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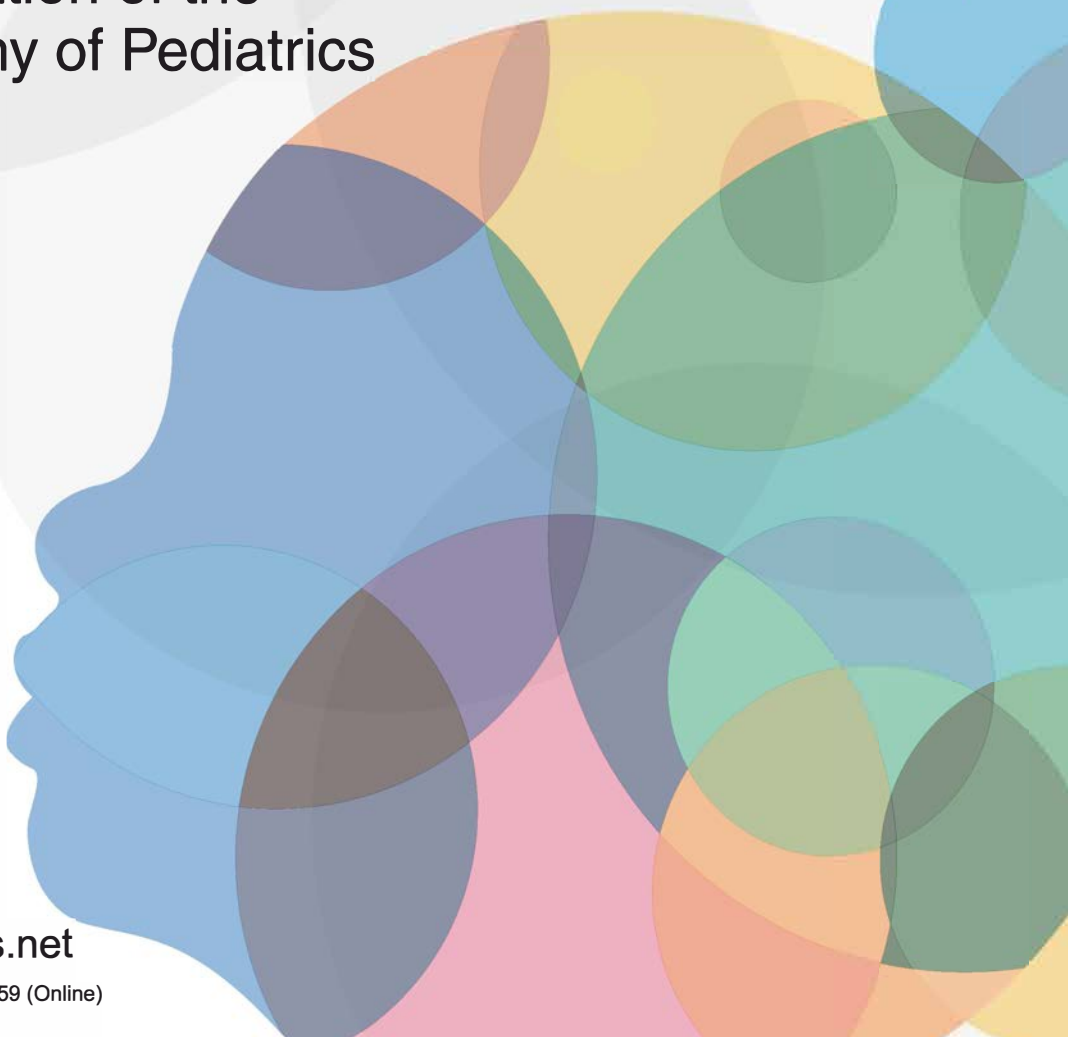

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CONTENTS

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with mon1078 circulation of print/e-copies to over 28,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

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EDITORIAL COMMENTARY

Presumptive Treatment of Acute Febrile Illness for Preventing Acute Encephalitis Syndrome: Does It Work?

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Scrub typhus is an important cause of fever without focus in Asia, and outbreaks have been reported from all over India. High case fatality is reported in patients of scrub typhus with central nervous system involvement [1]. The current gold standard, Indirect immunofluorescent assay (IFA), is neither perfect nor practical. The antibody based tests are not positive in early illness. Besides, in endemic areas where there is likely to be circulating antibodies, an appropriate cut-off is needed to reduce false positives.

Recurrent outbreaks of acute encephalitis syndrome (AES) during post-monsoon season have been reported from Gorakhpur for over three decades. After the introduction of the JE vaccine, the incidence of JE in the Gorakhpur division declined and currently it accounts for less than 10% of AES in that area [2]. Scrub typhus was incriminated as a major cause of AES in outbreaks reported in 2015 and 2016 [3]. Scrub typhus was also reported as an important cause of acute febrile illness (AFI) from the same area [4]. Considering the high mortality and lack of good diagnostic facilities in the area, Indian Council of Medical Research (ICMR) recom-mended empiric treatment with oral doxycycline in cases of acute febrile illness and intra-venous azithromycin to treat established AES [5]. The study by Thangaraj, *et al*. [6] in this issue of the journal shows that the intervention is effective in reducing the progression of AFI to AES.The authors did not look at the etiology of AFI in the present study but about 37% of the cases had undifferentiated febrile illness. However, it must be pointed out that in an earlier study from the same area, 18% of patients with acute febrile illness had IgM antibody positive for scrub typhus, most of these had mild illness and recovered without specific treatment [4].

Both doxycycline and azithromycin are equally effective as treatment for scrub typhus. While these antimicrobials appear to have reduced the progression to severe form of scrub typhus, the effects of this therapy on malaria or other bacterial infections, particularly typhoid fever, are not clear and have not been studied. Data on the burden of malaria and typhoid during the post monsoon season in this region during this period would have provided key insights into the possibility for the additional therapeutic benefits to the childhood population.

In the MORDOR trial [7], a 14% reduction in all-cause childhood mortality among under-5 children in Malawi, Niger and Tanzania was reported with mass adminis-tration of one dose of azithromycin given every six months for two years. This is postulated to be due to the prevention of deaths due to respiratory infection, diarrhea and malaria in treated children as well as their close contacts. However, presumptive treatment for acute febrile illness risks the development of antimicrobial resistance in microorganisms. There is also a risk of over-use of this presumptive treatment beyond the season of transmission by all categories of health providers.

Antimicrobial resistance is a global health threat that is estimated to cause at least 700000 deaths annually [8]. India has one of the steepest antibiotic resistance rates among bacteria that cause community and healthcare acquired infections [9]. Indiscriminate use of azithro-mycin beckons accelerated emergence of macrolide resistance.Treating patients empirically is justified as a quick response measure during the peak season of transmission but bears the risk of antimicrobial resistance and cannot be the mainstay of approach to control scrub typhus.

The common causes of fever besides scrub typhus in the community include acute respiratory infections (mostly viral), dengue fever, malaria, and typhoid fever. It has been seen that algorithms that use a combination of clinical and laboratory tests improve diagnosis and optimize treatment [10]. The National Essential Diagnostic List developed by ICMR reiterates use of ELISA at the level of the district hospital [11]. It is time for India to invest in strengthening the capacity of public health facilities to rapidly diagnose causes of febrile illnesses such as dengue fever, influenza and typhoid *etc*,

and develop a clinical algorithm incorporating point of care tests for management of AFI with rapid turnaround, which could be used at the level of primary health center. Use of rapid diagnostic tests has reduced the overuse of antimalarial drugs. Efforts are needed to expand the use of point of care tests for other common causes of febrile illness, which will optimize disease management. Future research efforts should focus on developing new antigen-based point of care tests to accurately diagnose scrub typhus in early phase, thereby reducing the number of patients treated empirically.

There is also a need for formative research into the modifiable risk factors for scrub typhus. Unlike adults who are at risk of scrub typhus due to their occupation, young children are likely to be at risk of exposure due to poverty-related poor sanitation practices and child rearing practices. Presence of vegetation or bushes near the house is a risk factor for scrub typhus. In Gorakhpur, children who had recent exposure to the outdoor environment (for defecation, playing or visiting agricultural fields), or engaged in storing firewood indoors, and handling fodder for cattle were found to be at a higher risk for acquiring scrub typhus [12]. Strategies for prevention of scrub typhus should therefore include providing sanitary toilets and focus on changing behaviors through policy initiatives like Swach Bharat Abhiyan.

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NOTICE

As a result of the COVID-19 pandemic and associated lock-down in India, printing and posting of the journal issues has been hampered. However, with the sustained efforts of the editorial team and the press, we have been able to continue disseminating the e-copy of the journal to all members. These e-copies are also available for download at the members' area of the Indian Academy of Pediatrics website (*www.iapindia.org*). Print issues will be posted once the postal services are fully restored. We look forward to your continued support for the journal during these difficult times.

EDITORIAL COMMENTARY

Typhoid Conjugate Vaccine: Is It Time for It To Be in the National Immunization Schedule?

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Typhoid is responsible for an estimated 11-21 million cases of febrile illness with 117,000 to 161,000 deaths worldwide annually [1].Though actual incidence rate of enteric fever in Indian population is lacking, three community-based studies conducted in India between 1995 and 2006 estimated the incidence of culture confirmed typhoid at 377 (178–801) per 100,000 person-years, with the highest incidence in early childhood [2]. The increasing rates of drug resistant *S. typhi*,including Extremelydrug resistant (XDR) *S. typhi*, in South Asia is also a cause for concern [3]. World health organization (WHO) recommends programmatic use of typhoid conjugate vaccine to prevent the incidence of typhoid and reduce antimicrobial resistance. This use of vaccine must go hand in hand with other preventive measures, such as improved sanitation, hygiene and access to safe drinking water for a visible reduction in burden of typhoid fever [4]. In India, the typhoid vaccine is not yet a part of the national immunization schedule. The high burden of typhoid in India, the increasing rates of drug-resistant typhoid and the availability of effective conjugate vaccines is likely to alter the vaccination scenario for typhoid.

In the current issue of *Indian Pediatrics*, Kundu, *et al.* [5] have reported an immunogenicity and safety trial of a new typhoid conjugate vaccine (TCV) and compared it with the pre-licensed Typbar-TCV, in healthy Indian children and adults. It was a single blinded, stratified randomized, multicenter, non-inferiority trial and included 240 consenting healthy participants 6 months to 45 years of age; 119 were enrolled in test arm and 121 in the comparator arm. Half of the included participants were children; there were 60 children in both arms. The study subjects were randomized (1:1) to receive intramuscular injection of either 0.5 mL of test vaccine or comparator vaccine, both of which contained 25 µg of purified Vi capsular polysaccharide of *S.typhi* conjugated to tetanus toxoid. Anti-Vi capsular immunoglobulin G titers were measured at baseline and at 6-weeks post vaccination. Seroconversion rate was found to be 94.8% in test arm and 91.6% in comparator arm. A similar robust rise in geometric mean titers (GMTs) of anti-Vi antibodies post-vaccination was noted in both test and comparator arms. Nearly 34% of participants in the intervention arm and 44% in the comparator arm reported adverse events, with no serious events being reported in both groups.

TCV induces production of antibodies against Vi-capsular antigen of *S.typhi* and high levels of these antibodies correlate with protection against typhoid disease [6,7]. High levels of IgA and higher avidity responses for IgA2 and IgG1 have been shown to be present in the protected individuals receiving TCV in human challenge models [7]. In immunogenicity trials of Vi-vaccines, anti-Vi IgG serves as a marker of protection, though the addition of IgA levels along with its avidity responses would be a potent co-relate of vaccine immunogenicity.

As also pointed out by the authors, this immunogenicity study should be followed up by efficacy trials with larger sample size to detect the actual efficacy of the test vaccine in preventing typhoid fever. Also, post-marketing surveillance will be necessary to detect the rates and types of adverse events when the vaccine will be used in heterogenous groups of population.

Studies on the licensed TCVs have shown that protection against typhoid persists for about 5 years after vaccination. There is some evidence to suggest that natural boosting occurs in persons living in endemic areas [8]. Till now, there is no evidence whether booster doses are required for the licensed vaccine and the current Indian Academy of Pediatrics Advisory Committee on Vaccine and Immunization Practices (ACVIP) does not recommend a booster [9]. The makers of this new TCV would also have to try and find answers to the questions regarding duration of protection afforded by the index vaccine and need for booster doses. Scheduling the vaccine so that it can fit into the National immunization

schedule is another issue which has to be addressed. The licensed vaccine has been found not to interfere with the immunogenicity of measles vaccine when given simultaneously at nine months of age [4,10] and that could be a potential time for the administration of the TCV.

In conclusion, we appreciate that an equally immunogenic TCV that is at par with the licensed vaccine may be available for use and would help enable programmatic inclusion of typhoid vaccine into the National immunization schedule. However, efficacy trials would be needed to prove that the vaccine prevents typhoid disease in the community setting. The timing of TCV vaccination, especially in relation to the current immunization schedule, the requirement of booster doses, and the ability to be administered concurrently with other vaccines need to be resolved.

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EDITORIAL COMMENTARY

Clinical Algorithm for Screening of HIV Among High-risk Children – Need of the Hour!

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Human immunodeficiency virus (HIV) transmission in children is most commonly due to vertical transmission [1]. Under the Prevention of parent to child transmission (PPTCT) program, all pregnant women are screened for HIV, which enables early diagnosis of HIV-exposed infants as they are at high risk for malnutrition, growth failure, developmental delay and repeated infections with common as well as uncommon organisms [1].Without treatment, about one third of infants living with HIV will die in their first year and 50% by the second year of life [1]. The National HIV program provides access to early diagnosis for HIV testing of infants and children younger than 18 months who are HIV-exposed, and ensures that they receive the required essential package of care as part of the country's commitment on achieving 90-90-90 target by 2030, which aims at ending the acquired immunodeficiency syndrome (AIDS) epidemic [1]. In an attempt to achieve the target, screening of sick infants/ children with unknown HIV exposure is important.

Perinatally-infected adolescents are more likely to suffer from chronic diseases, neurodevelopmental delay, growth and pubertal delays, unlike adolescents who acquire HIV behaviorally [1]. In 2014, it was estimated that 15% of all persons living with HIV in United States had undiagnosed HIV infection [2]. As per the US Preventive Services Task Force Recommendation (USPSTF) recommendation, persons aged 15-65 years should be screened for HIV at least once, and younger adolescents and older adults at increased risk should also be screened [3]. As per World Health Organization (WHO) 2010 guideline, it is strongly recommended to use the clinical algorithm and serologic test in the absence of virologic testing in sick infants for presumptive clinical diagnosis of HIV infection [4]. The adverse social and economic factors like poverty, broken families, parental sickness/drug abuse, and stigmatization by the society are the factors hindering access to medical care [1]. Integrated Management of Neonatal and Childhood Illness (IMNCI), which is adapted from the global version of Integrated Management of Childhood Illness (IMCI), is a strategy to address high infant mortality and to meet sustainable developmental goals with target of reducing under five mortality to 25 per 1000 live birth [5,6]. There are mainly seven clinical features included in the IMCI/HIV algorithm for the clinical diagnosis of HIV infection in children – pneumonia, persistent diarrhea, ear discharge (acute or chronic), very low weight for age, oral thrush, parotid enlargement, and generalized persistent lymphadenopathy [7].

In an African study [8], the performance of the IMCI HIV algorithm in a cohort of 444 HIV-exposed Kenyan infants was studied. The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 58%, 87%, 52% and 90%, respectively. It was noted that sensitivity was lowest at 1 month of age, when majority of HIV infections already had occurred and initiation of treatment is most important. The use of IMCI was estimated to delay diagnosis in HIV-infected infants by a median of 5.9 months. Oral thrush (67%), lymphadenopathy(55%) and pneumonia (55%) were the most commonly identifiedfeatures in HIV-1 infected infants. However, IMCI still is useful in identifying older children with undiagnosed HIV-1 infection, acquiring infection through late breastmilk transmission [8]. Sensitivity and specificity estimates of HIVclinical algorithms over various studies have ranged from 9-89% and 42-99%, respectively [8].

Integrated Management of Adolescence and Adult Illness (IMAI) is a facility level health care service, which presents a syndromic case management protocol to diagnose and manage common adult illnesses [9]. The sensitivity and specificity of IMAI acute care algorithm in a HIV positive Ethiopian cohort was above 85% and above 92%, respectively [10].

In this issue of *Indian Pediatrics*, Sinha, *et al*. [11] present a cross-sectional study on the utility of Indian Council of Medical research (ICMR) modified integrated

algorithm as a screening tool in sick children for pediatric HIV case detection in health care facilities. The WHO generic IMCI-HIV screening algorithm for children up to 5 years of age, modification from Integrated Management of Adolescence and Adult Illness for children 5-14 years of age and 'other clues' for all children which includes risk factors and certain clinical conditions of WHO staging of HIV infection were used as screening tools. The HIV prevalence estimated in this study was 19.1% (5% in <5 years and 28% in 5-14 years), which is high, and is attributed to screening of sick children. The important predictors of HIV infection noted in this study were parents with HIV, unexplained fever (>1 month) and orphaned child. The strength of this study is the use of standard algorithms from IMCI HIV algorithm and IMAI which were modified as screening tools [11]. However, this screening algorithm could not be validated.

This study [11] is a multicentric study, but the population was limited to one state. Authors highlight the need for routine surveillance of HIV infection amongst children aged 5-14 years considering the high proportion of this population [11]. They concluded that one should have a high index of suspicion to consider the clinical diagnosis of HIV infection, when an infant/child with unknown HIV status butwithrisk factors like orphaned child, child having a single parent, child with high risk behavior, presents with symptoms and/or signs as per the clinical algorithm of WHO-IMCI. However, since this study included children predominantly above 1 year of age, the validity of algorithm in infants, especially HIV-exposed infants, needs to be evaluated.

The need of the hour is to have an estimation of HIV disease burden in symptomatic infants/children with risk factors at community level. It is important to understand that the modified integrated algorithm is a screening tool and not a diagnostic test. It is important to sensitize the healthcare workers regarding the use of this algorithm with appropriate training. The utility of this modified integrated algorithm needs to be further tested in different field studies in different states of India to confirm that these results are replicated.

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Malaria Elimination in India: Bridging the Gap Between Control and Elimination

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India observed a significant reduction in malaria cases in the previous year, reaffirming our trust and efficiency of the existing tools to achieve malaria elimination. On 25 April, 2019, countries around the world marked World Malaria Day under the theme "Zero malaria starts with me". This provides an opportunity to rejoice the success and re-evaluate ongoing challenges in the fight against this preventable and treatable parasitic disease. We highlight the potential gaps in the malaria elimination program, and underscore potential solutions and strategies to implement, improve and intensify the success of the national goal of malaria elimination by 2030.

