes of podocytes seen as diffuse effacement on electron microscopy (**Fig. 2c**); which is the hallmark of the disease.

**FSGS:** The classical lesion in FSGS is a focal solidification of the glomerular tuft by an acellular extracellular matrix that is positive on PAS and silver stains (**Fig. 2d,e**). The segmental sclerosis is often accompanied by attachment to the Bowman's capsule called as "synechie" formation. These lesions are identified in only a portion of the glomeruli and do not

#### Box II Features to Look for in Renal Biopsy with Different types of Processing

##### Light microscopy

Glomerular proliferation or sclerotic changes can be identified best

Basement membrane thickening can be identified  
Tubulointerstitial damage like tubular atrophy and fibrosis can be seen

Blood vessels may show medial sclerosis

##### Immunofluorescence

Helps in identifying immune deposits like C3, IgG, IgM, IgA, fibrin etc.

##### Electron microscopy

Most useful in identifying the structural defects of podocytes like effacement in MCD, identifying the exact location of immune deposits (subepithelial or subendothelial), basement membrane thickening or thinning (in Alport disease and thin basement membrane disease)

involve the entire glomerular tuft; hence the term focal and segmental. FSGS can further be pathologically classified as glomerular tip, perihilar, cellular, collapsing and mixed variants according to Columbia classification. On IF study, segmental glomerular staining for IgM and C3 is identified which represents a non specific entrapment in the area of sclerosis. Staining for immunoglobulins is generally negative (**Fig. 2f**). EM

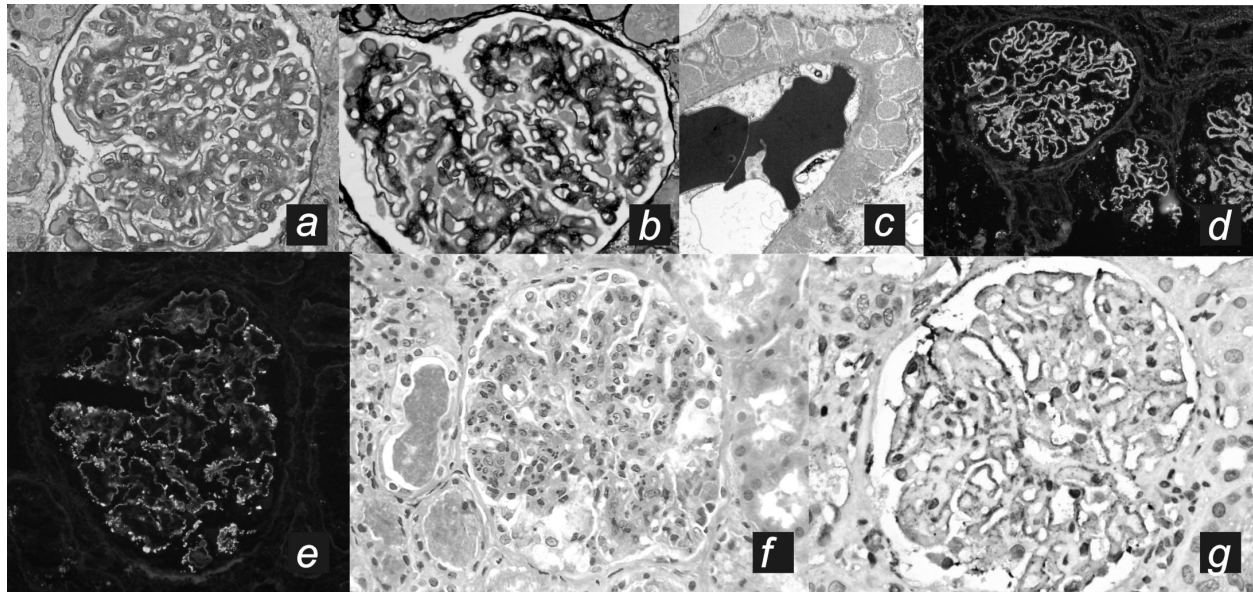
shows effacement and obliteration of podocyte foot processes, mesangial sclerosis (**Fig. 2g**).

**MGN:** This is a disease caused by immune complex deposition in the sub-epithelial zone i.e. over the basement membranes of the capillary loops. The capillary basement membranes show spike formation due to deposition of type IV collagen around this material in an

**Table I Salient Features on Renal Biopsy in Different Conditions**

Condition	Light microscopy	Immunofluorescence	Electron microscopy
<i>Minimal change disease</i>	Glomeruli look unremarkable, no significant increase in mesangial matrix & cellularity, normal looking BM, blood vessels look normal, tubules may show hyaline droplets	No or minimal immune deposits	Diffuse effacement of podocyte foot processes
<i>Focal segmental glomerulosclerosis (FSGS)</i>	Focal solidification of glomerular tuft by acellular extracellular matrix positive on PAS & silver stains; changes in few glomeruli; tubular atrophy & interstitial fibrosis may be seen	No to minimal immune deposits (C3 & IgM)	Epithelial cell detachment from glomerular BM, extensive foot process obliteration, mesangial sclerosis & collapsed glomerular loops
<i>Mesangioproliferative glomerulonephritis (MesPGN)</i>	Diffuse or focal increase in mesangial cells & matrix, BM normal, blood vessels look normal, tubules may show atrophy	No to minimal deposits of IgA, IgM, IgG along mesangial capillary walls	Mesangial deposits of immune complexes
<i>Membranous nephropathy</i>	Glomeruli are enlarged with mild increase in mesangial matrix & cellularity, thickened capillary walls with prominent spike formation; best seen on PAS & silver stains.	The immune complexes deposited in the peripheral capillary walls are granular deposits, positive for IgG & C3; IgA & IgM may also be seen	Granular electron dense deposits in subepithelial zone on outer aspect of the glomerular BM
<i>Membranoproliferative glomerulonephritis (MPGN)</i>	Lobular accentuation of enlarged glomeruli, mesangial hypercellularity & splitting of BM	Primarily mesangial & sub-endothelial C3 deposits; C1q, C4 deposits may occur	Subendothelial & mesangial electron dense deposits, increased mesangial matrix, podocyte foot process fusion
<i>IgA nephropathy</i>	Mesangial hypercellularity, endocapillary proliferation, segmental sclerosis & varying degree of tubular atrophy & interstitial fibrosis	Granular deposits of IgA in the mesangial areas	Mesangial, subendothelial & subepithelial immune deposits
<i>Crescentic glomerulonephritis</i>	Presence of crescents (extracapillary proliferation of cells resulting in collapse of glomerular capillary loop) in >50% glomeruli; there may be cellular, fibrocellular or fibrosed crescents	Immune deposits are absent in paucimmune condition while there may be C3, IgG, IgA, IgM deposits in immune mediated conditions	Rupture of GBM and Bowman's capsule, focal effacement of podocyte foot processes
<i>Alport syndrome</i>	May show variable thickening of the GBM	Absence of $\alpha 3$ , $\alpha 4$ and $\alpha 5$ chains of type IV collagen from BM of glomeruli characteristic	Thinning of the membrane that later change to basket weaving & lamellation of GBM

BM: basement membrane; GBM: glomerular basement membrane.



**Fig. 2** Minimal Change Disease: A: PAS stained section of a glomerulus in Minimal Change Disease showing only mild increase in mesangial matrix (x400x); B: IgG stained cryosection showing lack of immune deposits and protein reabsorption granules in parietal epithelial cells (x200x); C: Electron micrograph showing complete effacement of foot processes of podocytes (x4300x). Focal and Segmental Glomerulosclerosis: D: HE stained glomerulus in focal and segmental glomerulosclerosis showing segmental sclerosis of glomerular tuft and foam cell infiltration [arrow] (x400x); E: JSM Stained section showing segmental sclerosis in glomerulus (x400x); F: Electron micrograph showing complete effacement of foot processes of podocytes (x4300x); G: C3 stained cryosection showing segmental deposits in glomerular tuft (x200x).

attempt to wall them off and decrease their inflammatory reaction (**Web Fig. 1a, b**). The glomeruli are enlarged with mild increase in mesangial matrix and cellularity. Activity in the form of endocapillary proliferation or crescent formation are not a feature of primary MGN but usually representative of a membranous nephropathy secondary to a systemic cause like SLE, other auto immune or infectious diseases. On IF, the immune complexes deposited in the peripheral capillary walls are classically identified as granular deposits, positive for IgG and C3 (**Web Fig. 1d**). Other immunoglobulins like IgA and IgM are often seen. Further a diagnosis of primary MGN may be confirmed by demonstration of anti-PLA<sub>2</sub>R antibodies in the podocytes by immuno-fluorescence staining (**Web Fig. 1e**). On EM, granular electron dense deposits are identified in the sub-epithelial zone on the outer aspect of the glomerular basement membrane (**Web Fig. 1d**).

**MPGN:** This term indicates thickening of the basement membrane accompanied by mesangial proliferation. The kidney biopsy in MPGN shows a classical lobular accentuation of glomeruli, mesangial hypercellularity and splitting of basement membranes on silver stains. Secondary MPGN pattern of injury is seen in cases of long standing infectious pathology, auto-immune conditions, dysproteinemias, transplant glomerulopathy and various other miscellaneous conditions. Primary

MPGN is caused by abnormalities of the alternate complement pathway and is known as C3 glomerulopathy. It is primarily diagnosed on IF by strong deposition of C3 in the kidney biopsy in the absence of immunoglobulin deposition. The diagnosis can only be confirmed on EM, based on which, it is further divided into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). Dense, band-like osmophilic deposits in the GBM on EM is the classical feature of DDD. C3GN is characterized by sub-endothelial, mesangial and sub-epithelial C3 deposits on EM.

**IgA nephropathy:** IgA nephropathy is one of the commonest forms of primary glomerulonephritis the world over. It is characterized by granular deposits of IgA in the mesangial areas identified on IF. On light microscopy, these biopsies present a diverse histological presentation ranging from no detectable histological finding to diffuse proliferative and crescentic glomerulonephritis. The grade of histological changes determines the clinical prognosis. The histological changes in the form of mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy and interstitial fibrosis have been graded by the Oxford classification into 4 grades each (0-4). A sum total of grades in all the four compartments represents the activity of the disease and determines the clinical prognosis [17].

*Lupus nephritis:* The renal biopsy in lupus nephritis shows a wide variety of changes which commensurate with the disease activity and have a bearing on the prognosis of the patient. The renal biopsy changes in lupus have been classified into 6 groups by the ISN /RPS classification system into Class I (minimal lupus nephritis), Class II (mesangial lupus nephritis), Class III (focal lupus nephritis), Class IV (diffuse lupus nephritis), Class V (membranous lupus nephritis) and Class VI (advanced sclerosing glomerulonephritis). Some modifications have been added to the classification [18]. The diagnosis is confirmed on IF by presence of a full house pattern in the form of immunoglobulins IgG, IgA and IgM along with complements C3 and C1q; deposits of immunoglobulins are also indentified in the walls of tubules and blood vessels.

*Tubulointerstitial changes:* The tubules should be examined for features of acute tubular necrosis as seen in AKI. The interstitium shows edema and a mixed inflammatory cell infiltrate. Other findings are interstitial fibrosis, tubular atrophy, arteriolar sclerosis, and occasionally, patchy mononuclear cell infiltration. The degree of chronic parenchymal damage in the tubulointerstitial compartment is an important prognostic indicator in all glomerular diseases and is assessed on PAS and MT stains. Blood vessels changes secondary to hypertension are often seen in glomerular diseases.

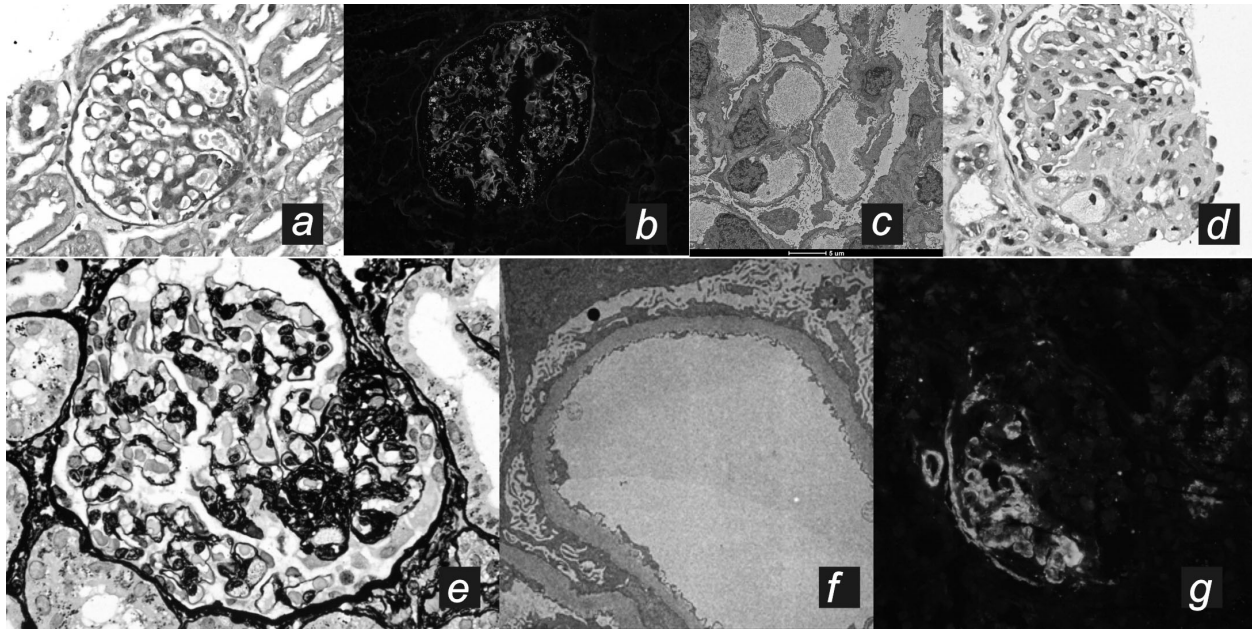
To conclude, interpretation of renal biopsy in children involves procuring an adequate sample for examination and processing it for light, immunofluorescence and electron microscopy. While renal biopsy is more useful for identifying glomerular diseases, it also provides sufficient information about tubulo-interstitial changes. The biopsy changes should be carefully interpreted along with the clinical findings for making a confirmatory diagnosis.

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**Web Fig. 1** Membranous Glomerulonephritis: PAS stained section of a glomerulus in membranous glomerulonephritis [MGN] showing thickened basement membranes with prominent spikes on silver methenamine stain [B] (x400x); C: Electron micrograph showing electron dense deposits in the sub epithelial location of the basement membranes (x5300x); D: IgG stained cryosection showing granular immune deposits in the basement membrane in case of MGN (x200x); E : Deposits on subepithelial surface of basement membrane positive for PLA2R (x400x). Diffuse Proliferative Glomerulonephritis (DPGN): F: HE stained glomerulus in DPGN showing endocapillary proliferation and infiltration by polymorphs [arrow] (x400x); G: JSM Stained section showing segmental sclerosis in glomerulus (x400x)

## Cluster Randomized Trial Evaluating Impact of a Community-based Microfinance Scheme on Childhood Nutritional Status

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### SUMMARY

The objective of this cluster randomized trial was to determine if Rojiroti microfinance, for poor Indian women in the state of Bihar, improves child nutrition. Women with children under 5 years formed self-help groups, and saved their money to provide loans to group members. After an interval of 6 months, they received larger external loans and *tolas* were randomized to receive Rojiroti immediately or after 18 months. The primary outcome measure was mean weight for height Z score (WHZ) of children under 5 years in the intervention *versus* control *tolas* who attended for weight and height measurement 18 months after randomization. Total 28 *tolas* to each arm were randomized and

data were collected from 2469 children (1560 mothers) at baseline and 2064 children (1326 mothers) at follow-up. WHZ was calculated for 1718 children at baseline and 1377 (674 intervention and 703 control) at follow-up. At 18 months, mean WHZ was significantly higher for intervention (-1.02) vs controls (-1.37; regression coefficient adjusted for clustering b=0.38, 95% CI 0.16 to 0.61, P=0.001). Significantly fewer children were wasted in the intervention group (122, 18%) vs control (200, 29%; OR=0.46, 95% CI 0.28 to 0.74, P=0.002). The authors concluded that in marginalized communities of rural Bihar, child nutrition was better in those who received Rojiroti microfinance, compared with controls.

### COMMENTARIES

#### **Evidence-based Medicine Viewpoint**

**Relevance:** Childhood malnutrition is a clinically and socially significant problem in many resource-constrained settings in the world. Besides affecting individual children and families, it has far reaching consequences on society in general. Naturally, its alleviation depends on many factors beyond nutritional supplementation (of children and their families). A recent collaborative study [1] by a group of researchers from the United Kingdom, non-governmental organizations and Patna Medical College, explored whether financial empowerment of women in disadvantaged rural communities (through the Rojiroti scheme) could impact the nutritional status of their children. In this scheme, women form self-help groups voluntarily, attend meetings regularly, contribute a nominal sum weekly, become eligible for very small loans from the pool of collected funds, and after six months can obtain loans up to Rs 3000 based on credit-worthiness. There is no restriction on what the loan amount can be used for. The investigators chose a cluster randomized trial design to compare rural units (described as *tolas*) that implemented the Rojiroti scheme with *tolas* that did not. Anthropometric measurements of children younger than five years old in both trial arms were done at enrolment, repeated after 18 months, and compared between the arms. Although a research question was not articulated

by the investigators [1], it can be framed as: What is the effect of community-based Rojiroti microfinance scheme (I = Intervention) on the nutritional status of under-five children (O=Outcome), in economically and socially disadvantaged communities in rural Bihar (P=Population) compared to no microfinance scheme (C=Comparator) at the end of an 18 month period (T = timeframe of outcome assessment)?

**Critical appraisal:** **Box I** presents a summary of the trial design and main results. The investigators chose a cluster RCT design to address the research question. Technically, this is the ideal design to evaluate efficacy of potential interventions in clusters of individual participants, wherein the effects (of the intervention) are expected/anticipated to spill over into/onto those who are not directly receiving the intervention, but are present in the same cluster. However, if the effect of the intervention is expected to have limited impact on non-participating individuals in the cluster, then an individual RCT is more appropriate. It is difficult to judge which of the two designs is superior to compare community effects through individual empowerment of some members, as was done in this trial [1].

The investigators used a computer program for randomizing pairs of *tolas*, although since only two *tolas* were randomized at a time, simple coin tossing is sufficient. Paired randomization obviated the scope for

### Box I Summary of the Trial

**Study design:** Cluster randomized trial with allocation of rural community units called *tolas* into the trial arms. The intervention was on women in the *tolas*, and the outcomes were measured in their children.

**Study setting:** Four tehsils of Patna district comprising about 60 *tolas*. A tola is described as a rural community with a population of approximately 500 people with similar social and economic background [1]. In general, the communities appear to be disadvantaged as evidenced by absence of health-care centres, lack of access to piped water, low level of women's education, social empowerment and economic status. However, all *tolas* had electricity supply and immunization coverage was over 95%.

**Study duration:** *Tolas* were recruited in three phases, during 2 months in 2012, two months in 2013, and 1 month in 2014. No other details were mentioned.

**Inclusion criteria:** Sixty *tolas* were selected for implementation of the Rojiroti scheme; however, the basis of selection and/or eligibility criteria were not mentioned. Any woman in the intervention tola could join the Rojiroti microfinance scheme. Women in the Comparison group (i.e control) *tolas* could not join the Rojiroti scheme, but could join other (unspecified) self-help group (schemes). All children <5 years in the *tolas* selected for Intervention and Comparison groups were eligible for outcome measurement, whether (or not) their mothers availed the Rojiroti scheme.

**Exclusion criteria:** None were described.

**Enrolment process:** The basis for selection of *tolas* was not specified. *Tolas* of similar size (definition unspecified) but at least 15 km apart, were paired, and randomly assigned to either the Intervention or Comparator group. Enrolment of *tolas* occurred in three phases viz 2 months in 2012 (20 *tolas* included), 2 months in 2013 (30 *tolas* included) and 1 month in 2014 (6 *tolas* included). Women in the Intervention *tolas* were invited to join the Rojiroti scheme through a "show of hands" and their children were enrolled with verbal consent.

**Intervention and Comparison groups:** The Rojiroti scheme was implemented in the intervention arm *tolas*. Nothing was done in the comparison arm *tolas*. Baseline demographic parameters of the *tolas*, participating women and their children were recorded in both groups. Anthropometric measurements of all under-five children were done using standard tools and methods, at baseline and also after 18 months; in both arms of the trial.

**Outcomes:** All outcomes were measured 18 months after enrolment, and compared between the two trial arms (*outcomes are listed in the last row*). Definition of two of the secondary outcomes was not provided in the article viz., proportion of women with freedom to travel without permission of a male relative, and forced asset sale.

**Follow-up protocol:** Research staff conducted anthropometric measurements in all children available 18 months after enrolment of *tolas*, irrespective of whether the children and/or their mothers participated in the trial.

**Sample size:** *A priori* sample size calculation was performed for a superiority trial, to detect a 0.26 z score improvement in WHZ from an estimated baseline of -0.96, with alpha error 0.05 and beta error 0.20. Assuming 10% attrition, the estimated sample size was reported as 60 *tolas*. The investigators observed approximately 40 under-five children per tola initially, hence assumed that there would be approximately 2400 children for anthropometric measurements across the 60 *tolas*.

**Data analysis:** Data of available children were analysed between trial arms, calculating unadjusted odds ratio. Subsequently odds ratio was adjusted for baseline nutritional status, age, gender and number of under-five children per family. It was decided post hoc to compare the outcomes in children in Intervention *tolas* whose mothers did (versus did not) join the Rojiroti scheme.

**Comparison of groups at baseline:**

- The *tolas* in the two arms were comparable for multiple parameters viz connection to a paved road, distance from a main road, presence of public distribution scheme shop, presence of government primary school, presence of other school, availability of primary health centre, access to ASHA worker and ANM, availability of piped water supply, and electricity.
- Participating mothers in the two arms were comparable in terms of the number who joined the Rojiroti scheme and age. However, there were statistically significant differences in terms of family land ownership, freedom to travel without permission, ability to read/write, and school attendance- all in favour of those who were in the Intervention arm.
- Children in the participating *tolas* were comparable in terms of median number enrolled per tola, gender distribution, mean age, proportion delivered at home, immunization status, and proportion having road-to-health cards. Most anthropometric parameters were comparable between arms, however HAZ and the proportion of children with MUAC <12.5cm, were both significantly better in the intervention arm. However, proportion with wasting was significant higher in the Intervention arm.

*contd....*

**Box 1 continued***Summary of results: Intervention versus Comparison arms*

## Primary outcome

- Mean (SD) WHZ: -1.02 (1.11) vs -1.37 (1.10), uOR\* 0.16, 0.61; aOR\*\* -0.03, 0.53

## Secondary outcomes

- Mean (SD) HAZ: -2.37 (1.29) vs -2.53 (1.25), uOR -0.04, 0.37; aOR -0.24, 0.10
- Mean (SD) WAZ: -2.13 (1.03) vs -2.37 (1.05), uOR 0.11, 0.43; aOR 0.04, 0.49
- Mean (SD) MUAC: 13.6 (1.1) vs 13.4 (1.1), uOR 0.03, 0.40; aOR -0.14, 0.38
- Proportion with wasting: 18% vs 29%, uOR 0.28, 0.74; aOR 0.33, 1.14
- Proportion with stunting: 63% vs 66%, uOR 0.60, 1.12; aOR 0.57, 1.64
- Proportion with underweight: 53% vs 63%, uOR 0.47, 0.84; aOR 0.29, 0.89
- Proportion with MUAC <12.5 cm: 13% vs 18%, uOR 0.41, 1.05; aOR 0.27, 2.23
- Proportion with MUAC <11.5 cm: 3% vs 5%, uOR 0.36, 1.33; aOR 0.10, 6.14
- Proportion of women with freedom to travel<sup>‡</sup>: 5% vs 5%, uOR and aOR not specified
- Forced asset sale: 2% vs 2%, uOR and aOR not specified

\*uOR is the 95% CI of the unadjusted odds ratio; \*\*aOR is the 95% CI of the adjusted odds ratio; <sup>‡</sup>travel without permission of a male relative.

allocation concealment. The outcome assessors were not blinded to the intervention, but the reasons for this were not specified.

Although, all 56 enrolled *tolas* were present at the end of the study (*i.e.*, zero attrition), there was significant attrition amongst individual participants (both mothers and children), between the randomization (*i.e.*, enrolment) step, baseline variable measurement step and outcome assessment step. For example, 2469 children were eligible for anthropometric data assessment across 56 *tolas* at enrolment, but WHZ data could be analysed in only 1718 (69.6%). Similarly, 2064 children were eligible for outcome measurement at the end of the study, but WHZ (primary outcome) could be analysed in only 1377 (66.7%). These attrition rates are considerably high, although they were comparable between the two groups. Further, it is disconcerting that one-third of the potential data was unavailable not because participants dropped out, but because the anthropometric data were not collected properly. This is unacceptable in a well-funded RCT with appropriate training of research staff.

It is also unclear what proportion of the children whose baseline data were collected, underwent data collection at the end of the study. This has two entirely different implications. First, if these proportions are significantly different between the two trials arms, a new confounding variable emerges. Unfortunately, the authors did not show this data. Second, if the intervention (*i.e.*, implementation of Rojiroti micro-finance scheme) is believed to impact the whole community (and not just the participating households), then we would expect to see

the benefits in children irrespective of whether or not they were present when the intervention started or whether their families availed the scheme. This seems to have been the assumption of the investigators in this study [1]. But if this is the case, it can be argued that pre and post intervention measurement of anthropometric measurements would be more meaningful than comparison between trial arms.

This raises another important issue. The statistically significant 'benefits' in the Intervention arm were not because children in this arm showed improvement in anthropometric measurements (as one would expect). In fact, 5 of 11 outcomes showed worsening over the 18-month intervention period. These include mean HAZ (declined from -2.00 to -2.37), mean WAZ (declined from -1.89 to -2.13), proportion with stunting (increased from 49% to 63%), proportion with underweight (increased from 44% to 53%) and proportion of mothers with freedom to travel without permission (declined from 8% to 5%). Even the other anthropometric measures showed no improvement, but merely remained unchanged over 18 months. Thus, the Intervention arm was proven superior [1] only because the Comparison arm showed far greater worsening of anthropometric parameters. The authors interpreted this as empowerment of the community to be resilient during food shortage, thus emphasizing the benefit of the Intervention. However, this explanation is unacceptable for three reasons. First, it assumes that under natural circumstances, children's nutritional status declines over time. However, the authors showed no data supporting this presumption [1]. Second, the proportion

of households forced to sell assets was exactly 2% in both arms, suggesting that apparent periods of food shortage did not translate to loss of assets in either arm. Third, analysis of the reasons for taking loans in the Intervention arm shows that a very small proportion was used for food and supplies (in terms of percentage as well as absolute amount).