Keyword: *Diagnosis, Epidemiology, Vector-borne disease.*

India has a long history of success and struggles with malaria control. The unsuccessful endeavor to eliminate malaria, and increasing morbidity and mortality bring back the elimination agenda in the health care priorities [1]. In 1976, there was a massive resurgence of malaria cases and *Plasmodium falciparum* resistance to chloroquine and vector resistance to insecticides were reported [1]. As a consequence, the modified plan of operations was launched in 1977 with a three-pronged strategy: early diagnosis with prompt treatment, vector control, and Information Education Communication (IEC)/Behavior Change Communication (BCC), resulting in the decline of malaria incidence again in 1984. Subsequently, Enhanced Malaria Control Project in 1997 and Intensified Malaria Control Project in 2005 were launched to combat malaria in high transmission areas of the country. New tools for malaria prevention and control were introduced by National Vector Borne Disease Control Program (NVBDCP) *i.e.*, monovalent rapid diagnostic tests (RDT) for *P. falciparum* detection in 2005; Artemisinin-based combination therapy (ACT) in 2006; Long-lasting insecticide-treated nets (LLINs) in 2009; antigen detecting bivalent RDTs for detection of both *P. falciparum* and *P. vivax* in 2013; and newer insecticides and larvicides in 2014-15. However, these strategies failed to build on its expected level of achievements. India moved towards global commitment for malaria elimination and endorsed a plan to eliminate malaria throughout the region by 2030 [2]. World health organization (WHO) has developed the Global technical strategy for malaria under the National framework for malaria elimination in India 2016-2030 to eliminate malaria (zero indigenous cases) throughout the entire country by 2030, and maintain malaria-free status and prevent its re-introduction. Therefore, we need to put all our efforts to achieve the desired success this time.

DISEASE BURDEN AND SURVEILLANCE

In 2018, an estimated 228 million cases of malaria occurred worldwide, compared to 251 million cases in 2010 [3]. In India, a population of 126 million was at risk of malaria with an estimate of 6 million cases in 2018 [3], while 0.43 million confirmed cases of malaria were reported by NVBDCP in 2018 [4]; although, discrepancies between various sources have been noted [5]. In India, malaria is highly endemic in rural and tribal areas of Madhya Pradesh, Maharashtra, Odisha, Rajasthan, Gujarat, Jharkhand, Chhattisgarh, Andhra Pradesh, West Bengal, and Karnataka. Further, districts with 30% or more tribal population comprising about 8% of the country's population contributed to 46% of total malaria cases, 70% *P. falciparum* cases and 47% malarial deaths in the country [6]. However, India has shown a 71% reduction in 2019 as compared to 2015 and this reduction was achieved by strengthening the surveillance measures, improving diagnosis and treatment, and intensive vector control measures using existing tools. For example, Odisha contributed 37.4% of total malaria cases in 2015 which reduced to 12% in 2019 using the

Durgama Anchalare Malaria Nirakaran (DAMaN) initiative and compre-hensive case management of malaria. To sustain the achieved reduction and moving forward to the elimination, we have to strengthen all the strategies using existing tools and by developing new tools.

CHALLENGES AND SOLUTIONS

Strengthening Malaria Diagnosis

Accurate diagnosis is the key to success in the elimination goal. Among the five Plasmodium species, *P. falciparum* and *P. vivax* cause the majority of cases and other species are rare, but the diagnosis is complicated by the varied distribution of both mono-infection and mixed infections [7]. Microscopy has always been the gold standard method but it requires highly skilled microscopist with genuine knowledge of different stages of Plasmodium species with capability to read low-density parasitemia - fulfilling such a requirement in rural India is a daunting task, as a consequence, more than a quarter of malaria cases are missed by microscopy [8]. RDTs are used where microscopy is not feasible. *P. falciparum* histidine-rich protein 2 (PfHRP2) antigen targeting *P. falciparum* is used in more than 90% of the malaria RDTs [9]. However, deletions of the *Pfhrp2* gene in the parasite, fluctuation in the expression level of Plasmodium Lactic Dehydrogenase (pLDH), and prozone phenomena are the major problems leading to inaccurate diagnosis of plasmodium species. Therefore, other potential biomarkers such as heme-detoxification protein, apical merozoites surface protein Pf34, Glutamate dehydrogenase, and hypnozoites-based serological marker should be validated to strengthen the RDT tool. Molecular methods such as Polymerase chain reaction (PCR) are feasible for the diagnosis of malaria (particularly low-density infection). However, these methods like conventional PCR, nested PCR, qPCR, multiplex PCR, and Loop-mediated isothermal amplification (LAMP) are less frequently used techniques due to longer time required, need for advanced equipment, expensive reagents and experienced personnel, and difficultly in organizing in most field conditions. A hemozoin-based magneto-optical detection device (Gazelle) may prove an alternative to RDT for accurate diagnosis in the field. These new markers/tools can make an impact on elimination efforts by addressing the problem of missed diagnosis.

The Frontline Staff

Accredited Social Health Activists (ASHA) and community health workers are the key players and leading contributors to the malaria elimination program as they are primary healthcare providers in the malaria endemics rural and tribal areas where government hospital and healthcare facilities are inaccessible. They provide diagnosis using RDT, and treatment, as well as advise them about the importance of preventive measures. Strengthening the qualitative and quantitative capacity of the ASHA may prove an asset in malaria elimination as children under the age of 5 are more vulnerable in the community for developing severe malaria. Tribal people are mostly dependent on traditional healers and unlicensed medical practitioners (UMP), which delays the correct diagnosis, and improper treatment may lead to severe malaria, as well as further transmission in the community [10]. Therefore, the stakeholders may think about providing training to unlicensed medical practitioners on national guidelines for malaria diagnosis and treatment to overcome this issue. An integrated community case management strategy along with ASHA/UMP may be needed to fight against malaria in the community.

Malaria in Children

Children aged below 5 years are the most vulnerable group and accounted for 67% of global malaria deaths in 2018 [3], and complicated malaria is more common in children than adults. The clinical symptoms (fever, vomiting, cough, difficulty in breathing and inability to eat and drink) of malaria in children may be mistaken for a viral syndrome or acute gastroenteritis. *P. falciparum* seems to be notorious for severe malaria but vivax is also presenting as severe malaria in children [11]. In high transmission areas, young children are at high risk of severe vivax-associated anemia, where the relapses phenomenon is frequent [12]. Children need portable, easy to take medicine adapted to their weight and age. Therefore, careful consideration should be given to the formulations of child-friendly antimalarials because children absorb and metabolize medicines differently [13]. Although the medicines for malaria ventures (MMV) has taken the initiative for discovering and developing new medicines [13]. The improper and inadequate drug and doses in the long term may create problems of drug resistance resulting in high morbidity and mortality in children as deaths in infants and children <14 years of age accounted for 20.6% in India [14].

Pregnant Women: A Vulnerable Group

Pregnant women are more susceptible to malaria, although the prevalence during pregnancy was substantially lower in areas of high transmission [15]. During placental malaria, *P. falciparum*-infected erythrocytes sequester in the placenta, causing health problems for both the mother and fetus, increasing risk for congenital malaria [16]. Therefore, in the malaria-endemic areas, pregnant women should be screened for

malaria if they have malaria-like symptoms or even in the cases of anemia, which not only helps malaria elimination but also delivering a healthy baby.

Migration Malaria and Surveillance Strategy

Migration malaria is also an important affair as it serves as a reservoir and seeds local outbreaks. Moreover, migrant workers who either take temporary shelter or coming from malaria-endemic areas could impede surveillance. Therefore, imported/migratory cases should be tracked by using surveillance networks, similar to GeoSentinel, EuroTravNet and TropNetEurop. Malaria elimination requires a strong surveillance mechanism that can reliably and rapidly detect the disease using the '1-3-7' strategy [17] and the '1-2-5' strategy [18] during the elimination phase to overcome the problem. Additionally, mobile surveillance tools may be efficient in real-time information sharing such as Solutions for Community Health-workers (SOCH) and Integrated Health Information Platform (IHIP) to prevent them from spreading disease and outbreak situations [19]. Therefore, the utilization of such networks may have importance in the malaria elimination program in India.

Asymptomatic/ Afebrile Malaria: A Reservoir

Afebrile cases do not show presentable routine symptoms but may become a source of parasitic transmission under a favorable setting. Asymptomatic malaria (the presence of sexual or asexual parasites and/or absence of clinical symptoms) poses a serious challenge worldwide [20]. Naturally acquired immunity and partial immunity with past exposure and age are the probable factors to asymptomatic malaria in the malaria-endemic areas that plays a significant role in transmission and malaria severity in children 2 to 5 years of age [21]. Therefore, proper attention is warranted in children; else they may act as a key reservoir of malaria infection.

Antimalarial Drug Treatment and Resistance

Schizonticidal and gametocidal drugs have been used to treat and prevent malaria for centuries. Chloroquine was first developed in the 1930s; but in 1973, chloroquine-resistance (CQR) was initially pointed out in Assam, India. The rise in CQR (*Pfcrt* gene, a molecular marker to track the CQR) contributed to a worldwide increase in malaria-related mortality. To combat resistant strains, several alternative synthetic antimalarial drugs (sulfadoxine-pyrimethamine and mefloquine) were deployed to treat and prevent malaria. Sulfadoxine-pyrimethamine (SP) is utilized as the second line of therapy after chloroquine-resistant in India. However, the mutation at the *dhps* and *dhfr* genes make it ineffective against the *P. falciparum* malaria. The introduction of ACT has made a thrilling effect on malaria treatment in many countries. At present, these drugs are successful; however, there are already hints that resistance to artemisinin has emerged [22]. Other factors that may contribute to drug resistance are the mutation in resistance markers, counterfeit or substandard treatments, improper doses, and artemisinin monotherapy. To avoid artemisinin resistance, triple artemisinin-based combination therapies such as artemether–lumefantrine plus amodiaquine are already in pipeline for the treatment of uncomplicated *P. falciparum* malaria [23]. In the case of *P. vivax*, a 14-day course of primaquine (gametocidal drug) is recommended in all transmission settings to overcome the issue of relapse but poor drug compliance is a major challenge.

However, the single dose regimen of tafenoquine may be helpful to improve the adherence issues associated with primaquine regimens. Clinicians must document the G6PD status because primaquine and tafenoquine both may induce hemolytic anemia in patients with a glucose-6-phosphate dehydrogenase deficiency (G6PD). Nevertheless, novel *P. vivax* anti-relapse medicines that targets hypnozoites are greatly needed. Implementation of Directly-observed therapy (DOT) reduces the anti-malarial resistance development, reappearance rate of the parasite, and may subsequently decrease *P. vivax* transmission [24]. This ultimate goal of developing new antimalarial drugs and modifying existing ones will take us one step closer to the elimination goal.

Plasmodium vivax: Roadblock in the Success

In India, *P. vivax* contributed 53.4% of the infections in 2019. It is often termed benign malaria but substantial increases in morbidity and mortality, especially in infants due to weak immunity is considered alarming. Pathophysiology of *P. vivax* such as a low-density blood-stage infection, hypnozoites, transmission facilitated by the early production of infective stages, mature gametocytes and more genetically diverse *P. vivax* populations have limited understanding. Vivax Duffy-negative phenotype and Fy glycoprotein (FYA) need proper understanding in the Indian context to fight against *P. vivax* malaria [25].

The risk of *P. vivax* parasitaemia is high in co-endemic regions (where both *P. falciparum* and *P. vivax* are equally prevalent) after treatment for *P falciparum* infection. This is probably due to fast acting and rapid parasite clearance property of artemisinin-based therapy against the treatment of falciparum malaria, in the area where short periodicity of *P. vivax* relapse cases occurred. Therefore, complete radical cure may be assured to prevent recurrent parasitaemia, reduce ongoing

transmission to ensure malaria elimination success [26].

Vector Control and Insecticide Resistance

National Malaria Program has distributed about 50 million Long Lasting Insecticidal nets (LLINs) to communities during 2016-2018 in India [4] as an intervention tool for malaria control and prevention to cover the 126 million populations that were under risk [3]. Among children under 5 years of age, LLINs provide up to 55% protective efficacy in preventing malaria attributed to mortality [27]. Operational success can only be achieved when universal coverage is attained and is at least 80% [28]. The major drawbacks of LLINs include personal discomfort and feelings of suffocation when humidity and indoor temperature are high. Therefore, child-friendly nets using color combinations and cartoon-based print may increase the use of LLIN. Thus, Zero vector durable lining (ZVDL) is designed to cover interior wall surfaces, utilizing slow-release technology that has the advantages of both LLINs and IRS, *i.e.* long-lasting residual use and no insecticide dusting [29].

Vaccines: The Last Piece of the Puzzle

There is no commercially available malaria vaccine currently. However, efforts to make an effective malaria vaccine are underway for the last three decades. Phase 3 trial of RTS, S/AS01 (Mosquirix) (at month 0, 1, and 2) in children aged 5-17 months showed vaccine efficacy of 28.3% against severe malaria in children [30]. *Pf*SPZ based genetically attenuated vaccines which halt the development in the early liver stages were found to offer protection to 55% recepients [31]. Limited understanding of how immunity develops against malaria poses a great challenge to researchers in designing effective vaccines. Recent advances in the generation of recombinant proteins, DNA and RNA based approaches may be useful in vaccine development [32].

Inter-sectoral Coordination

Several government organizations, such as the ICMR through Malaria Elimination Research Alliance-India and NVBDCP are moving forward to fill the gaps with research and innovative strategies. India Health Fund and several non-governmental organi-zations such as TATA Trust and Godrej have also taken an initiative to work on parasite control, vector control, technology-integration, and awareness and behavioral change. Moreover, the success story of neighboring countries like Sri Lanka and China echoes the importance of public-private partnerships to accelerate malaria elimination efforts. ICMR and Sun Pharma Ltd have partnered for malaria elimination activities in Mandla district of Madhya Pradesh [19].

CONCLUSION

Healthcare communities have undertook serious efforts to reduce malaria cases in India, but it is still threatening millions in India. This time the elimination efforts would require targeted approaches and strategies starting from the village level to the national level. At the same time, we need to take care of all the possible gaps such as human resources, robust surveillance, and hotspot targeted interventions by proper utilization of existing as well as new tools. All the laboratory-confirmed positive cases should be advised to stay under mosquito net until parasite clearance to avoid community transmission. Universal and continuous availability of drugs, diagnostic and essential malaria commodities are to be ensured for effective management of community malaria. If the lessons learned from elimination efforts are properly utilized, the malaria elimination goal mayvery well be achieved on time.

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OBITUARY

Prof. Pranab Kumar Bhaumik (1935-2020)

Dr. Pranab Kumar Bhaumik, ex-Professor and Head, Department of Paediatrics, Medical College, Kolkata, left for his heavenly abode on the 1st of June, 2020, at the age of 84 years. His three sons, daughters-in-law and grandchildren survive him.

Dr. Bhaumik was born on 17th September, 1935 at Medical College, Kolkata. He was the only son of Dr. Prabhat Chandra Bhaumik, a physician and freedom fighter and Smt.Parul Bala Debi. After graduating with MBBS degree from NRS Medical College, Kolkata, he earned his MD in Medicine from SSKM Hospital and joined the West Bengal Health Services. After his initial posting at North Bengal Medical College, he was transferred to Medical College Hospitals, Kolkata, Department of Paediatrics (Shishu Niwas) – considered to be the hotbed of Paediatrics, where he spent the rest of his illustrious academic career. One among the many stalwarts of the department, he rose to become the Professor and Head, a post he held till his retirement. In his own words, the hospital where he was born also gave him the best years of his career.

Professor Bhaumik was regarded as one of the doyens of pediatrics in West Bengal. His astute clinical acumen, and excellent bedside teaching skills made him one of the most admired teachers. He was highly respected for his punctuality, discipline, honesty, and dedication to his profession. He was admired for his sharp yet subtle wit and camaraderie with his peers and students alike. His ward rounds were famed for the great learning experience they provided. He was a man of unfaltering principles who believed that a doctor's service can never be equated with monetary exchanges, and exemplified this by selflessly treating patients coming from every strata of society with equal quality and care. Though so profound in knowledge, he liked to maintain a low profile, abhorring publicity and flamboyance.

Dr. Bhaumik was the father of three sons, the younger two, being twins.Unfortunately, owing to some chronic indisposition of his wife Geetanjali, soon after the birth of the twins, Dr. Bhowmick was entrusted with the added responsibility of taking care of his sons, his ailing wife and his aged parents, beside his hospital work, in the early days of his career. In spite of limited resources, he never compromised on his values. He led an austere life, with minimal needs, without undue excesses. He was a stickler for values and principles and instilled the same among his students who are well spread out in different parts of the world, and cherish the wonderful time spent under his guidance.

Dr. PK Bhaumik was the president of the Association of Health Service Doctors, and also the past president of West Bengal IAP in 1993. After retiring from active service, he continued his academic associations with IAP, attending state conferences in various capacities.

Though he was ailing for the past one year intermittently, and lost his wife in January, 2020 he lived a fruitful life in his humble abode at 42 Scott Lane, Kolkata, which was considered a pilgrimage by his students. His vast knowledge, teaching skills and unparalleled service to society touched and enriched the lives of aspiring medical students, junior doctors, colleagues, innumerable children and their parents. With his demise, an era in West Bengal pediatrics has ended. His memory will remain eternally etched in the hearts of all his patients, students and colleagues.

RESEARCH PAPER

Effectiveness of Presumptive Treatment of Acute Febrile Illness With Doxycycline or Azithromycin in Preventing Acute Encephalitis Syndrome in Gorakhpur, India: *A Cohort Study*

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Objective: To estimate effectiveness of presumptive doxycycline or azithromycin treatment in preventing progression of Acute Febrile Illness to Acute Encephalitis Syndrome in Gorakhpur.

Study Design: Prospective cohort study.

Study Setting: Primary healthcare centers and Community healthcare centers of Gorakhpur district, Uttar Pradesh.

Participants: Children aged 1 year to less than 15 years with fever of 3 days to less than 15 days duration attending three selected peripheral health facilities in Gorakhpur during August to October, 2018.

Procedure: 35 medical officers in three selected Primary Healthcare Centers/Community Healthcare centers were sensitized on the treatment strategy. After sensitization, study participants were enrolled and information about prescription of doxycycline or azithromycin was collected. Participants were telephonically followed-up to know their progression status from AFI to AES.

Main outcome measure: Incidence of acute encephalitis syndrome among acute failure illness patients who received presumptive doxycycline or azithromycin treatment and those who did not receive this treatment.

Results: Of the enrolled 930 AFI patients, 801 (86%) were prescribed doxycycline or azithromycin and 725 (78%) could be telephonically followed-up. Progression to acute encephalitis syndrome was seen in 6 of the 621 patients who received presumptive treatment, and 5 of the 104 who did not receive the treatment. The relative risk of developing acute encephalitis syndrome among acute febrile illness patients who were prescribed presumptive treatment with doxycycline or azithromycin was 0.20 (95% CI: 0.06-0.65). The effectiveness of presumptive treatment with doxycycline or azithromycin strategy was 79.9% (95% CI: 35.4-94).

Conclusion: PDA treatment to children presenting with fever in peripheral health facilities of the study blocks in Gorakhpur during August-November, 2018 had good effectiveness in preventing progression of acute febrile illness to acute encephalitis syndrome.

Keywords: *Acute undifferentiated febrile illness, Japanese encephalitis, Management, Scrub typhus*.

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Seasonal outbreaks of acute encephalitis syndrome (AES) have been occurring in four districts of Gorakhpur and three districts of Basti division of Uttar Pradesh, India since last four decades [1-3]. These outbreaks occur during monsoon and post monsoon season every year, with cases peaking during August and September before declining in late November. Outbreaks predominantly affect children aged less than 15 years and are associated with high case fatality ratios, ranging between 15 to 25% [3,4]. Japanese encephalitis accounts for less than 10% of AES cases, while the etiology of remaining AES cases remained largely unknown [5]. Studies conducted during 2014–2017 outbreaks revealed presence of IgM antibodies against *Orientia tsutsugamushi* (OT) in about two thirds of AES cases, suggesting scrub typhus as the major etiology of AES outbreaks [6-9]. Entomological studies have also confirmed transmission of scrub typhus pathogen in this region [10].

Accompanying Editorial: Pages 607-8.

Most scrub typhus infections are subclinical, only a few children develop febrile illness and a small proportion of these patients develop neurological manifestations [9,11]. Hence, early administration of appropriate antibiotics is crucial in preventing progression of acute febrile illness (AFI) due to scrub

typhus to AES. Based on the epidemiological, serological and entomological findings, the Indian Council of Medical Research (ICMR), in consultation with various stakeholders, developed strategies for prevention and control of AES for each tier of health care system, focusing on early diagnosis based on clinical as well laboratory investigations and appropriate treatment with doxycycline or azithromycin (ICMR, Unpublished document). For peripheral health facilities, the recommended strategy is to investigate AFI patient for various etiologies including JEV, dengue, scrub typhus, leptospirosis and malaria as per feasibility and treat appropriately. If facilities for laboratory investigations are not available, which is the case in most peripheral facilities in Gorakhpur division, it was recommended that patients presenting with fever of three or more days duration during August-November (when AES cases peak) be presumptively treated with either doxycycline or azithromycin, based on clinical suspicion. In 2016, Government of Uttar Pradesh issued guidelines to the health facilities of districts in Gorakhpur division for this presumptive treatment [12]. We conducted this study in selected peripheral health facilities in Gorakhpur district during an outbreak season in 2018 to estimate the effectiveness of presumptive doxycycline or azithromycin (PDA) treatment strategy in preventing progression of acute febrile illness to AES.

METHODS

We conducted the study in three blocks (administrative subunit) *viz*, Bhathat, Campierganj and Jangal Kaudia in Gorakhpur district. As per the AES surveillance data from the BRD Medical College, Gorakhpur, these blocks, together accounted for 17% of the AES patients reported from Gorakhpur division during 2016-2017. The primary health care in these blocks is delivered through three community health centers (CHCs), 9 primary health centers (PHCs) and 82 health sub-centers (HSCs), whereas the district hospital, Gorakhpur and BRD Medical College, Gorakhpur, respectively are the secondary-care and tertiary-care hospitals in public sector in the district.

We sensitized 35 Medical Officers (including three pediatricians) and seven pharmacists from all the primary/community health centers in the three blocks about etiology of AES in the region. We planned the sensitization meetings separately in each of the three study sites. We sensitized the medical officers in a face-to-face two hour training session, explaining the AES scenario in Gorakhpur division, findings of investigations conducted to know the etiology of AES in Gorakhpur, and the rationale for the presumptive treatment along with treatment algorithm for management of AFI including dosage of doxycycline or azithromycin by weight as by well as age. The recommended dosage was 4.5 mg/kg/day in two divided doses for five days for doxycycline and 10 mg/kg/day in single dose for five days for Azithromycin [13]. Other than sensitization of Medical Officers about the PDA treatment strategy, the study team did not influence the prescription pattern.

The Institutional Ethics Committee of the ICMR-National Institute of Epidemiology, Chennai approved the study protocol. We enrolled all patients aged between 1 to less than 15 years with fever of three or more days to less than 15 days (Acute febrile illness, AFI) duration presenting to the outpatient departments of the selected health facilities. All AFI patients were referred to the study team stationed at the PHCs/CHCs, after they had completed the consultation with medical officers and had received the prescribed medicine at the pharmacy. We enrolled AFI patients after taking informed written consent from their accompanying caregivers. We collected their demographic information and clinical details. We abstracted information about prescription of doxycycline or azithromycin from the medical prescription, and whether the drug was dispensed. We telephonically followed-up AFI patients three days and five days after attending the health facility to collect information about consumption of doxycycline or azithromycin, and their clinical status including recovery, and improvement or worsening of clinical condition. For children who did not improve or recover, we continued the follow-up beyond day 5.

AFI patients with change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk), and new onset of seizures (excluding simple febrile seizures) were considered as patients of AES [14]. For children who progressed to AES, we collected information about the new symptoms and treatment sought including hospitalization. We visited all patients who were hospitalized, collected information about their clinical and laboratory investigations. These patients was and sera were tested for presence of immunoglobulin M antibodies against *O. tsutsugamushi* using commercial ELISA (Scrub Typhus Detect, Inbios International Inc, Seattle, USA).

Statistical analysis: We compared the incidence of AES among AFI patients who received PDA treatment with that of AFI patients who did not receive PDA, by calculating the relative risk (RR) and its 95% confidence interval (CI). The effectiveness of PDA treatment strategy was calculated by 1-RR formula [15]. We also calculated relative risk of developing AES among Acute

undifferentiated febrile illness (AUFI) patients who were prescribed PDA. We conducted sensitivity analysis to account for uncertainty of the outcomes among AFI patients who could not be followed up. We considered three assumptions: (*a*) incidence of AES among patients who received and who did not receive PDA treatment was same, as found in our study, (*b*) none of the patients lost to follow-up progressed to AES, and (c) all patients lost to follow-up progressed to AES.

RESULTS

During August to October, 2018, we enrolled 930 AFI patients from three health facilities in the study. Of these, 560 (60%) had consulted a private practitioner before attending the public health facility. Majority (83%) of them had visited traditional healers in their nearby villages for the initial febrile illness episode. At public health facilities, 801 (86%) were prescribed doxycycline or azithromycin.

The mean age of AFI patients who received doxycycline or azithromycin was higher than those who did not receive doxycycline or azithromycin (7.5 *vs* 6.2 years, *P*=0.001). The median duration of fever in both the groups was 5 days (Inter-quartile range 4-7 days). The proportion of AFI patients who were prescribed PDA ranged between 76.4% (Campierganj) to 92.7% (Jangal Kaudiya).

We could telephonically follow-up 725 (78%) AFI patients. Of these, 621 (85.6 %) had received doxycycline or azithromycin treatment –489 (78.7%) received azithromycin and 132 (21.3%) received doxycycline (***Fig.* 1**). The remaining 97 (13.4%) received other antibiotics (fluoroquinolones, 41, penicillin derivatives 31; cephalosporin, 13; and sulfonamide, 12) while 7 (1%) did not receive any antibiotics.

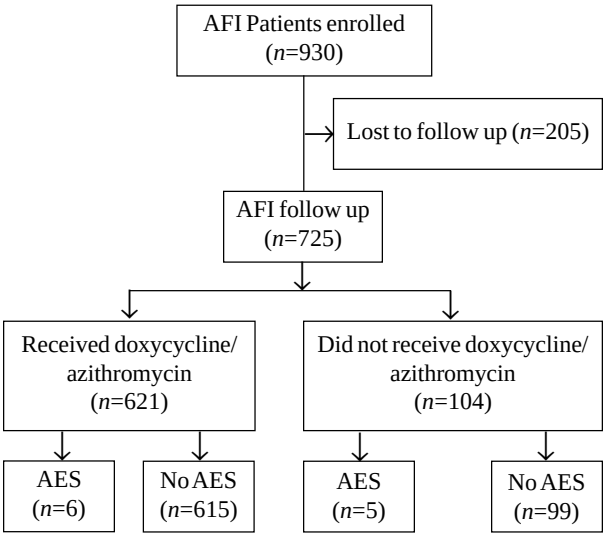

Fig. 1 *Flowchart showing acute febrile illness (AFI) patients enrolled and those developing acute encephalitis syndrome (AES)*

Six of the 621 AFI patients who received PDA treatment and five of the 104 who did not receive PDA treatment progressed to AES (cumulative incidence 0.96% and 4.8%, respectively). The relative risk (95% CI) of developing AES among AFI patients who were prescribed PDA treatment was 0.20 (0.06-0.65). The age adjusted relative risk (95% CI) was 0.19 (0.06-0.62). The effectiveness of PDA treatment strategy was 79.9% (95% CI: 35.4–94). Two of the six AES patients who received PDA treatment and three of the five AES patients who did not receive PDA treatment had IgM antibodies against *O. tsutsugamushi*.

Of the 725 AFI patients, 454 had focal symptoms such as cough, abdominal pain, loose stools, burning micturition. The remaining 271 were considered as acute undifferentiated febrile illness (AUFI). Among the 271 AUFI patients, 236 (87.1%) were prescribed PDA. Three of the 236 AUFI patients who received PDA treatment and three of the 35 who did not receive PDA treatment progressed to AES. The relative risk (95% CI) of developing AES among AUFI patients who were prescribed PDA treatment was 0.14 (0.03-0.70).

The results of sensitivity analysis as per assumptions regarding AFI patients lost to follow-up is shown in ***Table* I**.

DISCUSSION

The findings of our study indicate that PDA treatment to children with AFI attending peripheral health facilities was effective in preventing progression of AFI to AES. Several studies also strongly recommend presumptive/empiric treatment with either Doxycycline or Azithromycin, where Scrub Typhus is endemic to minimize risk of death and severity of the disease [16-19]. Untreated AFI due to Scrub Typhus progress to AES by vascular injury to meninges [20]. Central nervous system involvement occurs as a part of systemic infection. Pathogen factors like strain type and evolution of the organism to escape host immune systems might also contribute towards progression of illness [21-24]. There were several reasons for considering presumptive treatment of AFI patients with doxycycline or azithromycin in Gorakhpur division. This includes lack of laboratory facilities for diagnosis of scrub typhus infection at primary care facilities. Moreover, serological tests for diagnosis becomes positive only around 5-7 days [25-27]. Other reasons include significant proportion of scrub typhus among the AFI patients, distinct seasonality of the

Table I Relative Risk of Progression to Acute Encephalitis Syndrome Among Acute Febrile Illness Patients Receiving Presumptive Doxycycline/Azithromycin Treatment, Gorakhpur, India, 2018

Assumption: Prescribed AES incidence among patients who received and who did not receive PDA treatment was same, as found in the study		
PDA	AES	No AES
Yes	8	793
No	6	123
Relative risk (95% /CI)	0.21 (0.08-0.60)	
Assumption: None who was lost to follow-up progressed to AES		
PDA	AES	No AES
Yes	6	795
No	5	124
Relative risk (95% /CI)	0.19 (0.06-0.62)	
Assumption: All patients lost to follow-up progressed to AES		
PDA	AES	No AES
Yes	186	615
No	30	99
Relative risk (95% /CI)	0.99 (0.71-1.4)	

AES: Acute encephalitis syndrome; PDA: Presumptive doxycycline/ azithromycin treatment.

disease during post-monsoon months, risk of progression of AFI patients to AES which is associated with high case fatality, and over-burdened public health facilities. Overreliance on traditional healers in rural areas results in delay in reporting to public health facilities. There are very few studies which have attempted to estimate the effectiveness of the presumptive treatment with either doxycycline or azithromycin among AFI patients. In a study by Phimda, *et al.* [28], both doxycycline and azithromycin given empirically to adult patients with AUFI, were found to be highly effective with success rates of 96.5% and 97.4%, respectively.

In our study, azithromycin was prescribed more frequently than doxycycline by medical officers. This could be due to hesitancy among medical officers to prescribe doxycycline among young children as well as lack of drug supply. DHR-ICMR guidelines recommend doxycycline as one of the most effective antibiotics for the treatment of suspected rickettsial infections in India [13]. Also short course (<10 days) of doxycycline treatment is not associated with any increased risk of dental staining, enamel hypoplasia, or tooth color differences [29].

Our study has certain limitations. First, we followed up AFI patients telephonically and not by house to house visits. We therefore had to rely on parents' responses about treatment. Parents of all the 725 children informed that their children had consumed doxycycline or azithromycin in the prescribed doses. Second, we did not test AFI patients for scrub typhus etiology. This would have provided accurate information about incidence of AES among scrub typhus positive patients. Third, we could not follow-up 23% AFI patients who received PDA treatment and 19% patients who did not receive PDA treatment. Patients were considered lost to follow up only when we were not able to contact patients either at day 3 or day 5 or beyond. We conducted a sensitivity analysis to account for uncertainty of the outcomes among patients who were lost to follow-up. Of the three assumptions, two assumptions indicated a protective effect for PDA treatment strategy, while the third assumption was remotely possible. Fourth, since PDA has been recommended for AFI patients in public health facilities and already been rolled out, it was not possible to evaluate its efficacy using a clinical trial design.

Prescribing doxycycline or azithromycin presumptively, to children presenting with fever in peripheral health facilities between August and October could reduce AES burden by preventing progression of AFI to AES. The Government of Uttar Pradesh has already issued guidelines to district and block medical officers to prescribe Doxycycline or Azithromycin to AFI patients attending peripheral health facilities of Gorakhpur and Basti divisions. However, the strategy needs to be strengthened at the block level. The medical officers have to be repeatedly sensitized on rationale for PDA treatment among suspected scrub typhus patients. A close monitoring of implementation of this strategy, monitoring resistance to these antimicrobials, and ensuring adequate supply of doxycycline and azithromycin would yield higher compliance on PDA treatment strategy by the medical officers. Further, significant reduction in the disease burden due to AES in the region would require sensitizing doctors in private sector as well.

Ethical clearance: Institutional Ethics Committee of ICMR-National Institute of Epidemiology, Chennai; NIE/IHEC/ 201507-01, dated 18 July, 2018.
Acknowledgement: Mr Kaushik Kumar for support in data collection.
Contributors: JWVT, NG, MM, MVM: conceived and designed the study; VS, AP, AD: collected data; KZ, AP: conducted laboratory investigations; SV, JWVT: analyzed the data; JWVT, MVM: prepared the first draft of the manuscript; KZ, VS, AP, SV, AD, MM, NG: provided critical inputs to revise the manuscript. All authors read and approved the final version of the manuscript.
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Competing interest: None stated.

WHAT IS ALREADY KNOWN?

- Treatment with doxycycline or azithromycin is effective in the treatment of rickettsial infections.

WHAT THIS STUDY ADDS?

- Presumptive doxycycline or azithromycin was effective in preventing progression of patients with acute febrile illness as well as acute undifferentiated febrile illness to acute encephalitis syndrome in Gorakhpur, India.

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RESEARCH PAPER

Immunogenicity and Safety of Typhoid Conjugate Vaccine in Healthy Indian Subjects: *A Randomized, Active-controlled, Comparative Clinical Trial*

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Objective: To compare the immunogenicity and safety of an investigational typhoid Vi conjugate vaccine (Test TCV) with a marketed typhoid Vi conjugate vaccine (Comparator TCV).

Design: Randomized, controlled trial.

Setting: Tertiary care and multispecialty hospitals.

Participants: 240 healthy subjects of 6 months to 45 years. Pediatric (<18 years) subjects were enrolled after day 21 safety assessment of adult subjects.

Intervention: Participants received a single-dose of test TCV or comparator TCV at baseline and were followed up for 6 weeks post-vaccination.

Main outcome measure(s): Primary variable was to demonstrate non-inferiority of the test TCV with the comparator TCV for seroconversion post-vaccination (≥4-fold rise in antibody titre). Secondary variables were seroconversion in the adult and pediatric cohorts, and geometric mean titre of antibodies while the safety was based on reported adverse events.

Results: A total of 117 subjects (Adult-58, Pediatric-59) and 119 subjects (Adult-60, Pediatric-59) in test and comparator group, respectively completed the study. The seroconversion rate with test TCV (overall-94.8%, adult-96.6% and pediatric-93.1%) was non-inferior to comparator TCV (overall-91.6%, adult-91.7% and pediatric-91.5%). The geometric mean titres of antibodies (EU/mL) at baseline (test TCV: overall-7.6, adult-10.0, and pediatric-5.7; and comparator TCV: overall-8.0, adult-12.0, and pediatric-5.3) and at end of study (test TCV: overall-1121.0, adult-1411.0 and pediatric-891.1; and comparator TCV: overall-1104.0, adult-1199.0 and pediatric-1014.0) were also comparable between the groups (P>0.05 for all). The most common adverse event was injection-site pain followed by fever in both the groups.

Conclusion: The immunogenicity and safety of test TCV is comparable to already marketed comparator TCV.

Keywords: *Conjugate vaccine, Polysaccharide protein conjugate, Tetanus toxoid, Typhoid vaccine.*

Trial Registration : **CTRI/ 2016/05/006975**

Typhoid (enteric) fever is a major public health disorder worldwide including India [1]. Several typhoid conjugate vaccines (TCVs) in which Vi capsular polysaccharide of *Salmonella typhi* is conjugated to the various carrier proteins have been developed to overcome the immunological drawbacks of the conventional typhoid polysaccharide vaccines [2]. Two such TCVs containing tetanus toxoid as the carrier protein have already been approved and marketed in India viz, Tybar-TCV (Bharat Biotech International Ltd.) [3] and Pedatyph (Bio-Med Pvt. Ltd.) [4]. The former contains 25 mcg of the Vi polysaccharide while the latter contains only 5 mcg of the Vi polysaccharide. TCVs can also be administered to infants and toddlers. The current study was conducted to evaluate the immunogenicity and safety of a new investigational indigenously developed TCV (Test TCV) in the target population.

Accompanying Editorial: Pages 609-10.

METHODS

This was a pre-licensure, randomized, multicentre, single-blind, non-inferiority, phase II/III clinical study

conducted at 8 centres (tertiary care or multispecialty hospitals) during June to November, 2016. The study was approved by the Regulatory Authority and the respective Institutional Ethics Committees of all the study sites. The study was registered prospectively with Clinical Trial Registry of India.

Prior to screening, a written informed consent with a prior consent for audio-video recording of the consent process was obtained from the adult subjects and guardians of the pediatric subjects; an assent was also obtained from the pediatric subjects aged ≥7 years. Healthy subjects of either gender aged 6 months to 45 years were considered eligible if the adult subjects or guardians of the pediatric subjects were literate enough to fill the adverse event (AE) details in the diary cards. The subjects were excluded if they had a history of hypersensitivity to any component of the vaccine, typhoid fever or vaccination against typhoid fever within the past 3 years, fever or infectious disorder of any origin of >3 days in the past month, any vaccination within the past 7 days; any febrile illness (≥37.5ºC) at the time of enrollment; any clinically significant systemic disorder, immunological disorder, coagulation disorder or thrombocytopenia; any anticoagulant, immuno-suppressive or immunostimulant therapy; administered blood, blood products or immunoglobulins within the past 3 months or planned administration during the study; pregnant and lactating women and female subjects not using acceptable contraceptive measures; participation in another clinical trial in the past 3 months; or history of alcohol or drug abuse in the past one year. Urine pregnancy test was done for adult females during the screening. The subjects were equally divided in the adult (18-45 years) and the pediatric (6 months to <18 years) cohorts; the enrolment in the pediatric cohort commenced after review of day 21 safety data of all the subjects enrolled in the adult cohort by an independent data and safety monitoring board. Pediatric cohort was stratified according to age into 6 month to less than 2 year, 2 to less than 5 year and 5 to less than 18 year.