How to explain the differences in the two arms at the end of the trial? One explanation could be that mothers in the Intervention arm were more empowered than mothers in the Comparison arm (literacy 21% vs 16%, school attendance 19% vs 13%, and freedom to travel without permission 8% vs 3%, and family land ownership 13% vs 8%). Perhaps this could account for better child-care practices even in the midst of acute shortages, thereby preventing the pattern of decline seen in the Comparison arm. However, these empowerment indicators were present in less than 20% mothers in the Intervention arm; hence, other unexplored factors are likely. Had the authors re-collected maternal baseline parameters at the end of the study, a clearer picture of women empowerment (if any) could be considered.

It should be remembered that children in the Intervention arm had superior HAZ than those in the Comparison arm. The impact of this on the final outcome is unclear, although height is impacted much later than weight and muscle mass, during food deprivation.

A noteworthy point is that the authors [1] did not report the number of deaths, or medical morbidities amongst the children in either arm. Thus, the data presented pertain only to survivors. It is well-recognized that children with worse nutritional state have greater likelihood of morbidity and mortality. Thus, the available children no longer represent all the eligible children. This compromises internal validity. It can be further argued that all-cause mortality data alone may be insufficient, and malnutrition-related morbidity should also have been measured.

The investigators reported that children in Intervention *tolas* had similar anthropometric outcomes, irrespective of whether or not their mothers participated in the Rojiroti scheme. They suggested that this indicated some kind of community effect spilling over into non-participating households. However, the proportion of participating women in each tola were not described, hence this assumption could be too simplistic.

It appears that 90% children in each arm of the trial possessed road-to-health cards. These cards provide valuable longitudinal anthropometric data. This would have enriched the study by providing some data for drop-out children, internal checks against spurious data

collected in the study, and also a 'last recorded' value for those older than 5 years at follow-up. Most important, the inflection time point(s) at which nutritional decline occurred could have been calculated.

Another missed opportunity in this study is that data were not analyzed in age bands, rather all under-five children were clubbed together and treated as single unit. This is important because growth rates vary by age in under-five children.

As in many such studies, interesting data emerged that were not the focus of the investigators. For example, more than 95% children in both arms were immunized [1]. This is somewhat surprising, considering that the overall immunization coverage (with BCG, 3 DPT, and measles vaccine among 12-23-month-old children) in Bihar during 2015-16 was 61.7%, coinciding with the national average of 62.0% [2]. How did the included children have such excellent immunization coverage? This could be because over 90% *tolas* had access to ASHA workers as well as ANM in their community. Or perhaps the reported immunization used some other definition of immunization, or data were collected unreliably. Since the baseline nutritional indicators of children in terms of proportions with stunting, wasting and underweight coincided with the overall NFHS-4 data for Bihar [2], the latter assumptions are more likely.

Each tola had only 500 people and around 40 under-five children. Although the age break-up of the *tolas* is not known, India's population pyramid suggests just under 10% of the population is in the age group 5-9 years [2]. This would translate to about 50 primary school age children in each tola. It is therefore impressive that all *tolas* had a primary school and some had other schools as well.

*Conclusion:* This cluster RCT [1] suggested that participation of disadvantaged rural women in a specific microfinance scheme could prevent decline in the anthropometric measurements of their under-five children over a period of 18 months. However, the validity of the trial is compromised by methodological issues and compromised power due to significant attrition. Hence it is difficult to draw firm conclusions from this trial or recommend further similar studies.

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### **Pediatrician's Viewpoint**

India is home to about one third of the stunted and half of the wasted under-five children present globally [1]. Malnutrition attributes to about 70% of the under-five deaths in India during 2017 [2]. Apart from morbidities and mortality, malnutrition is a key determinant for optimal cognitive growth and development and overall health and productivity in adulthood [3]. The UN Sustainable Development Goal-2 targets elimination of child malnutrition by 2030 [4]. Child health and nutritional status is reflecting a socioeconomic gradient [5]. The economic growth in recent times has not optimally transformed into reduction in childhood malnutrition [6].

India has been making efforts towards reducing the burden of malnutrition and the health adversities through various programs including the nutrition supplementation and nutrition rehabilitation centers. Recently National Nutrition Mission (NNM, also called Poshan Abhiyan) has been initiated by Government of India, which targets reducing stunting, undernutrition, anemia and low birth weight by 2%, 2%, 3% and 2% annually, respectively by 2022 [7]. Globally, several efforts in past have targeted the nutritional status of children and women through various livelihood, agricultural and conditional cash transfer systems with varied results [8].

The current study documented the impact of the Rojiroti microfinance effort through Self help groups in Patna district, Bihar over 18 months period [9]. Although this study was conducted in Bihar, the context and underlying factors are applicable to several parts of India. Malnutrition is a constant challenge for the pediatrician. In clinical practice, the pediatricians assess nutritional status and give nutritional counselling including breastfeeding, but the real change in family practice and nutritional status depends on the food security, availability and home food environment. Research from India revealed the roles of social and economic competing forces for persistence of undernutrition [10]. Although this article does not include clinical dimension, but has relevance for the pediatricians and child health and nutrition functionaries.

The pediatricians have multiple opportunities and roles to play in this context for all categories of clients, especially those from the weaker social and economic strata. Age-appropriate counselling and empowerment of

the parents and families for preventive care including nutritional practices (breastfeeding, weaning and complementary feeding, especially targeting the locally available nutritious foods ingredients), routine immunization, vitamin A and deworming schedule and general hygiene and sanitation at household level must be practiced by all pediatricians. Rational medication and supplementation prescription practice can be critical in minimizing the out of pocket expenses for the families. Apart from the prescription, appropriate counselling for medicine and supplementation adherence and continued feeding during and after the illness are to be emphasized.

The pediatricians also have a stewardship role in healthcare financing. While major share of the curative healthcare services is provided by the private sector, the preventive services are delivered by public sector. Out of pocket expenditure (OOPE) amounts to about 75% of healthcare expenditure in India and the catastrophic healthcare expense is an important cause of impoverishment for the families [11]. The catastrophic health related OOPE was also observed in the current study [9]. Thus, the treating pediatrician has a responsibility to understand the financial implications of their clinical decisions. The communication by the pediatricians to be effective for parents, family and the community, it must be clinically appropriate, transparent and sociocultural context compatible.

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### **Nutritionist's Viewpoint**

Childhood malnutrition is increasingly recognized as an important public health problem, for its adverse effect on health and child survival, as well as for long term growth and development. India is at the epicentre of this global public health problem, with 22 million children wasted and over eight million severely wasted at any one time [1]. Hence implementation of evidence-based strategies for prevention and management is topmost priority for increasing child survival and productivity.

Malnutrition is a complex and multi-dimensional issue, affected by poverty, inadequate food consumption, inequitable food distribution, suboptimal infant and child feeding and care practices, equity and gender imbalances, poor sanitary and environmental conditions and limited access to quality health, education and social services. Social protection involves policies and programs that protect people against vulnerability, mitigate the impacts of shocks, improve resilience and support people whose livelihoods are at risk. Social protection programs can improve food security at household level, quality, and diversity; decrease undernutrition; and help children reach their full potential [2].

In the present study [3], authors assessed the effect of

microfinance initiative on the nutrition status of children in a marginalized population. The study suggests that, though micro-finance has been able to reduce the deterioration in nutrition levels in the children of extremely poor families, it has not been able to actually improve or even maintain the nutrition levels. This may be due to the low-income gains from the scheme. From a policy point of view, there are important conclusions which may be drawn. One inference which may be drawn is that schemes which directly tackle malnutrition and help provide food to children must be continued and encouraged in the poor states of the country.

Many nutrition-specific interventions to prevent wasting and other forms of malnutrition are delivered at community-level in India through Anganwadi Services under the umbrella of the Integrated Child Development Services (ICDS) scheme. Nutrition-specific interventions are also delivered during the VHSND or on separate days, including growth monitoring, the promotion and support of infant and young child feeding (IYCF), micronutrient supplementation and supplementary feeding. While the schemes, programs and delivery platforms are nationwide in scale, the coverage, and quality of interventions are insufficient to achieve the impact required. It would be beneficial to channelize efforts and funding to boost the efficacy of such schemes.

To conclude, while microfinance schemes have their own importance, they may not be the way to address nutritional issues among children. A truly multi-sectoral approach will achieve optimal nutrition outcomes through greater coverage.

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## Long-term Outcome of Children with Recurrent Abdominal Pain

We report on long-term follow-up [mean (SD) duration, 44.7 (4.3) mo] of 48 out of 132 children with recurrent abdominal pain, who were a part of an earlier study at our hospital. 31 (64.5%) children still experienced pain; 26 (54.1%) reported their pain to be better than before, 4 children reported it to be same as before, and one child reported it worse than before. 17 out of 31 children had pain fitting into one of the categories of functional gastrointestinal disorders in the Rome III criteria; most commonly functional abdominal pain ( $n=6$ ) and functional constipation ( $n=3$ ). In majority of children with functional recurrent abdominal pain, pain may persist over the next 3-4 years, but shows slight improvement in frequency and severity.

**Keywords:** *Constipation, Functional abdominal pain, Outcome.*

Recurrent abdominal pain (RAP), especially functional abdominal pain, is one of the most common chronic pain conditions of childhood. There is a paucity of studies on the long-term outcomes of children with recurrent abdominal pain and its relationship with any treatment strategy during initial phase, especially from low- and middle-income country settings. The objective of our study was to evaluate long-term persistence and severity of gastrointestinal symptoms in children with recurrent abdominal pain of non-organic etiology, and to compare abdominal pain-related manifestations in children with recurrent abdominal pain who received drotaverine or placebo for a 4-week period about 3-4 years ago as a part of an earlier randomized placebo-controlled trial [1].

This follow-up study was carried out over a period of 8 months ending in May, 2017 in the Pediatric gastroenterology and hepatology clinic of a public tertiary-care hospital in India, catering mainly to urban poor population. The study was approved by the Institutional ethics committee (Human research) of the institute. Written informed consent was obtained from parents and assent was obtained from children aged  $\geq 7$  years.

All children who were part of an earlier randomized control trial comparing efficacy and safety of drotaverine hydrochloride in children with recurrent abdominal pain [1] were eligible to be enrolled in this follow-up study. Parents of such children were telephonically contacted and a date was fixed on which they had to report to the hospital. Children were

evaluated by history and a detailed physical examination. In case of a complaint of abdominal pain, the Questionnaire on pediatric gastrointestinal symptoms – Rome III version (QPGS-RIII) [2] was completed. QPGS-RIII was answered by parents if the child was younger than 10 years of age. In case of children older than 10 years, it was filled up by the child with inputs from parents. A single interviewer assisted the parents/children in comprehending the questions. Any diagnosis of the abdominal pain as per Rome III criteria was recorded. Information about symptoms suggestive of any other functional gastro-intestinal disorder (FGID) was also recorded. Primary outcome measures included presence/absence of abdominal pain as per Apley criteria [3] and any FGID as per Rome III criteria [2]. Secondary outcome measures included pain status (as compared to previous enrolment), frequency of abdominal pain, number of pain-free days, and number of children missing school.

Descriptive analysis was done for primary outcome measure. The frequency of abdominal pain and missed school days in last 4 weeks, and severity of the most recent episode were compared between those who received drotaverine or placebo in earlier trial by Mann-Whitney test. Pain status (absent or better vs. same or worse) between these two groups was compared with chi-square test, and proportion of children missing school was compared with Fisher exact test.

Out of the 132 patients enrolled in the original study [1], we were able to contact only 48 children (22 boys). The mean (SD) age was 11.2 (2.53) years and the mean (SD) duration since enrolment in first study was 44.7 (4.3) months. Complaints of abdominal pain were still present in 31 (64.5%) children; however, 26, 1 and 4 children reported the pain to be better, worse or same, respectively in comparison to the previous study. Twenty-five children had abdominal pain that satisfied the Apley criteria [3]. Abdominal pain that satisfied the Rome III FGID criteria [2] was seen in 17 children; relevant categories being functional abdominal pain ( $n=6$ ), functional constipation ( $n=3$ ), functional dyspepsia ( $n=2$ ), and functional abdominal pain syndrome and functional constipation ( $n=2$ ). Functional abdominal pain and functional constipation, irritable bowel syndrome, abdominal migraine, and non-retentive fecal incontinence were seen in one child each.

Other gastrointestinal complaints (not satisfying



Rome III diagnostic categories) in these patients were: pain on defecation (10, 20.9%); vomiting/regurgitation (8, 16.6%); diarrhea (7, 14.6%); passing a lot of gases (6, 12.5%); repeated burping (6, 12.5%); abdominal distension (5, 10.4%); constipation (3, 6.3%); and retrosternal pain (2, 4.1%).

The median (IQR) pain score [4] was 5 (2-6). The median (IQR) episodes of abdominal pain in the last 4 weeks were 3 (1-8), with median (IQR) number of pain-free days in the last 4 weeks (at the time of enrolment into present study) was 26 (20, 27). Five children reported  $\geq 1$  day(s) of school absence in the last 4 weeks. Higher proportion ( $P=0.02$ ) of children who received drotaverine in the previous study (25/25) in comparison to placebo (18/23) had pain that was absent or better than before. The median (IQR) number of pain episodes in last 4 weeks was also significantly less in the drotaverine group in comparison to placebo group (0 (0, 2.5) vs. 2 (0, 6);  $P=0.03$ ) whereas the median (IQR) number of pain-free days was comparable in two groups (28 (25, 28) vs. 26 (24,28);  $P=0.054$ ). The number of children missing school due to abdominal pain in last 4 weeks were one and four, respectively in the drotaverine and placebo group ( $P=0.18$ ).

In an earlier study [5], 60.1% of the children with abdominal pain experienced complete improvement and 39.1% of the patients experienced partial or no improvement over a mean follow-up period of 18.7 months. They also observed that patients in the partial improvement group developed new FGID with long term follow up. Another follow-up study [6] of 392 children with functional abdominal pain over an average of 9.2 years reported that 41% still met criteria for a FGID, which is comparable to proportion observed in our study.

Increased psychosocial stress can lead to excess autonomic discharge from the brain to the gut [7]. Increased stress also contributes to visceral hyperalgesia that contributes to the symptoms of FGID. Symptoms may lead to more stress that can further exacerbate the symptoms. It is possible that breaking this vicious cycle by use of a short course of antispasmodic agent resulted in long-term benefit in our study.

Our study had a major limitation of large follow-up loss due to frequent change of contact details. Another limitation was that the patients when enrolled into the

earlier randomized controlled trial [1] were not given a diagnosis as per the Rome III criteria. Hence we could not carry out a direct comparison of their present Rome III diagnosis with their previous one.

This study suggests that though abdominal pain may persist over next 3-4 years in two-thirds of children with functional recurrent abdominal pain, it shows slight improvement in frequency and severity.

*Contributors:* BR, DS, MN, MP: contributed to study conception and design, material preparation, data collection, data analysis and preparation of the final manuscript.

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## Serial Computed Tomography Findings in a Child with Coronavirus Disease (COVID-19) Pneumonia

Novel coronavirus disease (COVID-19) is a highly infectious disease with its outbreak in China in late 2019 [1]. The novel coronavirus is reportedly affecting more adults than children [2,3]. Here, we provide computed tomography (CT) findings in a typical pediatric case with confirmed COVID-19 infection.

An 11-year-old boy, the close contact of confirmed COVID-19 infected father, presented to hospital with high fever for 10 days. He was confirmed COVID-19 infection by throat swab specimen test using Realtime RT-polymerase chain reaction (RT-PCR) method.

His symptoms relieved somewhat after interferon  $\alpha$ -2b combined with aerosol therapy in a local hospital. On admission, arterial blood gas analysis showed a low PaO<sub>2</sub> of 69.6 mmHg. Chest CT was performed, which showed patchy ground-glass opacities in left lower lobe with air bronchogram (**Fig. 1a**). He was diagnosed as COVID-19 pneumonia. During hospitalization, the child received recombinant human interferon alpha-2b (rhIFN $\alpha$ 2b) twice-a-day through nebulization combined with Complementary and alternative medicines. Supportive care including nasal cannula (maximum oxygen requirement 2L/min) was administered. CT done one week

later (day 7) showed scattered ground-glass opacities in left lower lobe (**Fig. 1b**). After two weeks of therapy, only slight sporadic ground-glass opacities in left lower lobe were found in repeat chest CT (**Fig. 1c**). Realtime RT-PCR on two throat swab specimens was negative for the COVID-19 at 14 weeks, 48 hour apart. The boy made a complete recovery.

This communication underscores the course of CT findings in COVID-19 pneumonia in a child without any co-morbidity, who improved after treatment.

*Authors' contributions:* GH,JC: conceptualized the study, collected data, WS: conceptualized the study, drafted the initial manuscript, and reviewed and JW: carried out the analyses; all authors reviewed and revised the manuscript, and approved the final manuscript as submitted.

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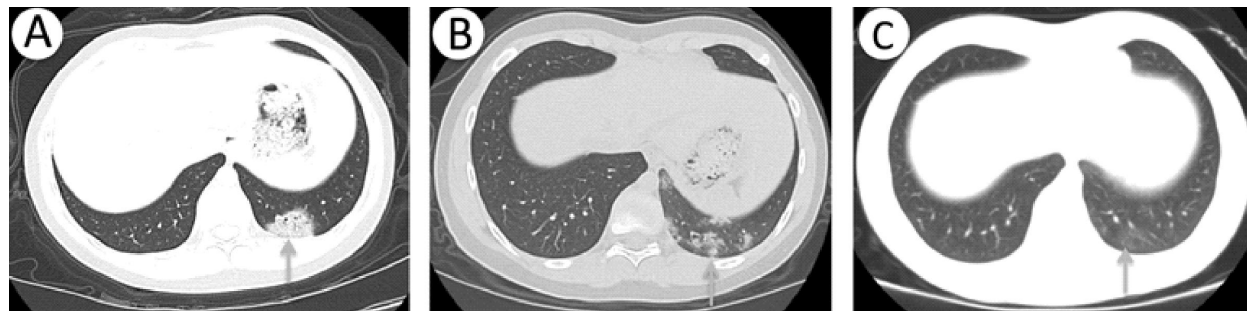
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**Fig. 1** Chest computed tomography (CT) scans in an 11-year-old boy with coronavirus disease-19. a) Chest CT performed on the day of admission shows patchy ground-glass opacities in left lower lobe with air bronchogram; b) Follow-up CT obtained on day 7 shows scattered ground-glass opacities in left lower lobe which were partly resolved; c) Follow-up CT obtained on day 14 shows slight sporadic ground-glass opacities in left lower lobe which have significantly resolved.

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## Urolithiasis due to Hereditary Xanthinuria Type II: A Long-term Follow-up report

**H**ereditary xanthinuria (HX) is a rare autosomal recessive disorder of purine metabolism. It results from deficiency of the enzyme 'xanthine dehydrogenase/oxidase (XDH/XO)' which catalyzes the final two steps in the purine degradation pathway (conversion of hypoxanthine and xanthine to uric acid). The resultant plasma accumulation and excess urinary excretion of xanthine is responsible for the arthropathy, myopathy, crystal nephropathy, urolithiasis, and renal failure seen in this disorder. Most patients belong to Middle East or Mediterranean region, and the disorder is rare in other parts of the world [1,2]. Two types of HX have been described; type I and type II, based on distinct mutation loci. It is difficult to distinguish the two subtypes on clinical and biochemical grounds, and molecular testing is needed for accurate phenotyping [1].

A 13-month-old male child, presented with recurrent episodes of orange colored graveluria and hematuria since the age of nine months. The child was born of a second-degree consanguineous marriage and family history was negative. Examination revealed a healthy appearing child with length 78 cm (75th centile) and weight 8.8 kg (10th-25th centile). The general and systemic examination was unremarkable.

Investigations revealed serum calcium 10.2 mg/dL, phosphorus 5.6mg/dL, alkaline phosphatase 678 IU/L, creatinine 0.4 mg/dL, blood urea 10 mg/dL, hypouricemia (serum uric acid <0.01 mg/dL) and hypouricosuria (24 hour urinary uric acid 0.4 mg/day, normal 250-750 mg/day; 24 hour urinary creatinine 88 mg/day, normal 88-106 mg/day). Radiograph of kidney ureter and bladder was normal, while ultrasonography revealed two calculi in the urinary bladder and concretions in the lower pole of left kidney. In view of low serum and urinary uric acid levels

and radiolucent nature of renal stones, xanthinuria was suspected. His hospital course was complicated by urethral obstruction which was relieved by catheterization followed by cystolithotomy at a later date. The bladder stones retrieved were subjected to X-ray diffraction study, revealing them to be of xanthine origin. A targeted gene sequencing revealed compound heterozygous mutation in the enzyme molybdenum cofactor sulfuryase (*MOCOS*) gene [heterozygous two base pair deletion in exon 6 (chr18:33785104\_33785105delCT) and heterozygous nonsense mutation in exon 11 (chr18:33831134T>G)]. Patient was diagnosed to be having HX type II and advised dietary purine restriction (avoidance of purine-rich foods including red and organ meat, shell fish, oily fish, seafood, sweetened beverages such as fruit juices and colas, yeast and mushroom, spinach, peas and whole pulses), and adequate oral hydration.

On follow-up, he had no further episodes of renal colic, graveluria or hematuria. The child maintained good compliance to dietary restrictions advised. His height and weight at nine years were 138.7cm (75th-97th percentile), and 32.1 kg (75th-97th percentile), respectively. Serial annual ultrasonography imaging and renal functions have remained normal with serum uric acid <0.01 mg/dL.

HX is a rare disorder of the purine metabolism that leads to urolithiasis. Renal stones can occur at any age, even in infancy [2]. The stones are radiolucent, and are seen in about 40-50% patients with this disorder. The diagnosis may be established with stone analysis, demonstration of an elevated urinary xanthine or hypoxanthine excretion, and measurement of XDH/XO activity in liver or intestinal biopsy sample. The finding of an orange-brown urinary sediment, orange-stained diapers, and profound hypouricemia are other important indicators. However, it is difficult to characterize the exact phenotype of the disorder (type I or II) based on these clinical and biochemical indicators alone, necessitating the use of molecular tests.

The mainstay of treatment is institution of a low-purine diet, and intake of plenty of oral fluids [3]. Urinary

alkalinization is of minimal therapeutic value, as the solubility of xanthine is only minimally enhanced at alkaline pH. Our patient showed excellent treatment response over a long follow up of nine years, which is in line with the short-term follow-up response reported in the literature [4,5].

To conclude, HX is a rare disorder of purine metabolism which should be suspected in children presenting with orange colored graveluria, hypouricemia, hypouricosuria and radiolucent renal stones. Molecular testing is essential for exact phenotyping, and should be pursued in all cases. Such children show excellent response to treatment with low purine diet and increased oral hydration, as exemplified in the case described.

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## Developmental Delay with Intermittent Twisting of Neck

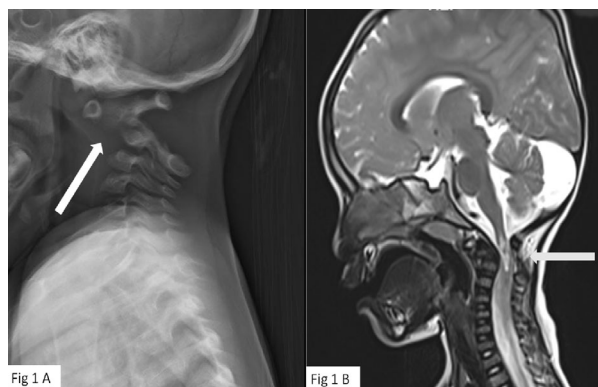
The hallmark of cerebral palsy (CP) is the presence of pyramidal or extra-pyramidal signs [1]. There are many disorders that can mimic CP [2]. One such mimicking condition is high cervical cord compression due to anomalies of the spinal cord [3].

A two-year-old boy, second of twins born of non-consanguineous marriage, was brought with inability to stand. He was delivered at eight months of gestation with a weight of 1.5 kg and no significant neonatal complications. His motor milestones were significantly delayed compared to his twin and spasticity was noticed from six months of age. The parents reported stiffness of his neck and limbs which was more on waking up, which would decrease within a few minutes. There were no seizures or regression of milestones. He was diagnosed to have mixed (spastic-dystonic) cerebral palsy. His language and social skills were age appropriate. At presentation, he was using two- word phrases and had attained daytime bowel and bladder control.

On examination, weight, height and head circumference were within normal limits. There were no

obvious dysmorphic features. His upper segment to lower segment ratio was 0.92 suggestive of truncal shortening. His vision and hearing were normal. There was hypertonia in all the four limbs and brisk deep tendon reflexes. The plantar responses were extensor bilaterally. Examination of the other systems was unremarkable.

Lateral X-ray of the neck (**Fig. 1a**) showed anterior dislocation of C1 vertebra. The pre-dentate space was widened and measured 13 mm. MRI did not show any



**Fig. 1** (a) X-ray Cervical spine lateral view flexed position showing widened pre-dentate space (white arrow); (b) MRI T2 weighted image sagittal section showing compression of the cord at C1 level (grey arrow).

periventricular or basal ganglia changes. MRI of the cervical spine (**Fig. 1b**) (confirmed atlanto-axial dislocation (AAD) causing compressive myelopathy at C1 level, without any other spinal malformations. Neurosurgeon prescribed neck collar, and advised follow-up for cervical spine stabilization. In view of the truncal shortening and AAD, he was also advised evaluation for skeletal dysplasia, but the parents deferred it to a later date.

Conditions which mimic CP should be considered – when there is absence of definite preceding perinatal insult; there is family history of developmental delay and spasticity; there is developmental regression or onset of new clinical signs of upper motor involvement; and when there is associated significant ataxia, muscle atrophy, or sensory loss [2]. Although neuroimaging is not essential for making a diagnosis of CP, MRI brain is abnormal in more than 80% of children with CP [4]. Current Western guidelines recommend MRI in children suspected to have CP [1]. The imaging not only uncovers the pathogenic patterns responsible for the CP but can also detect structural malformations of the brain and neuro-metabolic problems which resemble CP [4].

Despite significant perinatal risk factors, the intermittent abnormal neck stiffness warranted meticulous examination and evaluation [3], which revealed AAD can be idiopathic or due to traumatic, inflammatory or genetic disorders like Down syndrome, achondroplasia, cleidocranial dysplasia and Morquio syndrome [4]. Neurological manifestations of congenital AAD in children result from progressive compression of the cervico-medullary junction and present as progressive quadriplegia. Patients with myelopathy may go undiagnosed for a long period because of very slow progression of the

disease process [3] and maybe mistakenly diagnosed as CP. Trauma or sudden movement can worsen symptoms in AAD. In the reported child, the increase in stiffness upon getting from sleep could possibly be due to the fact that while he was lying down, neck positioning could have caused an increase in stiffness. Poor cervical posture during sleep could cause increased biomechanical stresses on the structure of the cervical spine and could result in cervical pain and stiffness [5].

This case highlights compressive myelopathy as a differential for CP, and underscores the importance of a good history-taking in all patients, especially those labelled as cerebral palsy.

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## Congenital Chylothorax with Lymphatic Malformation and Successful Antenatal and Postnatal Management

Neonatal chylothorax is an abnormal accumulation of lymphatic fluid in the pleural space which can be either congenital or acquired. Nearly 90% of all *in utero* pleural effusions are chylothorax [1]. The estimated incidence of congenital chylothorax is 4 per lakh [2], with mortality ranging from 30-50%. [3]. We herein report a late preterm

girl identified antenatally at 31 weeks of gestation with severe bilateral pleural effusion for which thoracoamniotic shunt was placed and subsequently diagnosed with congenital chylothorax after delivery.