A centralized block randomization plan of block size four was generated from *www.randomization.com* and a unique sequence of randomization numbers from this plan was provided to each study site. Eligible subjects were randomized (1:1) to receive a 0.5 mL single-dose of either the test TCV (Cadilla Healthcare Ltd., Ahmedabad, India) (Batch No. BO09S03) or the comparator TCV (Batch No. 76DL15026) which contained 25 mcg purified Vi capsular polysaccharide of *S. typhi* conjugated to tetanus toxoid. As the antigenic composition of the test TCV mimics that of Typbar-TCV, it was selected as the comparator (Comparator TCV). Comparator TCV has also been prequalified by the World Health Organization (WHO) in December, 2017 and it is indicated for active immunization against *S. typhi* infection in 6 months to 45 years age group [5]. Comparator TCV was procured from the market for this study. The vaccine was administered in the upper arm or in the anterolateral aspect of the upper thigh for younger children, at baseline (day 0) following which the subjects were closely observed for at least 30 minutes for any immediate AEs. Loading of the injection for vaccination was done out of sight of the subjects/ guardians to maintain single-blinding. The subjects were later followed up on an outpatient basis on day 7±3, 21±7 and 42+14.

Diary cards were given to the adult subjects or the guardians of the pediatric subjects to record solicited local (pain, redness, swelling and induration) and systemic (fever, headache, nausea, vomiting, malaise, arthralgia and myalgia) AEs for 7 days post-vaccination and unsolicited AEs till the end of the study. Any abnormality in the vitals or physical examination was also to be reported as an AE. The severity of AEs was graded as mild, moderate or severe as per the defined criteria (supplementary table) and causality was assessed as per the WHO's criteria for AEs following immunization [6]. In addition, the investigators also graded the tolerability to the vaccine based on the reported AEs.

Two mL blood samples were collected at baseline and 6 weeks post-vaccination for assessment of anti-Vi IgG antibody titre by the commercial Vacczyme ELISA kits (Binding Site Group Ltd., UK) at the central accredited laboratory. The primary outcome was seroconversion rate which was defined as four-fold or higher rise in anti-Vi antibody titre post-vaccination as per the WHO recommendations [7,8]. The secondary outcomes were geometric mean titre (GMT) of antibodies and seroconversion rate and GMT of antibodies in both age cohorts. The safety variables were local or systemic AEs, serious AEs (SAEs) reported, if any, and overall tolerability evaluation by the investigators based on the reported AEs as follows: Excellent - no AE, Good - mild AE(s), Fair - moderate AE(s) and Poor - severe or serious AE(s).

Assuming the seroconversion rate of at least 95% based on the published results of the comparator vaccine [9], a sample size of 238 subjects (1:1 allocation) was calculated to demonstrate the non-inferiority of the test TCV as compared to the comparator TCV considering 90% power, 2.5% level of significance and dropout rate of 15%.

Statistical analysis: The test TCV was considered non-inferior to the comparator TCV if the lower limit of 95%

CI for the difference between their seroconversion rates was above the pre-defined non-inferiority limit of -10% [8]. The GMTs between the groups were compared using the unpaired *t*-test while the GMTs within the groups were compared using the paired *t*-test after log transformation of antibody titres. The seroconversion rate and the incidence of AEs was compared using Chi-square or Fisher's exact test. Immunogenicity was assessed for both per-protocol and modified intention-to-treat analysis (defined as all randomized subjects who completed the study including the subjects with protocol violations) while all the vaccinated subjects were considered for the safety assessment.

RESULTS

In this study, 240 subjects (120 pediatric, 123 females) were randomized (***Fig.* I**). The mean (SD) age, height, weight and body mass index of the subjects were 16.1 (12.5) years, 130.2 (35.8) cm, 37.1 (22.9) kg and 19.0 (4.8) kg/m^2 respectively. The baseline characteristics of the subjects are as mentioned in ***Table* I**.

The seroconversion rates for the overall population, and the adult and the pediatric cohorts were 94.8%, 96.6% and 93.1% in the test group and 91.6%, 91.7% and 91.5% in the comparator group, respectively. The difference between proportions (95% CI) were 3.2% (-3.2%, 9.7%), 4.9% (-3.5%, 13.3%) and 1.6% (-8.1%, 11.2%) for the overall population, and the adult and the pediatric cohorts, respectively. The seroconversion rates for the age groups of 6 m to <2 y, 2 to <5 y and 5 to <18 y were 100%, 90% and 90% in the test group and 81.8%, 100% and 94.4% in the comparator group respectively; (P>0.5).

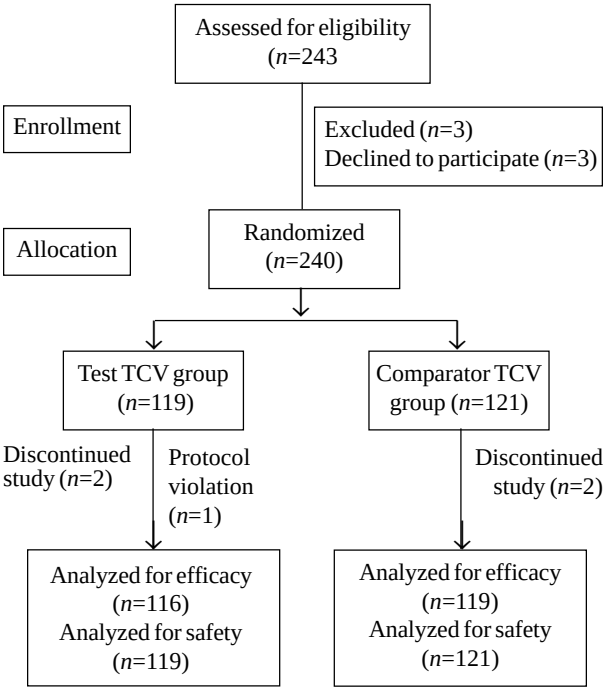

Fig. 1. *Study flow chart.*

A significant rise in the GMTs of anti-Vi antibodies was reported post-vaccination in both the study groups and in various age groups (P<0.0001). The GMTs of antibodies at the end of the study were comparable between the groups (P>0.05) (***Table* II**). The results of seroconversion and GMTs of antibodies were similar when analyzed by modified intention-to-treat analysis (data not shown).

In this study, 33.6% and 43.8% subjects in the test and comparator group respectively had reported AEs (P=0.11). The characteristics of AEs reported in the overall population and the adult and the pediatric cohorts are given in ***Table* III**. All the AEs resolved within 7 days of their occurrence with 91.5% AEs in the test group and 93.6% AEs in the comparator group getting resolved within 3 days of occurrence. There was no SAE reported during the study in either of the two study groups. Most of the AEs were mild in intensity, 93.2% in the test group and 81.7% in the comparator group. A certain, probable or possible association of AEs with the vaccine was seen in 88.1% and 85% of test and comparator group respectively. The overall tolerability assessment was excellent, good, fair and poor in 66.4%, 31.1%, 2.5% and 0% subjects in the test group, and 56.2%, 33.9%, 9.1% and 0.8% subjects in the comparator group, respectively (P=0.09).

Table I Baseline Characteristics of the Study Population

Characteristic	*Test group*		*Comparator group*	
	Adult n=59	*Pediatric n=60*	*Adult n=61*	*Pediatric n=60*
Median Age (*y*)	26.4	3.1	24.8	3.2
Males, *n*	21	35	26	35
*Baseline titer**	10.1 (7.8, 13.8)	5.6 (4.5, 7.1)	12.0 (8.4, 17.0)	5.2 (4.1, 6.7)
6 mo to <2 y	–	4.0 (3.6, 4.5)	–	4.5 (3, 6.7)
2 y to <5 y	–	5.1 (3.5, 7.4)	–	4 (3.4, 4.6)
5 y to <18 y	–	8.3 (5, 13.9)	–	8.2 (4.3, 15.5)

**Data presented as geometric mean titer (95% CI) in ELISA units/mL;P>0.05 for all inter-group comparisons.*

Table II Geometric Mean Titre of Anti-Vi Antibodies at Study Completion

Population type	*Test group*		*Comparator group*	
	n	*Geometric mean (95% CI)*	*n*	*Geometric mean (95% CI)*
Overall	116	1121 (857.2, 1467)	119	1104 (845.8, 1441)
Adult	58	1411 (1104, 1803)	60	1199 (960.2, 1498)
Pediatric	58	891.1 (551.7, 1439)	59	1014 (618.3, 1664)
6 mo to <2 y	18	1115 (628.4, 1979)	22	637.1 (201.5, 2014)
2 y to <5 y	20	709.3 (262.3, 1918)	19	1307 (739, 2313)
5 y to <18 y	20	914.8 (352.1, 2377)	18	1370 (672, 2793)

P>0.05 for all inter-group comparisons.

Table III Local and Systemic Adverse Events Reported in Study Subjects Receiving Typhoid Conjugate Vaccine

Parameter	*Test group*			*Comparator group*		
	Overall (n=119)	*Adult (n=59)*	*Pediatric (n=60)*	*Overall (n=121)*	*Adult (n=61)*	*Pediatric (n=60)*
Subjects with AEs	40 (33.6)	27 (45.8)	13 (21.7)	53 (43.8)	30 (49.2)	23 (38.3)
AEs reported	59	38	21	93	45	48
Local AEs	39	29	10	49	30	19
Pain	30 (25.2)	23 (39.0)	7 (11.7)	39 (32.2)	26 (42.6)	13 (21.7)
Swelling	5 (4.2)	3 (5.1)	2 (3.3)	6 (5.0)	1 (1.6)	5 (8.3)
Redness	4 (3.4)	3 (5.1)	1 (1.7)	3 (2.5)	2 (3.3)	1 (1.7)
Irritation	0	0	0	1 (0.8)	1 (1.6)	0
Systemic AEs	20	9	11	44	15	29
Fever	*7 (5.9)	5 (8.5)	#2 (3.3)	*17 (14.1)	5 (8.2)	#12 (20.0)
URTI	3 (2.5)	0	3 (5.0)	8 (6.6)	1 (1.6)	7 (11.7)
Diarrhea	3 (2.5)	1 (1.7)	2 (3.3)	1 (0.8)	1 (1.6)	0
Myalgia	2 (1.7)	2 (3.4)	0	6 (5.0)	4 (6.6)	2 (3.3)
Malaise	1 (0.8)	0	1 (1.7)	4 (3.3)	2 (3.3)	2 (3.3)
Headache	1 (0.8)	0	1 (1.7)	2 (1.7)	1 (1.6)	1 (1.7)
Arthralgia	1 (0.8)	1 (1.7)	0 (0.0)	2 (1.7)	1 (1.6)	1 (1.7)
Vomiting	1 (0.8)	0	1 (1.7)	2 (1.7)	0	2 (3.3)
Nausea	1 (0.8)	0	1 (1.7)	0	0	0
Urticaria	0	0	0	2 (1.7)	0	2 (3.3)

*AE: Adverse events; URTI: Upper respiratory tract infection; Data presented as no. (%); P>0.05 for all inter-group comparisons except *P=0.05 and #P<0.05.*

DISCUSSION

In the present study, seroconversion rate post-vaccination with the test TCV was non-inferior to the comparator TCV, and GMT of antibodies post-vaccination were comparable for both the vaccines. The safety of the test TCV evaluated in terms of reported AEs was also comparable to the comparator TCV.

The seroconversion rate with the comparator TCV reported earlier varied from 91.9-100% in various age groups [9,10]. The seroconversion rates reported with Pedatyph were 83% [11] and 100% [12] in pediatric subjects. The seroconversion rates with varying concentrations of another TCV, Vi-CRM_{197} (1.25 mcg, 5 mcg, 12.5 mcg and 25 mcg) in adult subjects in phase I and II studies were also in the range of 95-100% [13]. The seroconversion rate reported for the test TCV in this study was also similar. Likewise, the GMT of antibodies post-vaccination in this study also correlated well with that reported for the comparator TCV in previous studies

WHAT IS ALREADY KNOWN?

- Typhoid conjugate vaccines are associated with a better immunological response as compared to the conventional unconjugated polysaccharide vaccines.

WHAT THIS STUDY ADDS?

- Immunogenicity and safety profile of the test typhoid conjugate vaccine is comparable to the already marketed vaccine in the target population of 6 months to 45 years of age.

in which similar antibody assessment method was used [9,10]; however, the GMT of antibodies post-vaccination with other TCVs could not be directly compared due to the difference in the antibody assessment method [11-16]. Further, the safety data reported in this study is also consistent with that reported for other TCVs [13,17] and typhoid polysaccharide vaccines [18-20].

The limitations included single-blind nature of the study as the difference in the physical characteristics and packaging of the test TCV and the comparator TCV precluded double-blinding. The study was conducted in a limited sample size (albeit sufficient to draw statistical conclusions) with a short-term follow-up. However, a long-term extension of this study is being conducted in which the persistence of antibodies around 3 years after primary vaccination will be evaluated.

Owing to the improved immunological properties, permission for use in younger children including infants and longevity of the immune response of TCV, WHO has recommended a single-dose of TCV from 6 months to 45 years of age in endemic regions to prevent typhoid fever [21]. The results of this study indicate that the immunogenicity and safety of the test TCV is comparable to that of the comparator TCV.

Contributors: RK, AKK, UN, SKJ, TRB, RV, SS, VKG: study conduct, medical care of the study participants and data acquisition; PD,RM: study concept and design, overall study coordination, data analysis and interpretation; PP: study concept and design and manufacture of the test vaccine. All authors had full access to clinical trial data. PD, RM: prepared the manuscript and other authors provided their feedback for revising it for the intellectual content. All authors have approved the final version of this manuscript. All authors agree with the interpretation of data and its representation in the manuscript.

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RESEARCH PAPER

Modified Integrated Algorithm for Detection of HIV Among Sick Children Aged 0-14 Year Seeking Care at Healthcare Facilities in India

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Objective: To test the ability and to identify unique criteria in a Modified Integrated Algorithm developed by Indian Council of Medical Research (ICMR) to detect HIV infection among sick children 0 to 14 years, seeking care in a health care facility.

Design: Facility based cross-sectional survey.

Setting: Four talukas of Belgaum District, Karnataka, India during 2013-2014.

Patients: Sick children 0-14 years seeking care at healthcare facilities in the study area.

Procedure: A total of 10 health care facilities were selected using specific criteria. Trained health care providers in these facilities used the WHO generic Integrated Management of Childhood Illnesses screening algorithm for HIV, applicable for children to 0-5 years and ICMR modified integrated algorithm for >5-14 years, to screen and test children for HIV, when they sought care in these facilities.

Main Outcome measure: Prevalence of HIV in children screened positive by the Modified Integrated Algorithm.

Results: Of the total 33342 children who visited the 10 health care facilities, 24342 were screened by the physician. Of the 527 screened positive sick children with suspected signs/ symptoms, 509 consented and were tested with age appropriate HIV testing. 97 children tested positive (HIV prevalence 19.1%: 5% in <5yrs and 28% in ≥5-14 years). The result of Classification and Regression Tree and logistics regression consistently identified parents with HIV and orphan child, as important predictor of HIV infection.

Conclusion: ICMR Modified integrated algorithm may be used as a screening tool in the public and private health care facilities to increase case detection of pediatric HIV.

Keywords: *Diagnosis, Identification, Parents, Tool.*

There is lack of information on the epidemiology of pediatric HIV in India with lack of universal screening for HIV [1]. The HIV case load among children remains unknown as the existing surveillance system in India does not include children. The pediatric burden is estimated/projected to be 6-7% of the adult HIV prevalence [2,3]. Under-diagnosis of pediatric HIV was attributed to the low sensitivity of screening tools at the community level with suggested addition of parental factors to improve the positive predictive value of the Integrated Management of Childhood illnesses- HIV (IMCI-HIV) algorithm [4]. However, this algorithm is applicable to ages up to 5 years only. Children up to 18 years constitute 41% of the total population [5]. Targeted screening of sick children seeking care at healthcare facilities may be possible if the available algorithm is modified for children of all ages. Identification of HIV infection and linkage with anti-retroviral treatment centers would improve child survival among HIV-infected children, currently reported to be less than half of that in adults [6]. This is an important step towards the highly ambitious UN goal of ending AIDS as a public health threat by 2030 [7]. The present study attempted age-appropriate modifications in the generic IMCI-HIV algorithm to create a modified integrated algorithm, and used it to detect prevalence of HIV in sick children 0 to 14 years old.

Accompanying Editorial: Pages 611-12.

METHODS

This cross-sectional study was conducted in four 'talukas' (sub-district administrative regions) of Belgaum District, Karnataka, India *viz*, Athani, Bailhongal, Gokak and Belgaum, during 2013-2014. The study protocol was approved by the ethics committee of St John's Medical

College and Hospital, Bangalore in October, 2012. Informed consent was obtained from caregivers of study participants.

Out of 628 available health care facilities, 113 where HIV testing and care was available were listed by using the following criteria: availability of a physician or a pediatrician, and a case load of at least 30 patients in a month. These 113 HCFs were further categorized into tertiary, secondary and primary, and government and private facilities. Ten facilities were selected by stratified randomization by a person not involved in the study.

WHO generic IMCI screening algorithm [8] for HIV covered children only up to 5 years of age. To extend the algorithm for children up to >5-14 years of age in the study, an ICMR constituted sub-committee suggested modifications in the WHO generic IMCI- HIV algorithm. The sub-committee incorporated features of Integrated Management of Adolescent and Adult Illnesses [9], and a category of conditions common to children of both age categories (0-5 and >5-14) was named as 'other clues for all children' from history suggestive of parental HIV infection. Few symptoms applicable to adolescents were marked with an asterisk, denoting using caution in application, due to the sensitive nature of the questions.

The WHO generic algorithm was used for ages up to 5 years. A child less than 5 years was referred for HIV testing if two or more of the following signs were present: pneumonia or severe pneumonia, persistent diarrhea or severe persistent diarrhea, ear discharge (acute or chronic), very low weight or severe malnutrition, oral thrush, parotid enlargement, and generalized lymphadenopathy.

For 5-14 year ages the Modified integrated algorithm was used. A child 5-14 years old was referred for HIV testing, if any one of the signs given in ***Box* I**, or any sign from the 'other clues' given in ***Box* II**, was present.

A child (aged up to <5 years) satisfying a minimum of two criteria for their age category or one criterion in 'other clues', and a child aged 5-14 years fulfilling a minimum of one criterion in their age category or under 'other clues', was defined as screen positive and referred for age-appropriate HIV testing.

Forty eight physicians/pediatricians posted at 10 healthcare facilities of the study area were trained at the District training centre, to use the Modified integrated algorithm. A post-training feedback evaluation and a weekly visit by the research officer to provide technical and supportive supervision and re-training was done.

Box I Adaptation from Integrated Management of Adolescent and Adult Illnesses Ages >5-14 years

A child 5 -14 years old should be referred for HIV testing if any one sign is present

1. Repeated Infections
2. Lymphadenopathy (PGL)-painless swelling in neck and armpit
3. Oral thrush or oral hairy leukoplakia
4. Esophageal thrush
5. Weight loss more than 10% without other explanation
6. More than 1 month:-
   - Diarrhea (unexplained)
   - Vaginal candidiasis
   - Unexplained fever
   - Herpes simplex ulceration (genital or oral)
7. *Other sexually transmitted infections
8. *Injecting drug use
9. *Sexually active person with multiple partners living in high HIV-burden area.

**Questions to be asked in a sensitive manner to adolescents only*

Box II 'Other clues' for Suspecting HIV Infection for all Children

A child of any age should be referred for HIV testing if any of the 'other clues' are found during history taking/examination

1. Herpes zoster
2. Skin or mouth conditions which are chronic (>3 mon) or refractory to standard treatment
3. Children with disseminated TB/suspected drug resistant TB (Pulmonary or extrapulmonary)
4. Gum/ mouth ulcers
5. Child has any opportunistic infection or condition listed in WHO stage 4 staging for HIV infected children
6. Children with developmental regression
7. Children with recurrent and persistent seborrheic capitis/dermatitis
8. Children with chronic lung disease

If the history suggests:

9. Unexplained death of parent
10. Orphan child
11. History of blood transfusion
12. Parent with HIV/HIV related illness
13. Parent with high risk behavior/occupation

Tools such as flow-charts, ready-reckoners and diagrams were provided and displayed at each of these facilities.

Children who fulfilled the screening criteria for HIV testing were referred for age-appropriate HIV tests: Children <18 months by DNA PCR, Children >18 months tested by ELISA. Trained counsellors provided pre-test counseling to the parent/guardian. Test results were obtained maintaining anonymity. HIV positive children were referred to the appropriate healthcare facility for care, support and treatment.

Data analyses: Data were entered in Microsoft Office Access. Statistical software SPSS IBM version 22.0 (Armonk, NY: IBM Corp.) was used for univariate and multivariable logistic regression analysis and statistical significance was tested using Wald statistics. Overall fit of the model was tested using Hosmer-Lemeshow Chi-square test with *P*-value >0.05 as the criteria for good fit. HIV prevalence across categories was compared by Chi-square test and mean values were compared by Student *t* test. The following study variables were included for univariate analysis: present status of pneumonia, persistent diarrhea in the past 3 months, ear discharge, history of loss of weight, repeated infection, painless swelling in the neck or armpit, weight loss >10%, diarrhea more than one month, vaginal candidiasis more than one month, presence of herpes simplex ulceration more than one month, oral thrush (or) oral hairy leukoplakia, esophageal thrush, multiple sexual partners, herpes zoster presence, chronic skin or mouth condition, presence of TB, WHO stage 4 condition for HIV children, developmental regression, persistent seborrheic capitis, chronic lung disease, unexplained death of parent, orphan child, blood transfusion history, parent with HIV related illness, and parent with high risk occupation. The variables that were found to be statistically significant at $P<0.05$, were included for multi variable logistic regression analysis.

A Classification and Regression Tree (CART) [10,11] model using Salford Predictive Modeler (SPM) software (evaluation version 8.0) was developed. CART is an exploratory data analysis and builds a tree through recursive partitioning in such a way that the data is successfully split into increasingly homogenous subgroups. In the present analysis, minimum number of observations for each terminal node was set as ≥30. Data collected from all 10 health facilities were included in the model. Children with HIV serology negative were labelled as HIV-negative and serology positive were labelled as HIV-positive.

RESULTS

A total of 33342 children visited the 10 healthcare facilities during the period 24 February, 2014 to 30 June, 2014. Among them, 24342 were screened by trained field investigators and confirmed by physician/pediatricians. Out of 527 sick children screened positive by the modified IMCI-HIV algorithm, 509 (mean age 6.8 y) consented and were tested with age-appropriate HIV tests.

Overall HIV positivity in 0-14 years (n=509) was 19.1% (n=97) (95% CI 15.7, 22.7); 5% in <5 years and 28% in ≥5-14 years. Age and gender profile of the study population is given in ***Table* I**. There was no significant difference in the age distribution between the genders (P=0.3). The mean age of boys was significantly higher than girls (P=0.005). HIV prevalence in different taluks is shown in ***Table* II**.

Only 14 out of 22 (64%) criteria in the modified IMCI–HIV algorithm were found to be useful in identifying HIV infected children. Univariate analysis identified eight variables (persistent diarrhea, discharging ear, very low weight, diarrhea, unexplained fever, orphan child, history of blood transfusion and parents with HIV) as significantly associated with HIV status. Final statistical model on multivariable logistic regression yielded three significant variables (unexplained fever, orphan child and parents with HIV); **(*Table* III)**. Using these three variables, correct classification of negatives and positives was 90% and 95%, respectively.

Table I Demographic Profile of Study Population (N=509)

Variables	*No. (%)*
Male gender	294 (57.8)
Age group (y)	
<1	15 (2.9)
1-5	196 (38.5)
6-10	182 (35.8)
11-14	116 (22.8)
*Educational status**	
Illiterate	10 (2.0)
Class 1-5	176 (34.6)
Class 6-12	87 (17.0)
Below school going age	233 (45.8)
Occupational status of parents/guardians#	
Daily wage earners	336 (66.0)
Salaried	53 (10.4)
Business	56 (11.0)
Housewife	20 (3.9)
Sex workers	5 (1.0)
Retired and others	11 (2.2)

*Data not available for *3 and #28 respondents.*

WHAT IS ALREADY KNOWN?

- Addition of parental factors to the IMCI-HIV algorithm improves the positive predictive value of the tool applicable for children younger than 5 years in low-resource settings.

WHAT THIS STUDY ADDS?

- A Modified Integrated Algorithm detected high prevalence of pediatric HIV in sick children aged 0-14 years.
- Unexplained fever for more than one month, a HIV-positive parent and being orphan were predictors of HIV infection among sick children in a low-resource and high-burden setting.

CART can statistically demonstrate which factors are particularly important in a model or relationship in terms of explanatory power and variance. Accordingly, these diagnostic measures were compared between logistic and CART model (***Web Table* I**). It was observed that while identifying the children of HIV parents and orphan, overall about 94% of HIV children may be predicted correctly. The diagnostic measure was compared between logistic and CART model which showed similar sensitivity (94.8% and 94%), specificity (90% each) and diagnostic accuracy (91.2% and 91%), respectively for identifying the children with HIV parents and orphans. The area under curve (AUC) is presented in ***Fig*. 1**. Apart from HIV parents and orphan children, presence of unexplained fever was captured as another significant variable in the logistic regression analysis. However, diagnostic measures did not vary significantly. Therefore, 'parents with HIV' and 'orphan child' are important with the order of priority scores being 100% and 50%, respectively as emerged by CART analysis.

DISCUSSION

In this study, the WHO generic IMCI algorithm was modified by addition of components from the Integrated Management of Adolescence and Adult Illnesses and 'other clues' for suspecting HIV infection in children ≥5-14 years. A higher age-specific prevalence of HIV was identified in ≥5 -14 year old children. The positivity rate among adults tested was reported as 2.7 in Belgaum in 2014. The prevalence in 0 - <5 year was similar as estimated from adult HIV projections. Earlier studies [12,13] have reported local adaptation of the WHO generic algorithm in improving diagnosis of pediatric HIV; however, they were limited to ages 0 - <5 years.

Most of the criteria in the Modified integrated algorithm were useful in identifying HIV infected children in this population. Unexplained fever more than one month, being an orphan child and having parents with HIV were the top three predictors of HIV test positivity, with high percent correct classification of negatives and positives unlike eight other common clinical features. Application of this algorithm in similar settings elsewhere should take this into consideration and make deletions in the algorithm based on background

Table II HIV Prevalence in Different Taluks

Taluk	*Study subjects*	*Prevalence, n (%)*
Athani	43	3 (7.0)
Bailhongal	65	2 (3.1)
Belgaum	332	90 (27.1)
Gokak	69	2 (2.9)

**Prevalence varied significantly between the Taluks (P<0.001).*

Table III Risk Estimation for HIV Infection (*N*=509)

Variables	*Odds Ratio*	*95% CI*	*P value*
Unexplained fever	2.64	1.16; 6.02	0.02
Orphan child	305.92	30.99; 3019.98	0.001
Parents with HIV	79.91	32.21; 198.24	0.001

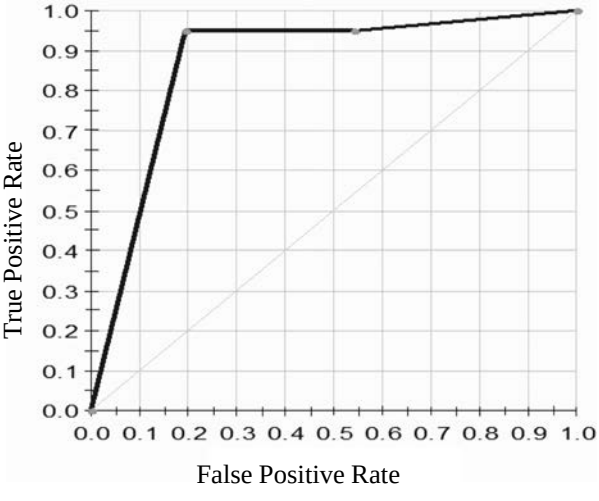

Fig. 1 *Receiver operating characteristic (ROC) curve for identifying children with HIV in the study area.*

prevalence. The modified integrated algorithm can thus be further modified and used to predict pediatric HIV infection in similar settings.

In addition to a binary logistic regression analysis, we performed a CART analysis [14], which is mathematically identical to certain familiar regression techniques, but presents the data in a way that is easily interpreted by those not well versed in statistical analysis. In a large public health project, CART is useful to present preliminary data to clinicians or other project stakeholders who can comment on the statistical results with practice knowledge and intuition. This process yields a well informed and statistically informative model than a singular clinical or statistical approach. The results of CART model and logistics regression model were in agreement and parents with HIV and orphan child had high priority scores with high sensitivity and specificity.

Limitation of the study was lack of validation of the algorithm, which required blood sample collection from children testing negative on the screening tool (questionnaire) in healthcare facilities. Both practitioners and patients resisted blood collection purely for research purposes. A higher prevalence of HIV as reported in the study is expected in the population of sick children. Considering the high proportion (30-40%) of population belonging to 5-14 year age group, policy makers should consider including HIV estimates in routine surveillance until universal coverage becomes a reality.

We conclude that the modified integrated algorithm developed by ICMR can be used as a screening tool in the public and private health care settings to detect pediatric HIV where universal screening for HIV is not yet available/feasible. The important predictors of pediatric HIV infection in settings with low prevalence and yet a high burden, as in many LMICs are parent with HIV, being orphan and unexplained fever more than one month.

Contributor: AS: coordinated the study, conceived the idea, wrote the proposal, monitored study implementation, contributed to statistical analysis, provided critical inputs to the manuscript and approved it; RW and RS were responsible for obtaining and field level compliance for ethics, regulatory and financial approvals, study implementation, data collection, and provided inputs for revising the manuscript; PV: conducted advanced statistical analyses, contributed to the manuscript, reviewed and revised the manuscript; RSP: conducted data analyses, reviewed the draft manuscript; and SI was responsible for regular guidance and support, reviewed the manuscript.
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Web Table I Comparison of CART and Logistic Regression Model by Diagnostic Measures

Diagnostic measures	*CART model*	*Logistic regression*	*95% CI*
Sensitivity (%)	94.0	94.8	88.5-97.8
Specificity (%)	90.0	90.0	86.8-92.6
Diagnostic accuracy (%)	91.0	91.2	88.2-93.2
PPV (%)	69.0	69.4	60.9-76.4
AUC	0.93	0.95	0.94-0.98

PPV: Positive predictive value; AUC: Area under the curve.

OBITUARY

Air Cmde (Retd.) Vasudev Vatwani (1938-2020)

Air Cmde (Retd.) Vasudev Vatwani was an alumnus of the prestigious King George Medical College Lucknow, where he began his journey into the world of medicine. After completing his under-graduate training from KGMC in 1963 he was commissioned into the Indian Army Medical Corps where he began his career as a young doctor. He completed his post-graduation in Pediatrics with Honors from Osmania University, Hyderabad. Thereafter he completed his Diploma in Child Health from the Armed Forces Medical College, Pune. He was a well-liked and admired pediatrician who was popular and respected both by the patients as well as his colleagues. He had an illustrious professional career and was a much respected teacher having a long stint at the prestigious Armed Forces Medical College, Pune as Reader as well as Associate Professor. He went on to become Senior Advisor and Professor in Pediatrics and was Head of Department, Pediatrics at large Command Hospitals at Lucknow and Udhampur, as well as, Head of Department at the premier Army Hospital (Research/ Referral), New Delhi. He continued to excel both academically and professionally and was promoted to the rank of Air Commodore and was the Principal Medical Officer at Headquarters Maintenance Command, Nagpur till his retirement in 1996.

Although he retired from active military service, the teacher and doctor in him was very much active; he continued with both clinical work and teaching. He set up the Pediatric department at Dr. DY Patil Medical College in Pimpri and was instrumental in getting the center recognized for post graduate teaching. He continued as Professor and Consultant in Pediatrics at Yashwantrao Chavan Memorial Hospital, Pimpri and at Walwalkar Hospital and BKL Walwalkar Rural Medical College, Chiplun until 2018. He was an examiner for various universities including Pune, Delhi, Lucknow, CPS Mumbai, MUHS Nashik, DY Patil University and Gujarat University. He was also a recognized Teacher for PhD at DY Patil University and has been a guide to multitude of post graduates. He was recognized for his vast knowledge and dedication to his patients and his profession, and respected and loved by his students who found him always open and accessible for all help and guidance.

During his career Air Cmde (Retd.) Vatwani undertook several original research projects, presented numerous papers at national conferences and contributed to many scientific publications and books. In recognition of his academic excellence and contribution, he was felicitated with a memento by the Armed Forces Medical College for his service from 1964-2014, commemorating 50 years of education, patient Care and research.

Air Cmde (Retd.) Vatwani was an active member of the IAP since 1971, an avid reader of, as well as a contributor to the IAP publications. He always kept abreast of the latest research, developments and guidelines in pediatrics and medicine. He was an exemplary human being who spent his life not only as a dedicated doctor but also as a much loved and respected guide, mentor and friend to his colleagues and students alike.

Air Cmde (Retd.) Vasudev Vatwani will be forever remembered for his vast knowledge, patience, humility and resilience.

RESEARCH PAPER

Growth Parameters of Turkish Children With an Autoinflammatory Disease Before and After Canakinumab Treatment

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Objective: To evaluate the effect of canakinumab on growth parameters of patients with autoinflammatory diseases. **Methods:** This retrospective study included Colchicine resistant familial Mediterranean fever (FMF), Mevalonate kinase deficiency (MKD), Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), Deficiency of adenosine deaminase 2 (DADA2) patients treated with canakinumab for at least six consecutive months. **Results:** Eleven patients with FMF, 9 with MKD, 3 with TRAPS, and 1 with DADA2 were included. The median age (range) at diagnosis and drug initiation was 6.06 (1.45-16.06) years and 9.72 (1.82-19.11) years, respectively. The mean weight, height, and BMI SD scores significantly increased after canakinumab. There were significant improvements in laboratory parameters and disease activities. However, growth parameters after the drug did not differ according to gender, the duration of diagnostic delay, and age at the diagnosis. **Conclusion:** Canakinumab seems to have a positive effect on growth in patients with autoinflammatory diseases by controlling disease activity and inflammation.

Keywords: *Familial mediterranean fever, Management, Outcome, Pyrexia of unknown origin*.

Autoinflammatory diseases are a group of disorders characterized by unprovoked, recurrent, sterile inflammation episodes [1], the various conditions reported include Familial Mediterranean fever (FMF), Tumor necrosis factor receptor associated periodic fever syndrome (TRAPS), Mevalonate kinase deficiency (MKD). FMF is the most encountered AIDs caused by mutation in *MEFV*, characterized by recurrent fever, serositis, arthralgia or arthritis [1,2]. TRAPS is caused by autosomal dominant mutations in *TNFRSF1A*. The clinical features include recurrent fever, abdominal pain, pleuritis, myalgias, arthralgias, periorbital edema, and conjunctivitis. Mevalonate kinase deficiency (MKD) is a rare disorder caused by mutations in *MVK*. The clinical features of MKD are early onset of recurrent fever episodes accompanied by lymphadenopathy, erythematous skin rashes, hepatomegaly, splenomegaly, arthritis, and gastrointestinal symptoms [3]. Auto-inflammatory diseases are disorders of the innate immune system results in overproduction of proinflammatory cytokines, including IL-1β [2]. FMF, MKD, and TRAPS are classified in IL-1–mediated diseases [1]. IL-1 blocking agents, including canakinumab, an anti-IL-1β monoclonal antibody, have been approved for the treatment of these diseases [2,4-6].

Growth parameters are well-known indicators of a child well-being that mostly affected in children with chronic inflammatory diseases or autoinflammatory [7-9]. Although, there are several reports on effect of colchicine on growth parameters of FMF [8,10,11], to our knowledge the effects of canakinumab on growth parameters of autoinflammatory diseases have not been investigated so far.

METHODS

This study had a retrospective design and included colchicine resistant FMF, MKD, TRAPS, and deficiency of ADA2 (DADA2) patients, treated with canakinumab for at least six consecutive months. All patients were diagnosed and followed by a same pediatric rheumatologist in our tertiary referral center. FMF patients were diagnosed according to Tel Hashomer Diagnostic criteria [12] and diagnosis were supported by *MEFV* analysis. Colchicine-resistant patients were defined according to Turkish FMF study group [13]. Disease activity of patients with FMF, MKD and TRAPS were calculated retrospectively before and after canakinumab by using the Autoinflammatory Diseases Activity Index (AIDAI) [14].

Diagnosis of MKD was confirmed by genetic analysis

and the patients with bi-allelic mutations in *MVK* were considered as MKD. TRAPS patients were diagnosed according to the genetic analyzes of *TNFRSF1A*. The diagnosis of DADA2 was confirmed by mutations in *CECR1*. We utilized the *MEFV, MVK, TNFRSF1A*, and *CECR1* analysis as molecular diagnostics tools by using a next-generation sequencing platform (MiSeq System, Illumina, San Diego, CA, USA).

Demographic parameters, including age, gender, clinical manifestations, medical data of the patients were retrospectively obtained from medical files. Complete blood count, acute phase reactants (APRs), including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), studied before and after canakinumab administration were also collected from medical files.

Growth parameters, including weight, height, and BMI were recorded. Height (cm) and weight (kg) were preferentially measured in the morning at each visit by the same operator with the same type of stadiometer (Harpender). Standard deviation (SD) scores of growth parameters were calculated by anthropometric references in Turkish children [15]. The study protocol was approved by local Ethics Committee. Written informed consent was obtained from legal guardians of each patient before the study.

Statistical analysis: The SPSS 20.0 statistical software (IBM SPSS Statistics) was utilized. Kolmogorov-Smirnov test, stem-and-leaf diagram, and the histogram was utilized for the confirming the normality of distribution of growth indices. Paired-sample t-test was used for comparing two dependent variables in the same study group and Wilcoxon signed rank test was used for two independent variables. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Totally 24 patients (13 males) with auto-inflammatory diseases were included to the study. Eleven (45.8%) patients had diagnosis of FMF, 9 had MKD, 3 had TRAPS, and one had DADA2. Present study also contains the data of 10 patients reported in the previous study [16], whose growth parameters were available. A girl patient had a Met694Val/null mutation in *MEFV* besides the diagnosis of DADA2, which was reported previously, elsewhere [3]. The median age at diagnosis was 6.06 (range, 1.45-16.06) years. The mean age at study time was 11.29±5.21 years. The median diagnostic delay was 2.67 years (0.24-15.56). The median age at canakinumab initiation was 9.72 (range, 1.82-19.11) years, and median follow-up during treatment was 1.59 (range, 0.56-4.33) years; and the median dose used was 10 (4-27) doses.