A 37-year-old lady, G3P1A1L1 was admitted at 36<sup>5/7</sup> weeks for delivery of hydropic fetus. Antenatal follow up had been uneventful till 31 weeks when ultrasonography showed hydropic changes in the fetus with bilateral pleural effusion and subcutaneous edema. A therapeutic fetal pleurocentesis was done with amniocentesis. Chromosomal analysis and microarray on amniotic fluid was negative. Mother had a negative indirect coomb's test, with serology negative for VDRL, and TORCH. Parvo

Virus PCR was negative, and she had a normal HbA1C and Hemoglobin electrophoresis. Pleural fluid examination showed 205 leucocytes per cu.mm, 80% lymphocytes, LDH 87 U/L and a protein of 1.8g/dL. Follow up scan at 33 weeks showed a return of significant pleural effusion. Rather than opting for preterm delivery, a right Rodeck thoracoamniotic shunt was placed. Subsequent USG showed resolution of effusion on the Right side with lung expansion and satisfactory interval growth with normal fetal Dopplers. The left pleural effusion was drained just prior to the delivery.

A female baby with birth weight of 3015 g was delivered at 36<sup>5/7</sup> week gestation by elective LSCS. Baby had signs of labored breathing at birth, and was intubated and ventilated. Chest X-ray showed right side pneumothorax and left side pleural effusion for which bilateral intercostal tube drains (ICD) were inserted. Pleural fluid was clear exudate (Protein – 2.6 g/dL) with 3638 cells/mm<sup>3</sup>, predominantly lymphocytes and 1.9% neutrophils. Post ICD insertion baby improved and was extubated to high flow nasal cannula (HFNC). Echocardiography and ultrasound abdomen and cranium were normal. Once feeds were started pleural fluid became milky in nature. Pleural fluid sent for analysis showed rise in triglyceride level from baseline 35.8 mg/dL on Day 1 to 134 mg/dL on day 6 confirming the diagnosis of chylothorax.

MRI Chest was done on Day 8 of life for central lymphatic anatomy and intrathoracic mass lesions. It showed prominent tortuous lymphatic channels along with prominent azygous vein (**Fig. 1**). Baby was started on medium chain triglyceride formula on day 9 of life in view of chylothorax. Feeds had to be discontinued and parenteral nutrition restarted along with injection Octreotide on day 12 because of increasing chyle drainage. Following this, chyle formation reduced and the intercostal drains were removed on day 16. Post drain removal there was an increase in pleural effusion (right > left) which was organizing and non-tappable. Octreotide infusion was increased in view of persistent collection (at 10 mcg/kg/hr). Immunoglobulin levels were low for which single dose IVIG was given. On Day 25, lymphoscintigraphy was done to rule out lymphatic dysplasia, which was reported as normal. Feeds were restarted on day 28, after which there was worsening in respiratory distress but there was no increase in pleural effusion; as monitored by ultrasound. Keeping the possibility of leaky pulmonary lymphatics causing increase in pulmonary interstitial fluid, diuretics were added, to which baby responded well and feeds were gradually increased. Diuretics were continued till day 41 of life. Octreotide infusion was tapered gradually. Clinical

exome testing done which showed no pathogenic variants causative of the phenotype, but variants of uncertain significance were detected (lymphatic malformation-3, OMIM#613480). Baby was discharged on day 44 of life on MCT- based formula (Pregestimil).

Congenital chylothorax can be an isolated finding or may be associated with genetic conditions. Early antenatal detection and management by placement of fetal pleuroamniotic shunt improves perinatal outcome by avoiding complications due to pulmonary hypoplasia [4]. Irrespective of the cause, initial postnatal management consists of drainage of pleural fluid, appropriate ventilation, total parenteral nutrition and dietary modification (conservative approach). Medication and surgery may be required in refractory cases. Most chylothorax cases improve spontaneously because of the natural course of the disease. In newborns it is important to distinguish neonatal chylothorax from congenital lymphatic dysplasia, as the latter is difficult to treat and has poorer prognosis.

As increased chyle formation is associated with immunological and nutritional complications, we had started octreotide on day 12. On reviewing literature [5,6] we could not find any practice recommendations for use of octreotide. The lymphatic malformation-3 may explain the localized edema in neck, genitals and probably in lungs, which persisted at time of tapering of octreotide infusion.



**Fig. 1** MRI image (T2 SPAIR, coronal diffusion weighted sequence) showing bilateral pleural effusion (R>L), prominent tortuous lymphatic channels in thoracic region extending into upper abdomen, with no evidence of any mediastinal mass.

To conclude, optimum management of such cases is still a matter of debate, but prenatal evaluation and management is associated with improved survival. Postnatally we should follow conservative approach for few weeks to give enough time for the lymphatics to heal and develop collaterals [6]. Refractory cases would require additional therapy.

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## Stumped by Potassium: A Rare Case of Familial Pseudohyperkalemia

Hyperkalemia is a common electrolyte disturbance requiring emergent intervention to avoid potential fatal arrhythmias. Pseudohyperkalemia should be kept in mind in the absence of symptomatology and other associated laboratory abnormalities. We present a rare case of pseudohyperkalemia detected incidentally during evaluation of a child with acute respiratory infection. Familial pseudohyperkalemia is an asymptomatic condition that is detected incidentally during evaluation if serum is stored below room temperature prior to testing. It is characterized by spuriously high serum potassium levels due to cold-induced 'passive leak' of red blood cell (RBC) potassium ions into plasma [1,2]. *ABCB6* gene (2q36) has been identified as the causative gene of this rare condition [3].

A 2-month-old baby, first born of non-consanguineous parents, presented to a peripheral health care setup with history of cough and fever for 2 days with some lethargy and refusal to feed. On examination, the infant was found to have mild tachypnea and tachycardia and was admitted for monitoring and supportive therapy. Hematological and

biochemical parameters were sent to rule out sepsis and dyselectrolytemia. All parameters were within normal limits except for the elevated potassium levels of 6 mEq/L. In view of high potassium levels, repeat sample was sent, which had serum potassium values of 6.8 mEq/L. The ECG did not show signs of hyperkalemia. Echocardiography revealed a structurally normal heart with good biventricular function. However, chest X-ray showed diffuse non homogenous opacities suggestive of bronchiolitis and a large homogenous opacity silhouetting the left cardiac border with a linear translucency surrounding it. Tumor lysis syndrome was initially suspected to be the cause of hyperkalemia but computed tomography of chest revealed that this anterior mediastinal mass was an unusually large, hypertrophied thymus gland and not a malignant mass. During PICU stay, baby remained asymptomatic but continued to have hyperkalemia. There were no dysmorphic features or abnormal genitalia suggestive of any recognizable genetic syndrome. Baby was worked up further with plasma renin activity and aldosterone levels for possibility of pseudohypo-aldosteronism. However, all investigations were within normal limits. Common causes of pseudohyperkalemia (cell lysis, extreme leukocytosis or thrombocytopenia, or use of EDTA anticoagulant) were ruled out.

Clinical exome sequencing was done to rule out pseudohypoaldosteronism type II; as common causes had been excluded for the cause of hyperkalemia. It

revealed pathogenic heterozygous variation (c.592G>T, p.Gly198Trp) in *ABCB6* gene, which is associated with Autosomal dominant familial pseudohyperkalemia type 2. This is a benign disorder associated with temperature-dependent anomaly in red cell membrane permeability to potassium that leads to high *in vitro* potassium levels in samples stored below 37°C [2]. The diagnosis was confirmed by doing parallel laboratory assessment of serum potassium levels incubated at 37°C and 4°C which revealed normal potassium levels at 37°C (4.8 mEq/L) and hyperkalemia at 4°C (6.0 mEq/L). Maternal and paternal serum sample did not reveal any abnormality.

Sampling errors including collection and handling may give rise to spuriously high potassium [4,5]. Pseudohyperkalemia may also be caused in the presence of leukocytosis and thrombocytosis [6,7].

Inherited defects in RBC membrane structure are rare causes of pseudohyperkalemia. Two common inherited defects in RBC membrane structure that predispose to pseudohyperkalemia include Familial pseudohyperkalemia and Dehydrated hereditary stomatocytosis.

Familial pseudohyperkalemia is inherited as an autosomal dominant trait caused by heterozygous variant in *ABCB6* gene. This genetic anomaly causes increased *in vitro* leak of potassium from erythrocytes to plasma/serum when blood is exposed (*ex vivo*) to temperatures below normal body temperature (37 °C). It is a benign condition with excellent prognosis and patients reported with this condition remain asymptomatic and this is usually an incidental finding. No treatment is required for this condition. However, correct diagnosis is important for prognostication and to avoid needless evaluation for more sinister causes. Serum potassium levels in some patients with familial pseudohyperkalemia variants show relatively large abnormalities on storage below room temperatures; therefore affected individuals are not suitable candidate for blood donation.

This case report emphasizes the importance of evaluation for rare causes of hyperkalemia once the

common causes have been excluded to ensure early and appropriate management if indicated and avoid unwarranted treatment for benign conditions.

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## Spontaneous Resolution of Congenital Hyperinsulinism With Octreotide Therapy

Hyperinsulinemic hypoglycemia is caused by dysregulated insulin secretion from the pancreatic  $\beta$ -cells. Congenital hyperinsulinism (CHI) is caused by genetic mutations in twelve known genes. Histologically, lesions can be focal or diffuse. Focal forms are often associated with paternal heterozygosity in *KCNJ11/ABCC8* genes, whereas diffuse forms are seen in patients with maternal heterozygous, homozygous or compound heterozygous mutations. 18F-DOPA PET/CT imaging can precisely localize the lesion in focal forms, thereby facilitating cure by focal lesionectomy unlike diffuse form is mostly resistant to medical treatment and needs subtotal pancreatectomy [1].

We report the case of a term non-dysmorphic male baby (weight 2400 g) born to a non-consanguineous couple in Myanmar. He was born through meconium stained liquor with low Apgar scores, required resuscitation and was ventilated for ten days. Hypoglycemia (1.6 mmol/L) was noted at six hours of age, which required mini bolus followed by glucose infusion rate of 5.6 mg/kg/min. On day six, he developed seizures with hypoglycemia and GIR was gradually escalated to 19.5 mg/kg/min. Diagnosis of hyperinsulinemic hypoglycemia was made in the presence of detectable insulin (10.7 mU/L) with hypoglycemia (0.3 mmol/L) and hypoketonemia (0.3 mmol/L). Medical treatment was initiated with nifedipine while awaiting supply of diazoxide. Diazoxide was initiated at a dose of 5 mg/kg/day and was gradually increased to 15 mg/kg/day over a week with discontinuation of nifedipine. Subcutaneous octreotide (dose of 7.5 mcg/kg/day) was added as GIR continued to rise on diazoxide. With adequate response to octreotide, diazoxide was later discontinued.

DNA samples of the proband and parents were sent to UK for genetic study. A novel heterozygous *KCNJ11* missense variant, c.866G>C p. (Gly289Ala) was identified in the proband. Sequencing of the *ABCC8* gene was normal. Sanger sequencing of *KCNJ11* gene for the familial variant indicated heterozygous mutation in father whereas the mother was negative. The clinical significance of the *P.* (Gly289Ala) variant is uncertain. A focal lesion was suspected with the paternal mutation and 18F-DOPA PET/CT scan was recommended.

DOPA PET/CT scan was unavailable in Myanmar and there was no funding source for overseas transfer. Treatment with octreotide was continued and GIR was

successfully weaned off with feeding increments to achieve full feeds by six months of age. At nine months of age, octreotide dose was auto-tapered to 3 mcg/kg/day while maintaining normoglycemia and discontinued at 9.5 months of age. His glucose profile remained stable on follow-up but neurodevelopmental assessment at 22 months of age showed moderate mental and motor retardation. Vision and hearing tested normal. He is currently enrolled in an early intervention programme.

CHI is a heterogeneous disease caused by mutations in at least twelve known genes [1]. Loss-of-function mutations in  $K_{ATP}$  channel regulating genes constitute nearly 90% of cases of diazoxide-unresponsive CHI, of which *KCNJ11* is associated in 10% [2].

The index case had diazoxide-unresponsive CHI that detected a novel paternally inherited *KCNJ11* missense variant of uncertain significance at p. (Gly289Ala). A different missense variant at the same residue was previously reported by Mohnike, *et al.* [2] in a patient with diazoxide-responsive CHI, which was shown to have arisen *de novo* in the proband.

Similar spontaneous resolution has been reported at 1.6 and 1.9 year in patients with CHI [3,4]. DOPA tracer uptake may not correlate with the capacity of the pancreatic lesion to secrete insulin and the clinical remission of CHI could be a functional process without apoptosis of mutated  $\beta$ -cells [5]. This finding prompts long-term follow-up of our case to ensure optimal glucose regulation.

Most patients with  $K_{ATP}$  channel gene mutations do not respond to diazoxide treatment as it exerts its effects by keeping the channel open, preventing  $\beta$ -cell membrane depolarization and release of insulin. Octreotide reduces insulin secretion by inhibiting intracellular entry of calcium and by decreasing the insulin gene promoter activity [6]. These differences in the site action possibly explain the treatment response in the index case.

In summary, normoglycemia should be maintained to prevent brain injury with high GIR and/or high caloric enteral feeds in infants with CHI. Octreotide can be tried in diazoxide unresponsive patients and spontaneous resolution can be seen in CHI. Genetic studies help indicate the type of mutation. DOPA-PET scan confirms nature of lesion prior to surgery, which however remain poorly accessible in resource-limited settings.