Patients with FMF had recurrent fever attacks accompanying with abdominal pain, increased APRs and were given colchicine together with canakinumab. One of the FMF patients also had polyarticular chronic arthritis which were treated unsuccessfully with etanercept before canakinumab. HIDS patients showed recurrent fever attacks together with gastrointestinal symptoms and enlarged lymphadenopathies. They were given colchicine before the diagnosis of HIDS. All three TRAPS patients had recurrent fever attacks and were given colchicine before canakinumab. One of the patients with TRAPS also had IgA nephropathy and was given methylprednisolone and cyclosporine before canakinumab [17]. The DADA2 patient had hepatosplenomegaly, nephrotic range proteinuria, low serum immunoglobulin G, and immunoglobulin M levels and was diagnosed with renal amyloidosis. He was given methylprednisolone, cyclosporine, and colchicine before canakinumab [2], colchicine treatment was continued thereafter with canakinumab.

Disease activities of the patients were evaluated, except for the DADA2 patient because of the unavailability of activity score. Only one FMF patient with chronic arthritis was not in remission according to the AIDAI score after CAN. White blood cell and platelet counts, ESR, and CRP levels significantly decreased after canakinumab (***Table* I**).

The mean weight, height, and BMI SD scores after therapy were significantly higher than before (***Table* I**). The growth parameters after canakinumab did not differ significantly with gender and age-group at diagnosis (<6 year and ≥6 year) or follow-up duration (less than or more than 3 years).

DISCUSSION

In the present study, mean height, weight, and BMI SD scores of the patients with autoinflammatory diseases significantly increased after canakinumab treatment. Growth parameters after canakinumab did not differ according to gender, the duration of diagnostic delay and age at diagnosis. Controlling disease activity with the drug in these patients suppressed ongoing inflammation, which may explain the significant improvements in growth parameters.

We recently reported the canakinumab experience in 14 colchicine-unresponsive FMF patients. Attack frequency, proteinuria, and acute phase reactants, including ESR and CRP, were significantly decreased after the drug [16]. In the present study, depicting improvement in growth parameters, acute phase reactants and disease activity in patients with AIDs on

WHAT THIS STUDY ADDS?

- Canakinumab treatment has positive effects on growth parameters in children with autoinflammatory diseases.

Table I Growth and Laboratory Parameters of Patients With an Autoinflammatory Disease Before and After Canakinumab Treatment (*N*=13)

Parameters	*Before treatment*	*After treatment*	*P*
White blood cell per mm^3, median (range)	8665 (4730-74200)	6350 (4300-12200)	0.003
Hematocrit (%), mean (SD)	34.7 (4.78)	36.9 (3.96)	0.1
Platelet count per mm^3, mean (SD)	406000 (123900)	269000 (73550)	0.01
Erythrocyte sedimentation rate (mm/h), median (range)	41 (22-120)	10.50 (2-36)	0.001
C-reactive protein (mg/dL), median (range)	4.1 (1.1-29.2)	0.1 (0.1-1.6)	0.001
AIDAI score, median (range)	26 (15-54)	0 (0-35)	0.001
Weight SD score, mean (SD)	-0.80 (1.13)	-0.25 (1.18)	0.002
Height SD score, mean (SD)	-0.35 (1.09)	0.04 (1.10)	0.006
Body mass index SD score, mean (SD)	-0.74 (1.20)	-0.14 (1.10)	0.005

AIDAI; Autoinflammatory Diseases Activity Index.

canakinumab further suggests its effectiveness in those patients.

The effect of anti-interleukin 1 blocking agents, either anakinra or canakinumab, were also presented in eight colchicine-unresponsive FMF patients in a previous report [18]. Moreover, the effectiveness of canakinumab for the treatment of autoinflammatory diseases has been investigated in another study, in where colchicine resistant FMF, MKD and TRAPS patients were included. It was efficacious in controlling and preventing flares in those patients [5].

Even though, the heterogeneity of the study population, small number of patients, retrospective design and data collection are the limitations, the rarity of the autoinflammatory diseases and having no data on growth parameters in those treated with canakinumab make the present study valuable. Another limitation of the study is the lack of investigation about environmental factors, including diet and physical activity. Therefore, prospective and even multicenter studies conducted on a large number of AIDs patients are needed to clarify the effect of canakinumab on growth in patients with auto-inflammatory disease.

*Contributors***:** SB, MY: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; RMKE,DD: collected data, carried out the initial analyses, and reviewed and revised the manuscript; DUA, DD: designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. *Funding*: None; *Competing interest*: None stated.

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Managing Children With Renal Diseases During the COVID-19 Pandemic

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The coronavirus outbreak is a rapidly evolving pandemic, placing unprecedented strain on health-care systems. COVID-19 presents challenges for management of children with renal diseases, especially those receiving long-term immunosuppressive medications, including renal transplant recipients and those with chronic kidney disease and acute kidney injury requiring dialysis. Our preparedness for managing this vulnerable group of children is the need of the hour. The purpose of this article is to provide guidance to caregivers and health care personnel involved in management of children with renal diseases and to ensure patient well-being, while protecting staff from infection.

Keywords: *Chronic kidney disease, Hemodialysis, Nephrotic syndrome, Transplant*.

Coronavirus disease 2019 (COVID-19) has been declared as a pandemic, given its global spread. Children account for 1-5% patients and are less likely to become severely ill compared to adults; though, preschool children and infants might have severe clinical features [1,2].

In March, 2020, the Indian Society of Pediatric Nephrology (ISPN) decided to formulate guidelines on managing children with renal diseases during the COVID-19 pandemic. A writing committee and advisory board was formed to draft guidelines, based on policies and guidelines from Ministry of Health and Family Welfare, Indian Society of Nephrology and international professional organizations, and evidence from systematic and narrative reviews, trials and other reports. Draft guidelines underwent multiple iterations before being finalized.

Are Patients With Kidney Disease At Risk for COVID-19 and Poor Outcomes?

Co-morbidities associated with mortality during COVID-19 are common in adult patients with chronic kidney disease (CKD), and those on maintenance dialysis. Children with CKD especially stage 4-5, those on hemodialysis (HD) or receiving immunosuppressive agents are considered immunocompromised. Patients with advanced CKD are malnourished and undergo maintenance HD in busy units, increasing the risk of infection. Analysis of confirmed patients with COVID-19 reported to the Center for Disease Control (USA) revealed that patients with CKD were 11 to 14-times more likely to be hospitalized and require intensive care, respectively compared to those without CKD [3].

Reports from China suggest a less severe course of the disease in dialysis compared to transplant recipients. At a dialysis center in Renmin Hospital, Wuhan, 37 of 230 patients on HD and 4 of 33 dialysis staff showed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection over 4-weeks [4]. Seven patients died, of which 6 had COVID-19. The incidence of COVID-19 in HD patients reported from China is similar to that from a similar cohort in Italy. Of 20 adult transplant recipients in Brescia (Lombardy, Italy) with COVID-19, 5 died, 4 were critically ill and 3 recovered. Similarly, among 21 HD patients with COVID-19; 5 died while 4 recovered [5]. In a report on 15 adult transplant recipients with COVID-19 from a single center in US, one-fourth were ventilated with one death, while 50% were discharged [6]. In contrast, another report from US reported a higher mortality among 36 adult kidney-transplant recipients with Covid-19 compared to general population as well as to patients more than 70 years old with COVOD-19 (28% *vs* 5% and 8-15%, respectively) [7]. However, none of the transplanted or dialyzed children were infected in Lombardy that

reported more than 8000 patients with COVID-19 [personal communication: G. Montini, Pediatric Nephrology Unit, Milano].

Experts feel that there is evidence that adult patients with CKD, especially those on dialysis, transplant recipients or receiving immunosuppressive therapy, are at increased risk for SARS-CoV-2 infection, with significant morbidity and unsatisfactory outcomes.

Recommendations for Patients and their Caregivers

Caregivers refer to parents/guardians taking care of health and personnel needs of children. Patients with CKD, those on immunosuppressive medications and transplant recipients, and their caregivers should follow appropriate advice to reduce the risk of getting sick. These measures include self-isolating and staying at home to minimize contact between people; avoiding non-essential travel, crowded places and large gatherings; washing hands frequently with soap and water; and adopting cough etiquette. Patients and caregivers should wear a triple-layer mask while visiting healthcare facility including dialysis units. In outpatient clinic, social distancing measures should be strictly followed along with other measure of personal protection. All used disposable gloves and masks should be placed in a lined container before disposing them with other household waste and wash hands with soap and water/alcohol-based hand rub.

Caregivers should ensure around 4 weeks stock of medications at home. They should contact their treating physician or hospital, by phone or email, if child has fever, cough, shortness of breath, with or without rhinorrhea, and muscle aches or chills.

Healthcare Personnel

Health care personnel (HCP) refer to those directly related to provision of health care services. HCP should receive information about COVID-19, and training on institutional and national protocols for evaluation and management [8]. Doctors, dialysis nurses and technicians must follow guidelines for prevention and control of infections and adhere to protocols for identifying and reporting patients of COVID-19. Clinical management of patients with COVID-19 is evolving, and doctors are advised to stay updated.

Teleconsultations with patients and their families are encouraged to minimize hospital visits. Simple strategies are employed to support mental well-being of children and their families, and mitigate anxiety and stress [9]. All staff members in the dialysis unit should be trained in donning and doffing of PPE [10].

Doctors, dialysis nurses and technicians should stagger their schedule to reduce exposure to infection, and have a reserve force that could be deployed for management of patients [11]. We endorse recommendations of the National Taskforce for hydroxychloroquine (HCQ) prophylaxis, for HCP involved in care of suspected or confirmed patients with COVID-19, and household contacts of laboratory confirmed cases [12]. However, there is a need to be cautious and avoid its indiscriminate use due to potential cardiac and other toxicities. This practice may change as more evidence emerges on benefits and safety of its use. HCQ should not be used for prophylaxis in children younger than 15 year and those with glucose-6-phosphate dehydrogenase deficiency. Caregivers and the patient should be informed about the rationale of therapy, contraindications and adverse effects.

CHILDREN RECEIVING IMMUNOSUPPRESSIVE THERAPY

Immunosuppression and anti-proteinuric measures are cornerstones of treatment in renal diseases. Immunosuppression was one of the most common underlying conditions in a report on 345 children with COVID-19 [2]. Patients receiving therapy with the following agents should be considered immuno-compromised: Corticosteroids (prednisolone, methylpre-dnisolone, dexamethasone): Prednisolone dose >20 mg daily for >4-weeks in the last 6-months,or >5 mg daily for >4 weeks with one or more immunosuppressive agents in last 6-months; Calcineurin inhibitors (tacrolimus, cyclosporine); Mycophenolate mofetil, azathioprine; Cyclophosphamide: any dose (oral or intravenous) within the last 6 months; Rituximab: any dose within the last 6 months; and, Plasma exchange in the preceding 6-weeks [13].

General Management

We advise that dose of immunosuppressive medication should not be changed, since the risk of disease flare is higher than the threat posed by COVID-19 in children. Patients should be advised to keep ~4-weeks stock of immunosuppressive medications. Hospital visits for non-emergency purposes are avoided and HCP contacted through telecommunication. The physician may consider deferring maintenance doses of IV cyclophosphamide or rituximab in patients in sustained remission, and low risk of relapse on case to case basis. Patients should be encouraged to maintain hydration.

Nephrotic Syndrome, Glomerulonephritis, Vasculitis

We recommend that the first episode and relapse of nephrotic syndrome should be treated promptly with

standard dose of prednisolone, as under normal circumstances. Delayed initiation of therapy might result in complications associated with anasarca and bacterial infections. Continuation of therapy may be discussed telephonically. No changes should be made in ongoing treatment of frequent relapsing and steroid resistant nephrotic syndrome.

Decisions regarding initiating immunosuppressive therapy in newly diagnosed patients with other glomerular diseases or vasculitis, especially those from hotspots/ clusters should be based on disease severity, renal histology and serum creatinine, severity of proteinuria and co-morbidities, and balancing the risk versus benefit of therapy [14]. We advise initiating immunosuppression in newly diagnosed patients with glomerular diseases or vasculitis, according to existing guidelines, except in children with asymptomatic or low-grade proteinuria and normal renal function. These patients may be initially managed with salt restriction, and blood pressure control using an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACE-I/ARB). As with nephrotic syndrome, no changes are advised in ongoing or proposed immunosuppressive therapy for patients with other glomerular disorders or vasculitis.

Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB)

SARS-CoV-2, binds to its receptor, ACE-2 for entry into target cells suggesting an increased ability of the virus to enter the lungs in patients on ACE-I or ARB [15]. While there is debate regarding safety of inhibitors of renin-angiotensin-aldosterone axis, few studies have evaluated their effects on severity of illness or mortality in COVID-19. Thus, therapy with ACE-I or ARBs should be continued [16]. Abrupt discontinuation of medications may be associated with uncontrolled hypertension, and its consequences.

Hydroxychloroquine (HCQ)

Therapy with HCQ should continue in patients who are already receiving the medication, e.g., for systemic lupus, vasculitis. Risk of depleting stock of HCQ needs to be considered and adequate stocks of medication should be ensured.

Renal Biopsy

It is suggested to prioritize patients with indications for renal biopsy during the pandemic. Biopsies that are necessary and have therapeutic implications, e.g., suspected allograft rejection, rapidly progressive glomerulonephritis, small vessel vasculitis and interstitial nephritis should be performed while those for less emergent indications, e.g., steroid resistant nephrotic syndrome, calcineurin toxicity and persistent hematuria may be delayed.

Patients on Immunosuppression With Suspected or Confirmed COVID-19

Children on immunosuppression may present with mild symptoms but have high risk of deterioration and require hospitalization. Early identification of severe pneumonia and severe acute respiratory illness (SARI) is important as it allows prompt admission to a designated hospital ward or intensive care unit, and initiation of treatment. Patient with suspected COVID-19 should be shifted to an isolation facility or designated COVID area as soon as possible.

An approach to management of a child on immunosuppressive medications with respiratory symptoms is summarized in ***Fig.* 1**. While there is no specific guidance on precise modification of immunosuppression, it seems prudent to reduce or withhold immunosuppressive medications, except stress doses of steroids in patients with severe COVID-19 requiring admission to intensive care units.

Given the lack of specific treatment, most patients with COVID-19 require supportive care alone. More than 500 trials evaluating 150 drugs are being conducted worldwide [17]. Consistent with national guidelines, we suggest use of HCQ (7-8 mg/kg/dose twice daily for day 1, and 7-8 mg/kg once a day from 2-6 days for >12-yr) in patients with severe disease and requiring ICU care [18]. The doses should be reduced by 50% for children in CKD stage 5 and those on dialysis. Caregivers should be informed about the rationale of therapy, and potential adverse effects, especially prolonged QTc interval. There is insufficient data to recommend the use of remdesivir, lopinavir/ ritonavir or other HIV protease inhibitors for patients.

CHILDREN WITH CHRONIC KIDNEY DISEASE

Since children with CKD stage 3-5 are considered vulnerable to infection with coronavirus, it is vital that children and caregivers follow above mentioned precautions. Patients and caregivers should maintain contact with their physicians, especially for symptoms of COVID-19 including fever and worsening respiratory symptoms. Paracetamol is safe for children with fever, but treatment with other non-steroidal anti-inflammatory drugs (ibuprofen, naproxen) should be avoided.

Patients should continue taking antihypertensive medications, targeting systolic and diastolic blood pressures to ~90^{th} percentile for age, gender and height. We recommend continued therapy with ACE-I or ARB in patients with CKD who are receiving such therapy.

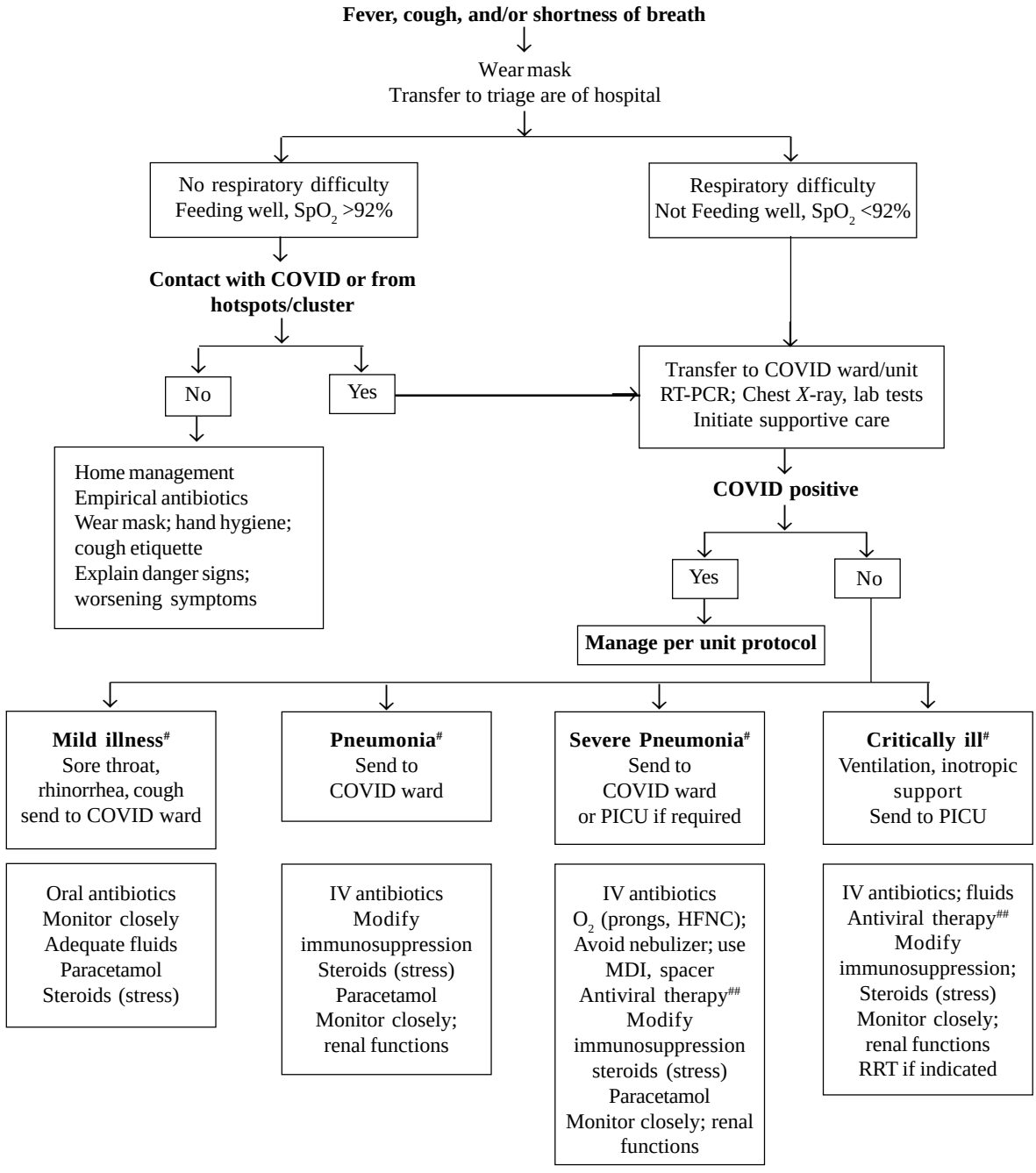

Fig.1 *Triaging and management of child on immunosuppression or with chronic kidney disease. (HFNC-high flow nasal cannula, MDI: metered dose inhaler, PICU: pediatric intensive care unit, RRT: renal replacement therapy) *Testing:`Nasopharyngeal, posteriorpharyngeal swab; endotracheal aspirate or BAL:RT PCR for COVID-19. Evaluate with blood counts (CBC); renal and liver function tests; coagulogram, Ddimer, fibrinogen; C-reactive protein; chest radiograph; blood culture #Non- severe Pneumonia: Cough or difficulty in breathing with fast breathing (<2-months: =60; 2-11 months: =50; 1-5 years: =40 breaths per minute); and no signs of severe pneumonia. #Severe pneumonia: Cough or difficulty in breathing, with at least one of the following: (i) central cyanosis or oxygen saturation (SpO2) <90%; (ii) severe respiratory distress (grunting, very severe chest indrawing); (iii) signs of pneumonia with one danger sign: inability to breastfeed/drink, lethargy/unconsciousness, or convulsions. Signs of pneumonia: chest indrawing, fast breathing (<2-months: =60; 2–11 months: =50; 1–5 years: =40 breaths per minute). #Critically ill: Features of acute respiratory distress syndrome; shock ##HCQ - Hydroxychloroquine 7-8 mg/kg/dose BD for day 1; 7-8 mg/kg once a day from days 2-6; avoid concomitant azithromycin since it can lead to arrhythmias. (Doses for children are extrapolated from that recommended in adults).*

Abrupt withdrawal of these agents might result in clinical instability and adverse outcomes.