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## A Low-cost Solution for Retrofitment of HEPA Filter in Healthcare Facilities Providing Care to COVID-19 Patients

The whole world is currently facing an unprecedented threat due to the spread of the COVID-19 virus. The healthcare workers seem to be particularly at risk from the disease given the high incidence of infection in healthcare workers caring for COVID-19 patients.

One of the major causes of risk to healthcare workers may be the increased viral load in their environment when treating the patients who release the viral particles as aerosols [1]. High Efficiency Particulate Air (HEPA) filters of higher grades are considered to be very effective (efficiency up to 99% as against N95 masks which are 95% efficient) in removing air-borne virus particles [2-4]. Ultraviolet light (UV) sterilization may also afford significant protection against the spread of the virus [5].

It is known that many healthcare facilities, especially in low- and middle-income countries, do not have isolation areas fitted with HEPA filtration. Even if they do, in the face of the current rapid increase in the numbers of COVID-19 patients requiring admission, the additional space that needs to be created may not have proper air management.

In this situation, one alternative may be to deploy adequate numbers of regular room air-purifiers with HEPA filters that are commonly used in households for air-pollution, especially the ones with UV light for sterilizing the passing air without releasing UV light into the open environment that may risk exposing the user directly. The United States Centers for Disease Control and Prevention has acknowledged in-room air cleaners as alternative technology for increasing room ventilation when this cannot be achieved by the building's heating, ventilation, and air conditioning system [3].

Such air purifiers placed at bed-level next to the admitted patients may significantly reduce the virus load in the environment. The air-purifiers may be recommended in

high aerosol generating zones like ICUs, operation theaters, procedure rooms, autopsy chambers and swab collection or processing stations. Other patient contact areas like triage areas and CT scan and X-ray units may also be of benefit. Similar purifiers placed in isolation setups for the suspected patients too may reduce the possibility of cross infections from the positive patients.

The use of this low-cost, easily available, off-the-shelf technology may provide HEPA filtration at COVID facilities lacking it, in a simple, cost-effective and plug-and-play manner with zero lag-time, potentially saving lives of frontline healthcare workers.

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## Challenging Times for Children With Transfusion-dependent Thalassemia Amid the COVID-19 Pandemic

A novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originally from Wuhan, China, has now become a pandemic. To curtail its spread, many countries, including India, have taken a judicious decision to have nationwide lockdowns restricting movements of citizens. However, this has made it difficult for children with many chronic conditions to continue their therapy.

Children with thalassemia major require periodic blood transfusions. In India, almost half of children with  $\beta$ -thalassemia major under-transfused [1]. With the lockdown in our country, patients and their parents would find it difficult to visit their routine clinics for blood transfusions. Moreover, the lockdown has drastically reduced the number of voluntary blood donations, thereby creating a shortage at blood banks. Despite the cancellation of all elective surgeries, blood units available for transfusion are less [2]. Although viral RNA has been detected in the plasma/serum of COVID-19 patients, the present data do not suggest the risk of transfusion transmission of SARS-CoV-2. However, certain International organizations have advised deferral of blood donation for 21 days after possible exposure to a confirmed case and for at least 28 days after symptom resolution in a positive case [3]. In addition, patients on iron chelation therapy may find it difficult to procure the drugs amid lockdown.

Eventually, there is an underlying risk of these children contracting COVID-19. Unlike sickle cell anemia, children with thalassemia are usually not at an increased risk of fatal pulmonary complications due to COVID-19. However, splenectomy and underlying comorbidities secondary to iron overload, notably secondary diabetes mellitus, cardiomyopathy and chronic liver disease, may increase the risk of complications and mortality in COVID-19 [4].

Certain solutions do exist. Blood transfusions could be carried at any nearest convenient healthcare facility instead of routine transfusion clinics. Healthcare authorities should strengthen mobile unit services for facilitating blood donation at doorstep while ensuring stringent precautions. Till blood stocks replenish, caregivers can bring a voluntary healthy donor at the time of transfusion. Physicians should educate children and caregivers about need for strict social distancing, hand hygiene and common symptoms of COVID-19. Tele-consultations may play a role in this regard. Children with associated comorbidities must be more cautious. Good glycemic control in patients with secondary diabetes should be ensured. Underlying subclinical hypo-adrenalism should be considered in every thalassaemic child with suspected COVID-19 and supplemented with stress-dose of glucocorticoids.

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## Fecal Shedding of SARS CoV-2: Implications for Disease Spread and Quarantine

COVID-19 has already spread to more than 200 countries affecting 1,210,956 humans and resulting in 67594 deaths worldwide [1]. It predominantly affects adults whereas children constitute about 1-5% of all confirmed cases [2]. Similar to adults, cough (48.5%) and fever (41.5%) are the most common manifestation in children [2]. However, a significant proportion (8-30%) of children have presented with gastrointestinal (GIT) symptoms too [2,3], suggesting the predilection of COVID-19 for the angiotensin-converting enzyme II receptor of GIT [4]. The overall incidence of GIT symptoms might be underreported as screening is solely based on respiratory symptoms as of now.

The above observations are well supported by recent studies. Wu, *et al.* [5] reported that 55% of patients' fecal samples were positive for SARS CoV-2 RNA by real-time RT-PCR, and it remained positive for 27.9 days. Importantly, the fecal sample remained positive longer than the respiratory samples [5]. In another series of 10 children, the rectal swab was positive in seven patients, and the viral RNA was detected in stool well after the respiratory tract sample turned negative [3]. These findings suggest that viral shedding from the gastrointestinal tract persists much beyond (~2 weeks) the respiratory system. This is thought to be due to low cycle threshold (Ct) or high viral load in stool sample as compared to nasopharyngeal swab [3]. Till now the infectivity of the fecal shedding is not proven, and there are chances of fecal viral genomic material shedding without any infective potential. However, this 'no evidence of infectivity' shall not be taken as 'evidence of non-infectivity'. Considering mild course of COVID-19 in children, these findings may not have much relevance for themselves but their probable potential carrier status will have strong implications over the containment strategies. Therefore, it will be wiser to follow toilet hygiene along with respiratory hygiene and etiquette.

Most current guidelines recommend discharging COVID-19 patients when they turn asymptomatic with two negative consecutive oropharyngeal swab RT-PCR done at least one day apart. However, the recent reports of persistent fecal shedding even up to three weeks after negative oropharyngeal swabs are of concern [3,5]. We understand that in current scenario, amidst a limited supply of kits, testing for fecal shedding may not be wise.

But, ignorance to their probable carrier status may continue the chain of transmission. Also, there are instances where patients were discharged after two consecutively negative swabs and later became symptomatic and were re-admitted. On re-admission, the repeat swab report came out positive [3]. However, these instances are mostly related to false negative results (either due to poor sampling technique or low sensitivity of the kit) of the earlier tests. The more robust animal studies suggest that the reinfection with SARS-CoV-2 does not occur [6]. However, to be on the safer side, shouldn't we go for more stringent steps and keep them in home-isolation for two more weeks after negative nasopharyngeal swab?

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## Impact of COVID-19 on Children and Pediatricians

During the 2009 H<sub>1</sub>N<sub>1</sub> pandemic, we had written about lessons learnt from the pandemic [1]. After a decade, we are in the midst of another pandemic due to a respiratory virus (SARS-CoV-2) [2]; we, herein try to highlight some of the similarities and differences in the public and government response to the epidemics, and its impact on children and pediatricians.

Agent, host and environment decide the course of an outbreak of infectious diseases. Both pandemic flu and SARS-CoV-2 spread by respiratory droplet, but it is thought that the mortality is higher in SARS-CoV-2 infected cases. While pandemic flu caused significant mortality in children, SARS-CoV-2 mainly kills people over 60 and with comorbidities. From the data published so far, it appears that children account for 1-5% of all cases and would generally have a milder disease compared to adults [3]. The less severe presentation may be attributed to less exposure or sensitivity to COVID-19, different immune response mechanisms, or higher levels of antibodies to viruses than in adults due to broader exposures to respiratory infections in winter. There is some interest in the possible role of measles [4] and BCG vaccine in providing protection against SARS CoV2; if true, India stands to gain from its recent Measles-Rubella vaccine campaign. However, we cannot be complacent and we need to be on the lookout for severe disease in 'high risk' children (immunocompromised, lung or airway disease, long term steroids, thalassemia, nephrotic syndrome etc.), in addition to continuing their ongoing management [5]. Seasonality of influenza is largely dictated by temperature and it remains to be seen how these factors affect SARS-CoV-2 transmission. Social determinants of health, including health equity and age-related illness, may play an important role in both pandemic flu and COVID-19 pandemic.

During the 2009 pandemic, India reported 27,236 laboratory confirmed cases of pandemic influenza A (H1N1) with 981 deaths [6]. The first case of the COVID-19 pandemic in India was reported on 30 January, 2020. As of 5th April, 2020, the Ministry of Health and Family Welfare has confirmed a total of 4643 active cases and 149 deaths in the country, with an increase predicted in coming days.

During the 2009 H<sub>1</sub>N<sub>1</sub> pandemic, few people in India had access to social media and the primary source of

information was television and print. Information about the number of cases and deaths worldwide and in India was available but not at the pace it is available today. In general, there was poor awareness about how the infection spreads and the simple public health measures that could be taken to prevent spread. In contrast, there has been a huge outpour of information and misinformation primarily attributable to the social media during the current pandemic. It was heartening to see increase in public awareness about social distancing, hand washing, use of hand sanitizers, and cough hygiene, and measures to prevent transmission of SARS-CoV-2. At the same time, a lot of fake news and videos about the disease went viral on social media adding to the panic and confusion among lay persons.

During 2009 H<sub>1</sub>N<sub>1</sub> pandemic, active public participation was limited. In contrast, the COVID-19 pandemic has sparked off a citizen's movement, with people standing at the frontline, shoulder-to-shoulder with governmental agencies. Several industrialists and celebrities have responded with financial contributions to the government funds and startups have come forward with innovations and technical expertise.

In 2009, the government response was much more limited to advisories on prevention of H<sub>1</sub>N<sub>1</sub> through television and print. During this pandemic, the government has been seen to be very proactive by taking measures like public education through social media, television, radio, mobile phones and by various measures like active contact tracing and restrictions on public travel. The entire country was put into lockdown from 24 March, 2020. This has implications for children's physical and mental health. Due to decreased physical activity and consumption of fast food children from privileged section of society may become overweight. More importantly children from less privileged sections of society may become malnourished. Excessive screen time during lockdown may cause eye strain and behavioral issues may crop up. Online and domestic child abuse may increase during this period. ICMR has been quite proactive with updates on diagnostic testing and management guidelines. Also seen is better coordination between various government departments like health ministry, law enforcement, transport authorities etc. Tackling the COVID-19 or any other pandemic, must not just be a point-in-time solution, but that it must always keep the larger objective of comprehensive, affordable public health in view. A robust community health framework is essential if we have to achieve this objective.

There is an urgent need to work on insufficient healthcare infrastructure and manpower improvement to

manage this and future pandemics. We should also look at indigenous manufacturing of high quality PPEs, point of care diagnostics and ICU equipment as these are crucial part of pandemic preparedness.

Finally, the pediatrician treating the sick child is a susceptible adult and due care must be taken by all pediatricians while examining children, particularly those with respiratory symptoms. Use of appropriate PPE, postponing routine visits (immunization visits can be continued as per WHO guidelines), allowing only one attendant with the child in the clinic, frequent sanitizing of the clinic, educating the clinic staff and parents accompanying children, appropriate use of telemedicine, avoiding throat examination, spacing out appointments, hydroxychloroquine prophylaxis are some ways in which pediatricians can minimize the risk to themselves. For pediatricians serving in ICUs, following strict guidelines issued by IAP [7] and government is of utmost importance.

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## Pediatric Palliative Care: An Innovative Approach to Pediatric Care for Children With Life-Threatening Conditions

Pediatric palliative care (PPC) is a specialized comprehensive care approach for children living with life-limiting and life-threatening illness. The focus is providing relief from the symptoms and the stress of the illness. The goal is to improve quality of life for both child and the family. The specially trained team which consists of a doctor, nurse, counsellor and sometimes, depending on resources, physiotherapist, play/music therapist, religious person, work together with other doctors of the

child as an extra layer of support. Palliative care is appropriate at any age and at any stage of illness and it can be provided along with curative treatment or as standalone.

The American Academy of Pediatrics states that “*the components of palliative care are offered at diagnosis and continued throughout the course of illness, whether the outcome ends in cure or death*” [1]. Access to palliative care is being considered a human right [2] and most pediatric hospitals in developed countries are working towards integrating the program to demonstrate better standards of care.

The palliative goals of care depending on the diagnosis and condition of the child can vary from supportive care during curative treatment to symptomatic management and end of life care. Children with these chronic illnesses might experience multiple



crises requiring intensive care which are stressful to them and their families. The palliative care team provides additional support during emergencies and health crises, while also helping to address the challenges of daily living. Therefore, an integrated palliative care program ideally consists of out-patient, in-patient, hospice and home care to maintain continuum of services. However, there are many successful PPC models across the world which have a different combination of these services.

A study published in 2017 estimated the global need for PPC to be 21.6 million, with 8.2 million children needing access to specialist palliative care service provision [3]. In India, these authors estimate that there are 1.6 million children in need of specialized pediatric palliative care [3]. Presently, there are very few trained PPC specialist doctors in India, which is both due to the lack of awareness about the existence of such a specialty, and limited provisions for training in this specialty. As

some centers are now providing training in this speciality, we feel that more young pediatricians need to take-up this specialty by utilizing available training facilities, so that the quality of life of children with life-threatening conditions can be improved.