Children on chronic ambulatory peritoneal dialysis (CAPD) should continue sessions at home following the standard protocol and precautions, avoid hospital visits, and maintain adequate stock of fluids and consumables. Automated PD (APD) machine should be disinfected using 70% alcohol-based solution before and after each treatment. They should keep in contact with the doctor or dialysis nurse, and inform promptly for fever, symptoms of COVID-19 and peritonitis.

If COVID-19 is suspected in CKD, then patient should be shifted to an isolation facility if available or to designated COVID hospital as soon as possible and managed as per standard guidelines (***Fig.* 1**).

Hemodialysis (HD) Units

Inpatient and outpatient pediatric dialysis facilities must be prepared for patients infected with SARS-CoV-2. The Ministry of Health and Family Welfare has prepared comprehensive guidelines for HD of COVID-19 patients [19]. The statement below is adapted from the above guidance, specifically addressing needs for children.

Children require HD in two situations: *(i)* maintenance HD for end stage renal disease,*(ii)* dialysis for acute kidney injury (AKI), related or unrelated to COVID-19.

An outbreak of COVID 19 in a dialysis facility is defined as two or more COVID-19 infections resulting from a common exposure, that is either suspected or laboratory-confirmed as SARS-CoV-2 [20]. After identification, the outbreak should be reported to the hospital authorities and appropriate measures should be taken as per Government of India guidelines [8].

General Recommendations

- Patients on HD are advised not to postpone their dialysis schedule. Phone numbers and contact information of the dialysis unit should be provided to the patients.
- Administrators need to ensure availability of consumables, including dialysate, dialyzers and tubing, catheters, fistula needles, disinfectants and medications.
- It is necessary to educate HCP, patients and caregivers about COVID-19, including hand hygiene, respiratory hygiene and cough etiquette, use of facemasks and disposal of contaminated items. Posters and literature (in local language) should be available.
- All dialysis personnel should use appropriate PPE, as per institutional policy.
- Dialysis waiting area, beds and nursing station(s) should be equipped with alcohol-based sanitizers along with paper napkins and foot operated plastic lined waste disposal bins.
- Duties of HCP should be organized as per institutional policy, with an overall aim to maintain a pool of reserve staff.
- Bed side rounds by group of staff, group-studies and office case-discussions involving teams should be minimized.
- Patients with features suggestive of respiratory infections (fever, cough) should be identified *before* they enter the dialysis area. Caregivers are instructed to call the unit to report fever or respiratory symptoms, so that they are directed to an appropriate triage in the hospital. At each dialysis visit, a staff member must perform a structured interview for patient and caregivers, asking for: history of fever, cough, respiratory difficulty and exposure to a patient with COVID-19.
- Children should be advised to use a triple-layer facemask while in the waiting area, during dialysis and until they reach home. Seats in the waiting area should be separated by at least 1 meter. To avoid overcrowding, children should be accompanied by only one attendant who should also wear a facemask.
- Dialysis patients, who have a parent or family member on 14-days quarantine, should continue to receive HD during this period. Once the family members or caregiver are confirmed SARS-CoV-2 positive, the dialysis patient should be isolated and instructed to *call the unit* before arriving for subsequent HD sessions, and to report fever or respiratory symptoms.

Dialysis Unit: During Dialysis and Disinfection

- If feasible, dialysis beds should be spaced at a minimum distance of 2 meters.
- Patients are instructed to wash their hands and fistula arm before starting dialysis. Puncture sites should be cleaned, and appropriately disinfected.
- Disposable gloves should be used when handling laundry from infected patients. Dirty laundry should not be shaken to minimize the possibility of dispersing virus through air.
- Bed linen should be changed between shifts, and used linen placed in dedicated containers.
- Disposable gowns must be discarded after use. Cloth

gowns are soaked in 1% hypochlorite solution for 20 minutes before sluicing, and transported to laundry [19].

- All surfaces and equipment in the unit should be cleaned and disinfected at least once daily, and after each patient shift. This includes bedside tables and lockers, dialysis machines, patient monitors, syringe pumps, sphygmomanometers, doorknobs, light-switches, counter tops, handles, desks, phones, keyboards, toilets, faucets and sinks. For surfaces such as carpeted floor, rugs and drapes, visible contamination is removed, followed by appropriate cleaners indicated for these surfaces. After cleaning, items should be laundered in accordance with manufacturer instructions and dried completely.
- Disinfection is done with either 1% bleach solution or 70% alcohol-based solution. Bleach is preferred for surfaces that do not soak up water (example: floor). Use of 70% alcohol based solution is recommended for disinfection of metallic surfaces like door knobs or handles

Dialyzing Patients With Suspected or Confirmed COVID-19

Most pediatric hemodialysis units in developing countries are small, comprising 3- 6 beds. In order to prevent transmission of infection, it is advised that patients with suspected or confirmed COVID-19 be dialyzed in a separate room, with separate access and with the door closed. If a separate room is not available, the suspected patient may be dialyzed in a corner or end-of-row station, maintaining at least 2-meters separation in all directions, preferably in the last shift of the day. The patient, as well as other patients should wear 3 layered masks while dialysis personnel, should wear appropriate PPE throughout the procedure.

Units that do not have enough space and/or dedicated work force for dialyzing suspected or confirmed COVID-19 patients should facilitate their transfer to a designated adult or pediatric HD units until the testing is negative. This plan should be communicated to the caregivers, which will help them prepare accordingly.

- It is recommended to use separate equipment, including stethoscopes, thermometers, saturation probes, and blood pressure cuffs, with cleaning and disinfection between shifts. Stethoscopes are disinfected with alcohol-based solutions. Dialysis personnel should not touch the patient or use stethoscopes, unless necessary.
- Surfaces and equipments located within 1-meter of the patient should be disinfected, as detailed previously. All disposable supplies are discarded.
- Dialysis personnel taking care of a patient with suspected COVID-19 should not look after other patients during the same shift. Staff should self-report symptoms of fever, cough or breathlessness.
- Institutional and national guidelines should be followed for managing patients with suspected or confirmed COVID (***Fig.* 2**).

Personal Protective Equipment (PPE) for Dialysis Personnel

- Dialysis personnel shall be instructed regarding the need for personal protection. They will be trained for donning and doffing of PPE, its proper use and disposal [10].
- We suggest the use of triple-layer masks, head cover, gloves, water-impermeable gown and shoe-covers for HCP working in the unit. Personnel involved in procedures involving aerosol generation, venepuncture and dialysis access should follow standard contact and droplet precautions, and should wear N95 mask and disposable face-shield [21]. ***Table* I** summarizes the protective equipment required for different levels of anticipated contact.
- Further, in children requiring plasmapheresis using HD machine and in the HD unit, all measures suggested in the hemodialysis section should be followed**.**

Dialyzing Children With COVID-19 and Acute Kidney Injury

The incidence of AKI in patients with COVID-19 ranges from 6-15% [22]. Patients with CKD on maintenance dialysis may require care in an intensive care unit. A proportion of patients with secondary bacterial infection will have septic shock, drug nephrotoxicity or worsening of existing CKD, severe enough to require renal replacement therapy (RRT).

The goal is to deliver RRT in a safe and timely manner. Children may need to be dialyzed in shared spaces with adults, if dedicated space is not available. Centres should anticipate surge in COVID-19 related AKI and the need for dialysis may outpace available facilities. As in any patient with AKI, indications for initiating RRT and choice of modality *i.e.*, peritoneal dialysis, HD, continuous renal replacement therapy (CRRT), and sustained low efficiency dialysis (SLED), is based on resources and expertise, and patient hemodynamic status. We suggest the following:

Fig. 2 *Algorithm for managing a child on chronic hemodialysis with COVID-19. RO Reverse osmosis, PPE Personal protection equipment, PICU- pediatric intensive care unit, HFNCHigh flow nasal cannula, HD- hemodialysis, HCQ Hydroxychloroquine; #Not critically ill: Non-severe pneumonia: Cough or difficulty breathing with fast breathing (<2-months: =60; 2–11 months: =50; 1–5 years: =40 breaths per minute); and no signs of severe pneumonia; #Critically ill: Severe pneumonia: Cough or difficulty in breathing, with at least one of the following: (i) central cyanosis or oxygen saturation (SpO2) <90%; (ii) severe respiratory distress (grunting, severe chest indrawing); (iii) signs of pneumonia with one danger sign: inability to breastfeed/drink, lethargy/unconsciousness, or convulsions. Signs of pneumonia: chest indrawing, fast breathing (<2-months: =60; 2–11 months: =50; 1–5 years: =40 breaths per minute) OR features of acute respiratory distress syndrome; shock.*

Table I Protective Equipment Required for Different Levels of Anticipated Contact

Category of staff	*Hand hygiene*	*Eye protection**	*N95 mask*	*Surgical mask*	*Apron*	*Gowns*	*Gloves*
Reception staff	Yes	–	–	Yes	–	Yes	Yes
Triage staff	Yes	–	–	Yes	–	Yes	Yes
HCP attending to the patient (routine examination)	Yes	Yes	–	Yes	Yes	–	Yes
HCP performing procedures like HD/PD in non-COVID case	Yes	Yes	–	Yes/N95 extended use	–	Yes	Yes
HCP performing aerosol generating procedures or HD/PD for a COVID suspect or confirmed case	Yes	Yes	Yes	–	Yes, full cover	–	Yes, and long shoe cover
Housekeeping staff	Yes	–	–	Yes	Yes	–	Yes
Security officer	Yes	–	–	Yes	–	–	–
Transport staff	Yes	–	–	Yes	–	Yes	Yes

*HCP: healthacare provider; *goggles; HD: hemodialysis; PD: peritoneal dialysis.*

- *Access*: Central venous catheter for HD or PD catheter should be placed with complete PPE. For patients who already have arteriovenous fistula, CRRT and SLED may be considered provided monitoring for potential complications of the procedure is possible [23].
- *Prescribing CRRT*: In centers having facility for CRRT, the treatment time for continuous veno-venous hemodialfiltration may be reduced to 10-12 hours in order to make the machine available for a greater number of patients. In case of shortage of replacement fluids, the dose could be reduced to 1000ml/m^2 instead of 2000 ml/m^2, especially after first few-hour and once metabolic control is achieved. Normal saline may also be used as replacement fluid.
- *Anticoagulation*: Centers dialyzing patients with COVID-19 have reported circuit clotting in CRRT and SLED if anticoagulants are not used. Anticoagulation is done, as per unit protocol. In case of non-availability of pumps for heparin, low molecular weight heparin may be used (enoxaparin single dose 0.5-1 mg/kg; dalteparin<15-kg: 1500 IU; 15-30 kg: 2500 IU) [24].
- In order to minimize exposure, the CRRT or HD machine may be set-up outside the patient area, and then taken into the room and connected.
- After treatment, all equipment should be disinfected with 1% sodium hypochlorite before being removed from the room.
- Transport of patients with suspected or confirmed COVID-19 to a central dialysis unit is not recommended. These patients should be dialyzed bedside, using portable reverse osmosis.
- Acute peritoneal dialysis should be considered when hemodialysis machines are not available. An automated cycler should be used to minimize patient contact. The drain fluid is disposed, are per protocol. All consumables like tubings, dialyzers and replacement solutions bags should be discarded.

TRANSPLANT RECIPIENTS

Kidney transplant recipients must be considered highly susceptible to SARS-CoV-2 infection. Data on COVID-19 in transplant patients is however limited. It has been observed that among adults renal transplant recipients with COVID-19, 60% require hospitalization and 25 -30 % require ICU care with mortality rate of 5% [6,25]. However, a recent study has shown high early mortality in transplant recipients than general population with Covid 19 infection [7].

General Precautions

Transplant recipients are advised to follow general precautions for patients with CKD.

- Movement outside the home, including for follow up hospital visits, should be restricted. Teleconsultation may be utilized to contact HCP.
- When outside the house, transplant recipients and caregivers should use triple-layer mask and prevent touching of nose and mouth.
- It is essential to maintain a 4-weeks stock of

medications. If the family is unable to obtain medications, the transplant team should be informed.

Transplantation During COVID-19 Pandemic

Unlike other solid organs, kidney transplantation is performed in a relatively stable patient, receiving maintenance HD. Transplantation is associated with marked immunosuppression, which might not be in patient's interest during the pandemic. Transplant recipients may also require respiratory support and ICU monitoring during the peri-operative period, facilities that are scarce during the outbreak. Using these facilities for an elective procedure might also reduce their availability for a critically ill COVID-19 patient. We believe that the risks of performing kidney transplantation outweigh the benefits to either the patient or the healthcare system. We recommend postponing live-related donor transplants until the outbreak has abated.

The National Organ and Tissue Transplant Organization (NOTTO) has advised temporary suspension of deceased and live related transplant program [26]. However, if pandemic lasts for longer duration, then reconsideration of recommendation is advised.

Transplant Recipients With COVID-19

Transplant recipients presenting with cough or shortness of breath with or without fever, history of contact with known patient, or with features of SARI should be screened for SARS-CoV-2 infection by RT-PCR of nasopharyngeal swabs. These patients may have atypical features such as coryza, diarrhea and fatigue. Fever is reported in 50-87%, while diarrhea and lymphopenia are observed in 30% and 50% patients, respectively [6,23]. One-third may have no radiographic findings. A high index of suspicion is necessary to diagnose COVID-19 in transplant recipients.

Supportive management for transplant recipients with COVID-19 is shown in ***Fig.* 3**. For patients with mild disease, reduction of immunosuppression is not recommended as this might result in allograft rejection. In sicker patients (with pneumonia, but not critically ill), the anti-proliferative agent (mycophenolate or azathioprine) should be discontinued. The dose of prednisolone is increased to 0.5-1 mg/kg when therapy with mycophenolate is stopped. Dose of calcineurin inhibitors (CNI) is reduced to target lower levels (Tacrolimus adjusted to achieve a trough of 4-6 ng/mL; Cyclosporine 100 -150 ng/mL). In critically ill children (requiring ventilation and inotropic support), CNI may be reduced further or discontinued [27,28]. Such patients are managed with steroid monotherapy, at a higher dose. Once recovery begins, immune-suppressants should be reintroduced and increased to pre-illness doses 14-days after two nasopharyngeal swabs are negative.

There is no evidence to support the use of antiviral treatment for COVID-19. Drugs being examined include lopinavir/ritonavir, remdesivir, favipiravir, HCQ, tocilizumab, interferon-α and intravenous immunoglobulins. Interaction of medications with CNI and sirolimus needs to be considered. Lopinavir/ritonavir, darunavir/ritonavir, chloroquine and HCQ can potentially increase CNI levels, while tocilizumab decreases CNI and sirolimus levels [29]. Other causes for fever, including bacterial or viral infections should be ruled out. Antibiotics should be used for empiric treatment of bacterial infections and modified based on culture sensitivity results.

CONCLUSIONS

The present guidelines of the Indian Society of Pediatric Nephrology on managing patients with kidney diseases during the COVID-19 pandemic are based on current literature and expert views. While children constitute a small proportion of patients with COVID-19, those with chronic disorders constitute a high-risk group and at-risk for adverse outcomes. Therapeutic guidelines are likely to change as evidence emerges from large case series and randomized controlled trials.

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Fig. 3 *Algorithm for management of renal transplant patient with suspected or confirmed COVID-19. (HFNC-High flow nasal cannula, HCQ- Hydroxychloroquine, PICU- pediatric intensive care unit), # Not critically ill: Non-severe pneumonia: Cough or difficulty breathing with fast breathing (<2-months: =60; 2–11 months: =50; 1–5 years: =40 breaths per minute); and no signs of severe pneumonia; # Critically ill: Severe pneumonia: Cough or difficulty in breathing, with at least one of the following: (i) central cyanosis or oxygen saturation (SpO2) <90%; (ii) severe respiratory distress (grunting, severe chest indrawing); (iii) signs of pneumonia with one danger sign: inability to breastfeed/drink, lethargy/unconsciousness, or convulsions. Signs of pneumonia: chest indrawing, fast breathing (<2- months: =60; 2–11 months: =50; 1–5 years: =40 breaths per minute) OR features of acute respiratory distress syndrome; shock.*

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Web Table I Summary of Intervention Trials Involving Children with COVID 19

Trial	*Country*	*Intervention*	*Age criteria*	*Status*
Application of Desferal to Treat COVID-19	Iran	Intravenous infusion of Deferoxamine	> 3 y	Recruiting
NCT04333550				
Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)	Italy (27 locations)	Tocilizumab 8 mg/kg	Any age	Recruiting
NCT04317092				
Randomized, Double-blind, Placebo-controlled Multi-center Study to Assess the Efficacy and Safety of Ruxolitinib in Patients With COVID-19 Associated Cytokine Storm (RUXCOVID)	Novartis Pharmaceuticals Incyte Corpoartion, Centers not specified	Ruxolitinib	age ≥12 y	Yet to start
NCT04362137				
Comparison of Lopinavir/ Ritonavir or Hydroxychloro-quine in Patients With Mild Corona virus Disease (COVID-19)	South Korea	Lopinavir/ritonavir Hydroxychloroquine sulfate	Age > 16 y	Recruiting
NCT04307693				
Evaluation of Efficacy of Levamisole and Formoterol+ Budesonide in Treatment of COVID-19	Iran	Levamisole Pill + Budesonide+Formoterol inhaler Lopinavir/Ritonavir + hydoxychloroquine	Age > 15 y	Recruiting
NCT04331470				
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Corona virus Disease (COVID-19)	15 countries ; lead US	Remdesivir	Age > 12 y	Recruiting
NCT04292899				
Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (COVID-19)	13 countries; lead US	Remdesivir	Age > 12 years, > 40 kg	Expanded access available
NCT04323761				
Pragmatic Factorial Trial of Hydroxychloroquine, Azithromycin, or Both for Treatment of Severe SARS-CoV-2 Infection	US	Hydroxychloroquine Azithromycin	Age > 12 y	Recruiting
NCT04335552				
A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	US	HB-adMSCs	Not specified	Enrolling by invitation
Treatment Of CORONAVIRUS DISEASE 2019 (COVID-19)	US	Anti-Sars-CoV-2 Convalescent Plasma	Not specified	Expanded access available

Contd...