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## Melioidosis Presenting with Membranous Tonsillitis and Erythema Nodosum

A 12-year-old boy presented with fever and cough of 12 days and painful skin lesions on legs for two days. He did not have any pre-existing medical illness, history of contact with soil, or groundwater. He presented in July, which is monsoon season in coastal Karnataka. On examination, his weight was 30 kg (75th percentile), height was 130 cm (50th to 75th centile), and vitals were stable. Oral examination revealed red and swollen tonsils with an exudative membrane on the medial surface. He had multiple erythematous, tender, nodular lesions of 10-20 mm size on bilateral lower limbs consistent with erythema nodosum. Systemic examination was unremarkable. Baseline blood tests showed hemoglobin of 10.5 g/dL, total leukocyte count of  $11.8 \times 10^9/L$  (P 80%, L 16%), platelet count of  $241 \times 10^9/L$ , erythrocyte sedimentation rate of 42 mm/h and C-reactive protein of 96 mg/dL. Throat swab and blood culture were sent, and he was prescribed intravenous amoxicillin/clavulanic acid and amikacin. His throat swab isolated *Burkholderia pseudomallei*, hence antibiotics were changed to intravenous ceftazidime (120 mg/kg/day). The child improved with resolution of symptoms over the next four days. He received ceftazidime for 10 days and was discharged on oral trimethoprim-sulfamethaxazole

(6mg/kg of trimethoprim) for three months. The child is well at six month follow-up.

Melioidosis, caused by soil saprophyte *B. pseudomallei*, is an endemic infection in India [1]. Due to diverse clinical manifestation and lack of routine bacteriological detection methods, melioidosis stays under-diagnosed and under-reported [2]. Typical clinical



Fig. 1 Erythematous nodular lesions seen on the lower limbs.

presentation of melioidosis includes suppurative lesions in head and neck, soft tissue infection, pneumonia, and septicemia [3,4]. Our patient presented with membranous tonsillitis and erythema nodosum, common entities in pediatric practice, but *B. pseudomallei* as the etiologic agent for the same has not been previously reported. Two patients with pharyngitis with pharyngeal culture-positive, and a single patient with urticarial rash and blood culture positive for *B. pseudomallei* has been reported by Lumbiganon, *et al.* [4]. A study by Wuthiekanun, *et al.* [5] reported 100% specificity and 36% sensitivity of throat swab culture for melioidosis. Due to low sensitivity, throat swab warrants the need for adjunctive tests.

A high index of suspicion is required to diagnose melioidosis due to its varied presentation, especially in the presence of predisposing conditions like exposure to soil, water, rainy season, or an immunocompromised state.

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## Sedation in Pediatric Bronchoscopy: Propofol versus Fentanyl

We read with interest the article by Gunathilaka, *et al.* [1] reporting on comparison of propofol and fentanyl for sedation in pediatric bronchoscopy. We wish to raise the following issues related to the article:

- (i) The authors state that the allocated assignment was not disclosed to the bronchoscopist and the patient. However, the independent observer who also decided the cough score, secretion score and physician satisfaction score was not blinded to the assignment and this could have caused assessment bias in the study. Additionally, the primary investigator was not blinded to the study arm. However, the stop watch reading to document the time of achievement of Ramsay score 3 (primary outcome) was done by the primary investigator himself, which may have increased the chances of assessment bias in the study. It would have been better that a third person not involved in the study

and blinded to the intervention was given the responsibility of assessing primary outcome (time to achieve Ramsay score 3).

- (ii) The baseline characteristics table shows that mean (SD) oxygen saturation was 99.1 (1.5) and 99.1 (1.4) in propofol and fentanyl groups, respectively. This implies that upper limit of oxygen saturation was more than 100% in both the groups, which is not possible.
- (iii) The results show that the mean (SD) time to achieve Ramsay score 3 (primary outcome) was 15.7 (4.4) seconds in propofol group. However, in secondary outcomes, the additional midazolam doses needed in propofol group was 11. But midazolam could only be used if the child was not sedated within 180 seconds. So the use of midazolam needs more clarification.
- (iv) The article mentions that intravenous midazolam was repeated every 1 minute if Ramsay score of 3 was not achieved. The onset of effect for midazolam is 1 to 2.5 minutes, the peak effect is at 3 to 4 minutes, and the duration of effect is 15 to 80 minutes [2]. In a meta-analysis done for the comparison of propofol and midazolam for bronchoscopy [3], in all the four included randomized controlled trials, midazolam

was given every  $\geq 2$  minutes if sedation goal was not achieved [3].

- (v) If midazolam was being used for sedation as mentioned above, then it is difficult to rely on the results because the time to achieve sedation and recovery would have also been affected by midazolam. Applying a regression analysis in the outcome variables would have been more justified [4].

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## Authors' Reply

We thank the readers for their interest in our article [1]. The authors have pointed out few issues; most of these were already addressed in the article. Following are our responses to the points highlighted [2].

- (i) We have mentioned various aspects of conduct of the trial in detail in the study methods. The limitation of the study being an open label study have been clearly mentioned in the discussion. For an open label study, we took various measures to reduce the risk of bias. However, to take care of the bias better, a blinded study - a double dummy design - would have to be performed. To reduce the bias, regarding cough score, secretion score, bronchoscopist and an independent observer assigned the scores independently (these details were mentioned in the manuscript).
- (ii) The mean and standard deviation values for oxygen saturation are correct. A standard deviation of 1.5 or

1.4 when mean value is 99.1 does not mean that some values were more than 100; this is a common misconception. The standard deviation is one of the measures of dispersion. For baseline saturation, the maximum value was 100% in both arms while the lowest values were 94% and 95% in the propofol and fentanyl arms, respectively; this suggests that there was a skew to left. The median (IQR) values were 100% (98%, 100%) and 100% (98%, 100%), respectively in the propofol and fentanyl arms.

- (iii) We have clearly highlighted the indications for use of midazolam in the methods. After the initial 180 seconds, there was another indication "In addition, midazolam was administered at a dose of 0.1 mg/kg (maximum dose of 5 mg) bolus at a time up to maximum of two doses, for those who had inadequate sedation to continue procedure irrespective of the arm [1]". The time to achieve adequate sedation was 15.7 (4.4) seconds in propofol group and no child received midazolam initially; however, 11 children received midazolam later during the conduct of the procedure in the propofol group for the above-mentioned indication.
- (iv) We agree with the details of midazolam provided by the authors. The frequency of administration of midazolam doses in our study is supported by the range of time of onset of action. We used the same protocol of administration of midazolam in the two arms of our study.
- (v) In the propofol group, no child needed midazolam to achieve appropriate sedation within first 180 seconds; some of them had to be administered midazolam later to maintain sedation for the overall procedure. Therefore, the superiority of propofol over fentanyl for the primary outcome is unlikely to be affected by adjusting for midazolam usage.

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## The Curious Case of a Zebra

During my undergraduate days, I developed an inclination towards pediatrics and decided to pursue my passion in the same speciality. The power of actually becoming competent in treating patients, prescribing drugs and saving tiny lives, gave meaning to ‘what a pediatrician can do.’

I was in my first year of pediatric residency. It was my turn to present the new patient in the post-emergency round. I narrated the findings of a year-old child who had severe wasting and stunting with normal routine investigations. I suspected a rare diagnosis and enthusiastically put it across, “Sir, I feel the patient is a case of Seckel syndrome.” I have always been very curious about unusual or rare findings in patients. I had the habit of reading further about them.

“Why do you have to make some rare diagnosis?” My lecturer asked me. “You know there is a saying in medicine, ‘If you hear hoofbeats, look out for horses and not zebras.’ Always think of common diagnoses first and then rarer ones. The majority of cases of wasting and stunting is because of malnutrition, tuberculosis or systemic illnesses like congenital heart disease, renal disease *etc.* Why not attribute the illness to commoner causes?” I replied that the patient had no salient findings in the history and examination related to any of the common causes and in addition had a beak-shaped nose. My senior colleague merely commented that having a different shape did not make it abnormal and we moved on.

The parents were really concerned about why the baby was not growing well, in spite of all the tests being normal. I was uneasy about the diagnosis and felt that further evaluation was required. The patient was counselled about the benign nature of the disease and we discharged him on multivitamins and dietary advice. One year later, the patient was readmitted having received a genetic diagnosis of Seckel syndrome from a geneticist at a premier institute.

I kept wondering about our traditional teaching of seeing a patient as a horse and not as a zebra. We are taught about common diseases and majority of patients are diagnosed correctly. We are also taught to assume that the simplest explanation is usually correct. This is to avoid patients being misdiagnosed with rare illnesses. However,

we seem to forget that zebras do exist. If we try to fit every patient into common diagnoses, getting a true diagnosis and treatment can become more difficult for sufferers of rare conditions. We have ample examples of clinical dilemmas like neonatal encephalo-pathy, cerebral palsy, failure to thrive, short stature, recurrent infections *etc.* in which genetic or metabolic causes may be identified. If we see the patient with unbiased differentials, there is a higher propensity of picking up a rarer diagnosis. We should be taught to consider the rarer differentials of the common presentations so that no child is ever missed.

In making the diagnosis in an individual case, calculations of probability have no meaning. The pertinent question is whether the disease is present or not. Whether it is rare or common does not change the odds in a single patient. The prevalence of a disease in a patient maybe 0.0001 per cent of population, but for the patient, it is 100 % disease. That’s why, making efforts to establish the diagnosis are important. The prognosis, treatment options and surveillance depend upon the correct diagnosis. It is practically impossible for each doctor to be updated in each and every aspect of all the known diseases. However, he should be aware of the common symptoms of the uncommon diseases. With this approach, the chances of missing the rarer diseases would be minimized. We can definitely keep our curiosity alive and read more about the uncommon or unusual presentation in a particular patient. We can consult experts. Eventually, this practice will yield lot more gains to the patient who turns out to be a zebra. Since zebras make up a certain percentage of the medical patients; howsoever small, these patients must also be ‘thought about’.

A novice resident can definitely be educated about common diseases, and differential diagnoses, but while training on an individual patient, we can at least ignite scientific curiosity. A student can be taught to use the correct, systematic way of how to approach a case. After all, as the saying goes, ‘give the people facts and we feed their mind for an hour, awaken curiosity and they feed their own minds for a lifetime’.

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**Bharati Vidyapeeth  
(Deemed to be University)  
Medical College, Pune (Maharashtra)**



**Post Doctoral Fellowships in Pediatric Subspecialties**

Greetings! Bharati Vidyapeeth Deemed to be University has been reaccredited "A" grade by NAAC and as on today is recognized by the UGC as one of the 20 universities in India for global promotion of education. Bharati Vidyapeeth Deemed to be University Medical College, Pune has an advanced Department of Pediatrics and state-of-the-art infrastructure with multiple well developed Pediatric subspecialties that offer Fellowship training of a national standing.

**\*\*Meritorious candidates after successful completion of their training program will be given the opportunity to pursue a 3-month "self-sponsored observership" at Birmingham Women's and Children's Hospital, NHS Foundation, UK.\*\***

**Courses Available**

No.	Fellowship Courses	Duration
1	Fellowship in Pediatric Critical Care	12 months
2	Fellowship in Neonatology	12 months
3	Dual Fellowship in Pediatric Critical Care and Neonatology	18 months
4	Fellowship in Pediatric Endocrinology	12 months
5	Fellowship in Pediatric Epilepsy & Neurology	12 months
6	Fellowship in Pediatric Infectious Diseases	12 months
7	Fellowship in Pediatric Hemato-Oncology	12 months
8	Fellowship in Development and Behavioral Pediatrics	12 months
9	Fellowship in Pediatric Genetics & Metabolic Disorders	12 months
10	Fellowship in Pediatric Rheumatology	12 months

**Eligibility:** MD / DNB (Pediatrics) / Equivalent Degree, age preferably less than 35 years

**Sponsored candidates from Medical colleges can also apply with relevant certificates and documents, last date of application submission being 31<sup>st</sup> July 2020. The fellowship course is offered purely on merit basis with 20% seats reserved for SAARC countries and other overseas students.**

The candidates will be selected on the basis of an interview which will be held in the 2<sup>nd</sup> week of August 2020 at BVDU Medical College, Pune. Selected candidates will receive free shared accommodation and a monthly stipend as per the University policy.

Eligible and interested candidates may apply with complete biodata and relevant certificates to -

**Dr. S. K. Lalwani, Vice Principal, Medical Director, Professor and Head – Pediatrics, 3<sup>rd</sup> floor, Bharati Hospital, Pune Satara Road, Katraj, Pune – 411 043, MAHARASHTRA. Phone: 020-24375541 Fax: 020-24375541.**

OR

E-mail your application with Curriculum vitae to [bvpedfellowship@gmail.com](mailto:bvpedfellowship@gmail.com) by 31<sup>st</sup> July 2020

**CHLOROQUINE IN SARS-COV-2**

When the Corona virus epidemic broke out in December, 2019 in China, scientists were struggling to discover a new drug. Repurposing an old drug was an attractive option because there was no time to develop a new drug from scratch. Early *in vitro* studies showed that chloroquine had fair anti-viral properties at micro-molar concentrations. Immediately trials in sick patients were begun in China and the first paper very briefly stated that early reports in 100 patients seemed favorable.

Then Raoult's group from Marseille, France published their findings in 42 adults of whom 26 received hydroxychloroquine and 16 acted as controls. Patients were of all categories- asymptomatic, upper respiratory infections and pneumonias. Hydroxychloroquine was given in a dose of 200 mg TDS for 10 days. Contraindications for use included G6PD deficiency, long QT syndrome and retinopathy. On the 6th day, 70% of patients treated with hydroxychloroquine were negative for viral testing compared to 12.5% of controls. Of the hydroxychloroquine group, 6 also received azithromycin. All those on the combination were virology negative compared to 57.1% on hydroxychloroquine alone.

There was much criticism of the paper because of the small sample size and some statistical flaws. However, the drug continues to be used in the frontline in some places. In China, chloroquine is used in a dose of 500mg BD for a maximum of 7 days in adults.

Biological plausibility of efficacy of chloroquine is robust. Hydroxychloroquine has a similar mechanism of action. Its advantage is lower toxicity in long term use. *In vitro*, chloroquine has shown efficacy against diverse RNA viruses such as Chikungunya, Dengue, Ebola, Zika etc. It has multiple mechanisms of action. It interferes with the glycosylation of the ACE2 receptor which acts as the entry point for SARS-CoV-2 virus. It interferes with biosynthesis of sialic acid molecules which are used by many of these viruses for production of their receptors. It increases the pH of endosomes. This prevents fusion of the viral particles with the endosome and blocks release into the cytosol. Its role in modulating immune response by inhibiting IL-1, IL-6 and TNF is well known in the field of rheumatology and may play a role in COVID-19 as well.

The ICMR has published guidelines for the prophylactic use of hydroxychloroquine for health care workers and asymptomatic contacts of COVID positive patients (<https://www.mohfw.gov.in>). They suggest a dose of 400 mg on day 1 and 400 mg once a week for 7 weeks for health care workers and 3 weeks in contacts.  
(*Int J Microbiological Agents* 20 March 2020)

**SURFACE DECONTAMINATION IN THE AGE OF CORONA**

Contamination of surfaces is an important route of transmission of SARS-CoV-2. Studies in students have shown that they touch their face upto 23 times per hour. A 5 second touch has been shown to transfer 31.6% of the viral load in certain viruses like Influenza A.

A review of 22 studies found that most coronaviruses can survive on metal, glass and plastic upto 9 days. An experimental study using aerosolized virus sprays found that the virus remains viable on stainless steel and plastic upto 72 hours, whereas it was undetectable on copper after 4 hours and cardboard after 24 hours.

It is recommended to clean commonly touched surfaces with detergent and water or common household bleach (0.1% sodium hypochlorite), which removes the virus in 1 minute. Small surfaces can be cleaned with 80% alcohol or 75% 2-propanol. Other biocidal agents such as 0.05-0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective.

Tracking the virus on every step of its journey from man to man and blocking its every move is the slow but sure path to redemption.

(*NEJM* 17 March 2020)

**HOW BHILWARA KEPT CORONA AT BAY**

The origin of the outbreak was a 52-year-old man with severe pneumonia admitted in an ICU in Bhilwara. When he deteriorated he was referred to Jaipur, where he subsequently died. He probably was the source of infection of 17 healthcare workers in a private hospital in Bhilwara. Drastic measures taken by the district officials have managed to prevent rampant spread.

What did they do? A strict curfew was immediately enforced. A door-to-door survey for symptoms was done for 2.5 million people in the city. 6445 people were put in home isolation. Police set up check points in every lane in Bhilwara to enforce curfew. Groceries, milk and medicines were supplied by local authorities *via* control rooms.

Contact tracing of more than 5000 outdoor patients and 600 indoor patients of the hospital that had admitted the index patient was meticulously performed. 42 hospitals were earmarked for COVID-19 positive patients and quarantine facilities for 1550 people in many local hotels were marked out. By early April the burgeoning epidemic seemed under control.

Extraordinary conditions need heroic measures!  
(*The Economic Times* 3 April 2020)

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**Low dose aspirin for prevention of preterm delivery in lower middle income countries (ASPIRIN Trial)** (*Lancet. 2020;395:285-93*)

Available evidence from a meta-analysis suggests that aspirin might decrease the incidence of preterm delivery as well, if initiated early in gestation. To explore it further, the authors conducted this multicenter, double blind, placebo controlled trial in seven community sites from six lower and middle income countries (LMIC) including India. A total of 11976 nulliparous pregnant women with singleton pregnancy were randomized to receive either lower dose aspirin (daily dose 81 mg) or placebo from 6-14 weeks. The incidence of preterm delivery before 37 wk (primary outcome) was lower in intervention arm as compared to control arm (11.6% vs 13.1%, RR 0.89, 95% CI 0.81-0.98). In secondary outcomes, there was a decrease in incidence of perinatal mortality, early preterm delivery (<34 wk), and incidence of gestational hypertension in women delivering before 34 wk.

**Fast versus slower increment of milk feeding in Preterm infants (SIFT trial)** (*N Engl J Med. 2019;381:1434-43*)

The researchers involved in this multicenter trial in Ireland randomized very preterm (<32 wk) or very low birth weight (<1500 g) infants to faster increment group (daily increment 30 mL/kg) or slower increment group (daily increment 18 mL/kg) until full feeding was achieved. The incidence of primary outcome *i.e.*, survival without moderate or severe neuro-disability at 24 months was similar between the groups (802 of 1224 infants (65.5%) in faster increment and 848 of 1246 (68.1%) in slower increment group, adjusted RR, 0.96; 95% CI: 0.92-1.01;  $P=0.16$ ); so was the incidence of major secondary outcomes like late onset sepsis (29.8% vs 31.1%) and necrotizing enterocolitis (5.0% vs 5.1%). Thus faster feeding increment appears a very promising strategy in stable preterm neonates and should be actively implemented.

**Neonatal hypoglycemia optimal treatment threshold (HypoEXIT) trial** (*N Engl J Med. 2020 February 6. doi: 10.1056/NEJMdo005675*)

Currently, there is no existing consensus regarding optimum treatment threshold for neonatal hypoglycemia of at risk neonates. The researchers of this multicenter non-inferiority trial involving 17 teaching hospitals in Netherlands randomized 689 neonates of >35 weeks with one or more risk factors for hypoglycemia (small for

gestational age, infant of diabetic mother or large for date) either in to lower threshold group (treatment initiated at glucose concentration of <35 mg/dL,  $n=348$ ) or traditional threshold group (treatment initiated at glucose concentration of <47 mg/dL,  $n=341$ ). The primary outcome (assessed in 82.5% and 86.5% infants in low and traditional threshold groups, respectively) was defined by Bayley scales of infant and toddler development, 3rd edition at 18 months of age with a non-inferiority margin of 7.5 points. There was establishment of non-inferiority for both cognitive [mean scores (SE), 102.9 (0.7) vs 102.2 (0.7)] and motor outcome [mean scores (SE), 104.6 (0.7) vs 104.9 (0.7)] between the groups. The mean glucose concentration was higher in traditional threshold group [61(0.5) mg/dl vs 57 (0.4) mg/dL]. Though, there were fewer and less severe hypoglycemic episodes in the traditional-threshold group, the infants in the group needed more frequent invasive diagnosis and treatment. However, in view of long term consequences of uncorrected hypoglycemia and medicolegal aspects, the trial needs to be interpreted cautiously in the Indian scenario.

**Choice of antenatal corticosteroid for improving outcomes of preterm birth (ASTEROID) trial** (*Lancet Child Adolesc hlth. 2019;3:769-80*)

Despite established benefits of antenatal corticosteroids (ANS), the choice of steroid remains a matter of debate. Hence the investigators tried to compare the maternal and neonatal benefits and side effect of most commonly used ANS (dexamethasone and betamethasone) in this randomized, double blind, placebo control, multicenter trial from 14 maternity care units of Australia and New Zealand. Between 2009 to 2013, 1346 eligible consenting pregnant women of gestation <34 wks were recruited randomly in to dexamethasone arm ( $n=679$ , two IM doses of 12 mg dexamethasone sodium phosphate given 24 h apart) or betamethasone arm ( $n=667$ , two IM doses of 11.4 mg betamethasone given 24 h apart). The primary outcome death or neurosensory disability at corrected age of 2 years were similar between both the groups (198 (33%) in dexamethasone group vs 192 (32%) in betamethasone group; adjusted relative risk 0.97, 95% CI 0.83 to 1.13;  $P=0.66$ ). However, the incidence of maternal side effects like discomfort at injection site was less in dexamethasone group (1% vs 3%;  $P=0.02$ ). Thus, the investigators concluded due to ease of administration, lower cost and lesser side effect profile dexamethasone can be a safe alternative ANS.

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# World leaders in Meningococcal Vaccination<sup>^</sup>



PRESENTS



**MENVEO**  
Meningococcal Group A, C, W135 & Y  
Conjugate Vaccine Ph. Eur.



**High efficacy\***  
with a clinically  
acceptable safety profile<sup>1</sup>

**Robust immune  
response**  
across age groups (> 2 years)  
against all four serogroups<sup>1,2</sup>

**~10 years**  
of global real world experience<sup>3</sup>

**Approved in  
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### Safety information:

#### Most common adverse events in clinical trials:

Injection site pain, erythema, induration, sleepiness, headache, irritability, malaise, eating disorder, nausea, vomiting, diarrhea, rash, myalgia, arthralgia, fever and chills.

\* The efficacy of MENVEO has been inferred by measuring the production of serogroup-specific anti-capsular antibodies with bactericidal activity<sup>6</sup>

<sup>^</sup> Meningococcal Vxs global IMS data

Reference : 1. S.A. Halperin et al, Vaccine 28 (2010), 7865–7872 2. Lalwani S, et al. Int J Infect Dis. 2015;38:36-42 3. GSK data on file- Sales summary- May 2019

4. ECDC factsheet about meningococcal disease, available at <https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet> (Accessed Nov, 2019)

5. Meningococcal Vaccine Safety, available at <https://www.cdc.gov/vaccinesafety/vaccines/meningococcal-vaccine.html> (Accessed Nov, 2019) 6. Menveo India

Prescribing information Version MNV/PI/IN/2019/03 dated 21 August 2019

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Abbreviated Prescribing Information of MENVEO (Meningococcal Group A, C, W-135 and Y Conjugate Vaccine Ph. Eur.)

**ACTIVE INGREDIENT:** Each reconstituted dose (0.5ml) contains: 10 µg Meningococcal group A oligosaccharide conjugated to 16.7-33.3 µg CRM197, 5 µg Meningococcal group C oligosaccharide conjugated to 7.1-12.5 µg CRM197, 5 µg Meningococcal group W-135 oligosaccharide conjugated to 3.3-8.3 µg CRM197, 5 µg Meningococcal group Y oligosaccharide conjugated to 5.6-10 µg CRM197. **Therapeutic Indication:** Active immunization of children (from 2 years of age), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W-135 and Y. **Posology:** Children (> 2 years of age), adolescents and adults: administered as a single dose (0.5 ml). Older people: Limited data in aged 56-65. No data in aged >65 years. Booster vaccination: May be given in subjects vaccinated with same, other conjugated or unconjugated polysaccharide meningococcal vaccine. Need and timing of booster dose to be based on national recommendations. Children under 2 years of age: Safety and efficacy not established. **Method of Administration:** Intramuscular injection, preferably in deltoid muscle. **Contraindications:** Hypersensitivity to any active substance, excipient or diphtheria toxoid (CRM197), or life-threatening reaction after administration of vaccine with similar components. Postpone in acute severe febrile illness. Minor infection not a contraindication. **Special Warnings and Precautions:** Take all precautions for prevention of allergic or other reaction. Appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reaction. Anxiety-related reactions (vasovagal reactions, syncope, hyperventilation or stress-related reactions) may occur; ensure procedure to avoid injury from fainting. Should not be administered intravascularly. Not protect against serogroups of *N. meningitidis* not included in vaccine. May not elicit protective immune response in all vaccinees. Waning of serum bactericidal antibody titers against serogroup A seen in studies; clinical relevance unknown. If individual at risk of exposure to Men A: consider booster dose. No data on use as post-exposure prophylaxis. Vaccination in immunocompromised individuals may not result appropriate protective antibody response. Increased risk of invasive disease in individuals with familial complement deficiencies and treatments that inhibit terminal complement activation (for example, eculizumab). Evaluate risk-benefit in persons at risk of haematomas following intramuscular injection. Interaction with Other Medicinal Products and Other Forms of Interaction: Can be given concomitantly with hepatitis A and/or B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies. Administer concomitant vaccines at separate injection sites (preferably contralateral). **Adolescents (11-18 years of age):** Can be co-administered with Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine, Adorbed (Tdap) alone or Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (HPV). Lower W-135 seroresponse on administration of MENVEO one month after Tdap; clinical relevance unknown. Children (2-10 years of age): No data on concomitantly administration with other childhood vaccines. Co-administration with other vaccines not studied. Administer concomitant vaccines at separate injection sites, preferably contralateral. **Effects on Ability to Drive and Use Machines:** Dizziness very rarely reported, may temporarily affect ability to drive or use machines. **Undesirable Effects:** Clinical Trial Data: A) Subjects aged 2 - 10 years: Very common (> 1/10): sleepiness, headache, irritability, malaise, injection site pain, erythema (≤50 mm), induration (≤50 mm) Common (≥ 1/100 to <1/10): eating disorder, nausea, vomiting, diarrhea, rash, myalgia, arthralgia, injection site erythema (>50mm), induration (>50mm), chills, fever ≥38°C Uncommon (≥ 1/1,000 to <1/100): injection site pruritus B) Subjects aged 11 to 65 years: Very common (> 1/10): headache, nausea, myalgia, injection site pain, erythema (≤50 mm), induration (≤50 mm), malaise Common (≥ 1/100 to <1/10): rash, arthralgia, injection site erythema (>50 mm), induration (>50 mm), fever ≥38°C, chills Uncommon (≥ 1/1,000 to <1/100): dizziness, injection site pruritus Post-marketing experience (all age groups) hypersensitivity including anaphylaxis, tonic convulsion, febrile convulsion, syncope, vertigo, injection site cellulitis, injection site swelling, including extensive swelling of the injected limb. Version: MEN/PI/IN updated 6-Sep-2019.

Registered medical practitioners can refer company website <http://india-pharma.gsk.com/en-in/products/prescribing-information/> for full Product Information.

Please report adverse events with any GSK product to the company at [india.pharmacovigilance@gsk.com](mailto:india.pharmacovigilance@gsk.com).

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For further information please contact:



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