Web Table 1 *continued*

Trial	*Country*	*Intervention*	*Age criteria*	*Status*
With Anti-Sars-CoV-2 Convalescent Plasma (ASCoV2CP)				
NCT04360486				
Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus	Egypt	Natural Honey	Age > 5 y	Recruiting
NCT04323345				
Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)	UK	Chloroquine or Hydroxychloroquine	Age > 16 y	Recruiting
NCT04303507				
Convalescent Plasma For Ill Patients By Covid-19 (COPLASCOV19)	Mexico	Convalescent plasma	Age > 16 y	Not yet Recruiting
A Real-life Experience on Treatment of Patients With COVID 19	Egypt	Chloroquine Favipiravir Nitazoxanide Ivermectin Niclosamide	Not specified	Not yet Recruiting
NCT04345419				
Efficacy of Nigella Sativa and Natural Honey Against COVID-19	Pakistan	Honey: Nigella Sativa / Black Cumin	Age > 5 y	Recruiting
NCT04347382				
Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19)	UK	Infusion of Human umbilical cord derived CD362 enriched MSCs	Age > 16 y	Recruiting
NCT03042143				
COVID-19 Ring-based Prevention Trial With Lopinavir/ Ritonavir (CORIPREV-LR)	Canada	Lopinavir/ritonavir	Age > 6 mo	Recruiting
NCT04321174				
Efficacy of Faviprevir in COVID-19 Treatment	Egypt	Favipiravir	Not specified	Not yet Recruiting
NCT04351295				
Hydroxychloroquine vs Nitazoxanide in Patients With COVID-19	Mexico	Hydroxychloroquine Nitazoxanide	Age > 5 y	Recruiting
NCT04341493				
Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections (NONTM)	Canada	Nitric Oxide 0.5 % / Nitrogen 99.5 % Gas for Inhalation Inhaled Nitric Oxide 160ppm balance air	Age >14 y	Active, not recruiting
NCT03331445				
Nebulised Rt-PA for ARDS Due to COVID-19 (PACA)	UK	Nebulised recombinant tissue-Plasminogen Activator (rt-PA)	Age ≥16 y	Recruiting
NCT04356833				

Source:https://www.clinicaltrials.gov/

Medical Education Amid the COVID-19 Pandemic

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The coronavirus pandemic has shaken the mankind to its core. Social distancing is the most important preventive strategy for the spread of this contagion, short of a vaccine. Implementation of the same has forced many countries in to a complete lock-down. Closure of schools and universities has made education uncertain at all levels. Medical education is no exception. In this pandemic, the need for uninterrupted generation of future doctors is felt more than ever in our living memory. Continuity of medical education is thus imperative. While "Live" patient contact is an irreplaceable tenet of clinical teaching, these extraordinary times demand exceptional measures. Pedagogical innovations involving technology and simulation based teaching (Online lectures, video case vignettes, virtual simulators, webcasting, online chat-rooms) need to be brought to the forefront. Since the medical educators have been pushed inevitably to rely on technology-based learning, they should not only embrace it but also develop and evaluate its sustainability and application in preclinical and clinical setting. Meanwhile, the students, whose medical education is stuck in this pandemic time, should realize that there is no better teacher than a first-hand experience, and they are eyewitnesses to the making of history.

Keywords: *Coronavirus, e-Learning, Medical student, Pedagogy.*

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The SARS CoV-2, a mutated sub-microscopic agent lacking a true existence of its own, has brought the world to a standstill (literally and metaphorically). Several countries have gone in to a complete lock-down to limit the spread of the Coronavirus disease 2019 (COVID-19) pandemic. The primary focus has rightly been on curbing the disease spread in the community, rapid development and re-organization of available medical resources to cater to the increasing patient load and adequate care of the infected ones. Most other things have taken a backseat. Education at all levels has become uncertain due to the mass closures of schools and universities. Medical education, particularly, at the medical school/undergraduate level, has been no exception.

HOW HAS MEDICAL EDUCATION BEEN AFFECTED?

The premise for closing medical universities is dual – medical students' safety may be jeopardized during clinical rotations putting them at risk of exposure to COVID-19 positive patients, and/or infected students may themselves become the portal of spread of the disease [1]. Even for preclinical medical students, social distancing measures have precluded the conduct of classroom-based teaching and discussions [2]. In the wake of this global emergency, medical education has been existentially challenged.

In certain countries like the US, the pandemic has coincided with the time of educational transition [3]. A steep rise in the infection rates has forced a complete removal of the students from the clinical rotations [4] and halting of all summative examinations. Several Canadian, UK and Australian schools have taken similar urgent steps [5,6]. As a result, scores of medical students have been affected with final year medical students stuck just short of graduation. In countries like India, where the educational transition has already occurred, the current clinical rotations have been halted. A particular concern is the implementation of the new competency-based curriculum for the students admitted in 2019. Almost all the institutions in the country had put up a day-by-day time table covering the entire phase 1, which is going to be disrupted. Additionally, it was about the time to prepare for the phase 2 in terms of objectives, integration and preparing schedules. Teachers of phase 2 also needed training for the new curriculum. This process has been paused. Medical students (admitted both pre-2019 and post-2019) will suffer a reduced exposure to certain clinical branches or a proportionally shortened rotation in all clinical branches. In the worst-case scenario, where the pandemic continues for an unforeseeable time, an extension of the medical training period may be warranted. In all situations, the medical students will be at a loss.

Thus, the medical educators need to rapidly evolve the methods of teaching to minimize the onslaught of disrupted medical education, while also building innovative systems to accommodate the medical student cohorts stuck in the time of this pandemic. Medical Council of India has come out with its guidance for medical students in the current situation [7].

WHY SHOULD MEDICAL EDUCATION CONTINUE?

There are three important reasons for ensuring continuation of medical education in this hour. Firstly, learning the science and art of medicine is a graduated process, it is imperative that a student completes one milestone before embarking on the next. A student who misses any part of the education is likely to find it difficult to join the dots later. Secondly, if clinical rotations are deferred for the current student cohort and clubbed with others, the density of learners would impair the clinical learning experience (especially in geographic areas like India where the learner density is already very high). Lastly, recognizing the possibility that the current pandemic may take a reasonable time to abate, there may arise a paucity of healthcare workers. In such situations, students may need to engage in certain aspects of patient care while the authorities ensure their safety, learning and if applicable, remuneration.

Therefore, it is essential that we adopt new ways that facilitate the ongoing knowledge and skill development of the next generation of health professionals.

MAINTAINING THE CONTINUITY OF MEDICAL EDUCATION

To answer this, we may first reiterate that undergraduate medical education the world over is divided into an initial foundation of preclinical teaching (lasting 12-24 months) followed by the core of clinical rotations or clerkships (lasting 24 months) in medical schools following the conventional model [1]. This is followed by internship where the student works with the treating team as a supervised learner. Finally, as per the concerned university's regulations, the medical student applies for/ appears for entrance exams to specialized courses (residency or post-graduation) during the final year of medical school or during internship.

Conventionally, the preclinical teachings have involved lectures, small group discussions and laboratory sessions. For the past decade, the medical fraternity has been trying to improvise pedagogy by introducing technology-based novel concepts such as flipped lectures and simulation-based learning [8,9]. Though, many medical schools have become well versed with these concepts, in several countries including India, technology-enhanced learning is still in its infancy. In wake of the COVID-19 pandemic, a number of medical schools have rapidly converted their entire pre-clinical curriculum to online formats involving online lectures, webcasting and virtual group discussions. However, such transition may be slower in places where technology enhanced learning is still developing and online lectures still need to be prepared, especially when a large part of the medical fraternity has been redirected to fight the COVID-19 pandemic. While enforcement of technology-based learning has become a necessity in this hour, we need to ponder upon the advantages and barriers it may pose. Online formats allow the students an easy accessibility to educational material as per their convenience, in their preferred environments and repeatedly. Pitfalls include isolation due to shifting from the medical school setting to home, reduced discussions with peers, increased dependence on email and an uninterrupted internet access, and a struggle to delineate boundaries between work and home [1]. There have been instances of many medical schools in India having started online lectures for students; however, most of these are conventional lectures delivered through electronic mode, without paying much attention to the pedagogical requirements of online learning. Additionally, very few have incorporated the assessment component in these.

Clinical teachings, on the other hand are best learnt bedside with a 'live' patient. Not only does the medical student get a first-hand experience of patient's clinical findings but also learns about the dynamics of patient interaction, psychology and counselling. In addition, development of a student's professional identity is often shaped by medical teachers who they see as role models and who can infuse the cultures of altruism. However, in the times of this contagious pandemic, an alternate model is needed wherein some form of clinical education continues despite curtailment of real patient contact. Cues can be taken from the past. During the SARS outbreak which preferentially affected the healthcare workers [10], an infection of 17 medical students provoked rapid closure of the Chinese university in Honk Kong in 2003 [11]. This period saw heavy reliance on technology-based learning to provide some continuum to clinical teaching. These included webcasting, videotaped vignettes, audio-recordings, problem-based learning tutorials on online chat rooms and mannequin simulators [11,12]. Over the years, technology has matured. The current situation demands use and furthering of these pedagogical innovations. Use of e-learning modules (flash multimedia and digitized images), patient surrogates such as virtual patients (to teach clinical

examination, procedural, diagnostic skills and communication skills) and virtual-reality simulators (to teach palpation, surgical and resuscitation skills) is needed. Simulators have shown to be as effective as live actor-patients for teaching purposes [13]. Despite the undoubted advantage of IT and simulation-based education, in the current situation, there are distinct disadvantages. The foremost is the fact that all these tools can be supplemental to clinical teaching but not a replacement. Secondly, setting up of a virtual learning environment or a simulation laboratory is costly and time taking, making it especially unsuited for the low and middle income countries. Thirdly, while virtual simulators will maintain the tenet of both non-contact with patient and social distancing amongst students, mannequin simulators will flout social distancing needs amongst students precluding their use currently.

Other important barriers that have prevented medical educators to dissipate e-teaching (during these emergent times and otherwise) include time constraints, poor technical skills, inadequate infrastructure and absence of institutional strategies. Proposed solutions include improved educator skills (which may not be feasible in the short-term, therefore tagging with people who already have these skills may help), inculcation of a positive attitude, and incentives/ reward for the time devoted to the development and delivery of online content [14].

While it may appear impressive to talk about online/ digital/simulation-based learning, the fact remains that in India, we are still far away from such modalities [15]. It requires planning, trained manpower and finances to embark upon such methods. In such times, it may be very useful to have a central agency (like MCI) to take the lead and develop pedagogically useful learning content. A mandatory component of formative assessment also needs to be included to ensure attainment of learning objectives. Having a common curriculum and rotation schedule for all colleges of India could prove to be a blessing in disguise, allowing us to have centrally prepared material. Many colleges in the public sector and some in private sector have good equipment which can be put to use. Availability of scattered expertise across institutions can be collated for better results. There have been some recent publications from India to highlight the role of social media as a tool for engaging students [16,17]. Similarly, existing professional networks can be used for webinars on important topics.

Last year, the MCI had embarked on a digital project to monitor teaching in colleges using closed-circuit television (CCTV) cameras and currently most colleges have such systems in place [18]. This infrastructure can be put to reverse use by streaming content from MCI to all colleges, which can subsequently be accessed by students by logging on to their institutional servers.

In addition to the use of above tools, there may be a few measures that may smartly squeeze some moments of clinical learning for the medical students. These include modification of the academic roster (preponing scholarly work and deferring clinical rotations to a later time frame) which may be feasible at certain medical centers as per their learning goals. Also, students may be involved in the tele-health consultations (which have become far commoner during this pandemic). Most importantly, they may serve as educators to their peers, patients and communities by developing educational materials and videos, thus influencing behaviors in a positive way to prevent the spread of the pandemic. Students may update themselves with authentic online resource related to the COVID-19 pandemic; learn via following the pandemic trajectory worldwide and understanding how the situations are being dealt. With updated knowledge, they may engage in projects involving development of videos (*eg,* videos demonstrating donning and doffing of PPE, proper mask fitting and hand washing techniques) or help in preparing indigenous PPE, in the process educating themselves. No number of lectures can match the impact of things learnt *via* first-hand experience of the SARS-Cov-2 pandemic.

As far as the postgraduate students are concerned, they have been deployed as a part of COVID workforce, their work areas defined as per their specialization subject and year of ongoing post-graduation. An infodemic of COVID-19 has flooded the social and news media. It is the medical educators' role to provide the residents with the most reliable and latest information from the official government and hospital websites. Repeated training regarding PPE, donning and doffing, COVID-19 sampling, patient handling, transport and treatment is being conducted *via* online reading material, videos, webinars and cloud computing platforms (Like Zoom, G Suite, Office 365). While the resident teams on duty are engaged in active learning of COVID-19, those who are in quarantine/ reserve teams may participate in self-directed online group discussions on other important topics of their specialty. Medical educators may guide in identification of these topics and moderate such discussions. Case vignettes may be presented and discussed. Many e-learning activities are already being conducted, albeit a formative assessment component needs to be integrated into the framework.

Thus, the options are continually evolving. ***Box* I** shows the various available tools while ***Box* II** enlists the

Box I Available Tools and Platforms to Continue Medical Education Amid the COVID-19 Pandemic

Available Tools

- Online videos, power point presentations, handouts, flash multimedia and digitised images developed by individual medical universities.
- Smartphones with user-friendly apps *e.g.,* dosage calculators, growth charts, Curofy, Docplexus, SCAT, web-based features e.g., PubMed for handheld devices, social media apps *e.g.*, Facebook, WhatsApp, and YouTube.
- Webcast (i.e. broadcast of recorded presentation over the internet) *e.g.,* Webcasts made by professional bodies like the Indian Academy of Pediatrics.
- Webinars i.e. broadcast of live presentation over internet allowing an interactive session e.g., webinars organized by IAP at the dIAP platform.
- Video conferencing (case discussion/panel discussion on computer platforms).
- Virtual simulation technology.

*Available Platforms**

- Cloud – computing platforms like Zoom, G-Suite which allow video conferencing.
- TUSK platform contains full-text syllabi, slides, lecture recordings (audio and video), class schedules, course evaluations, dissection guides, a quiz and case maker, grade book, and other resources made available by the faculty, *e.g.,* Christian Medical College, Vellore has utilized it to educate their undergraduates while they work in rural areas.
- Online Google groups Ex: Listserv is being used as an e-learning platform in the FAIMER fellowship conducted at various centers in India.
- Telemedicine software system developed by the Centre for Development of Advanced Computing connects many medical institutes of India.
- EDUSTAT is the first Indian satellite meant exclusively for distance education *e.g.,* lectures are being delivered for medical undergraduates in Punjab.

*Prepared from ref. 15 and 16. *These are a few most prominent examples and not an all-encompassing list.*

various possible strategies that may be used for continuing medical education in these times in the Indian set-up. The most reasonable strategy will be for every medical school to model continued pre-clinical and clinical teachings to match with the available resources.

METHODS OF ASSESSMENT AND LICENSURE

In medical universities, where students were in the phase of transition to the next years, examinations have been delayed. For example, in the US, the second and third year undergraduate summative examinations have been put on hold and the organization that operates these testing centers has temporarily closed its facilities [3]. Such delays are demotivating for the exam-going students and may put their career path on the back foot, if the closures extend. In universities where the final year medical students have been selected for a residency, early graduation should be considered a viable option. The medical education systems are already emphasizing the need for achievement of core competencies rather than mere completion of a stipulated time period in a subject. Therefore, in these pressing times, it may be suitable to give leeway to medical universities to decide which medical students have completed the necessary competencies for graduating to the next level, as already done in the US [5]. This will not only provide a boost to the students but also add to the healthcare work-force, who can step up per the demands of the situation. In India, the same situation of transition applies to the final year residents who are at the cusp of their post-graduation. The MCI has directed them to continue working in their respective universities to add to the anti-COVID workforce. An early post-graduation for these residents based on sturdy assessment merits a thought. An internal committee may be formed by MCI to decide criteria for eligibility for such an expedited degree.

Nevertheless, an important point to contemplate is the method of summative assessment to be employed while maintaining social distancing. In the past, during the SARS outbreak in 2003, the summative examinations at certain universities were conducted *via* telephone conference-based viva voice [11]. Though, it is subject to

Box II Possible Strategies to Continue Medical Education for Different Groups Amid the COVID-19 Pandemic

Medical undergraduate (UG) students.

- Attend online teaching per faculty prepared roster.
- Engage in self-assessment and peer assessment to ensure attainment of desired learning objectives.
- Discuss with faculty for moderating the setting of desired learning objectives.
- Serve as educators to their peers, patients and communities by developing educational materials and videos regarding COVID-19.
- Engage in supervised telehealth consultations
- Engage in projects involving development of indigenous PPE.

Medical postgraduate (PG) students

- The PGs may be involved in care of COVID-19 patients/samples/imaging as per their specialty; quarantined/reserve PG teams should engage in online teaching concerned to their specialty and use all strategies as suggested for UGs.

Medical educators/faculty

- Prepare resource material for online power point presentations, videos, webinars, webcasts.
- Prepare formats for online case discussions.
- Prepare a roster/schedule for various pre-clinical and clinical online teaching.
- Device methods of formative assessment integrated with above.
- Continue medical education training using.

University administrators

- Invest in improving educator skills in imparting online teaching.
- Invest in developing an online pedagogical repository.
- Provide incentives/ reward to involved faculty for the time devoted to the development and delivery of online content.
- Inculcate a positive attitude in all involved in e learning/teaching.
- Collaborate public and private sector resources (both technology and education material) to allow rapid chalk out of e-content with wide dispersal.
- Engage MCI in supervising and guiding all universities in delivery of online-teaching.
- Take feedback from universities for continuous improvement of e-teaching methods.

availability of an uninterrupted internet access, it may be feasible in dire situations. Supplemental methods may involve online web-based clinical case viva, demonstration of practical skills on virtual mannequins and use of digitized images for spotters. In a routine situation, these methods of assessment would sound very odd, but we are living in extraordinary times demanding extraordinary measures. In India, most undergraduates are in the second quarter of their respective academic years and have a long way to go before appearing for their summative examinations. However, whether the ongoing technology-based teaching efforts/ self-learning efforts are leading to fulfillment of desired learning objectives is a definite concern. Formative assessments should therefore be integral to such efforts. Using either existing quizzes apps or indigenously developed ones can be shared amongst institutions for this purpose. Gamification is another upcoming modality; though, it will need time to be cultivated. Meanwhile, self-assessment and peer assessment are methods which may be suited to current situation and may be encouraged while educators moderate this process.

PLAN FOR THE FUTURE

A solid take away from the situation that we face today is that we need to prepare for continuing medical education, not only for now but also for possible future contagions. An excellent approach to continuing teaching and training in medical education field was published a decade back based on whether only patient-student contact is to be curtailed or all forms of contact (patient-student, student-student, teacher-student) need to be disrupted [19]. The ongoing pandemic has already put resource development for continuing education on a fast track. However, it will be reasonable to invest in these pedagogical innovations over the long-term and develop a repository of the requisite sources beforehand.It may also be the right time to prepare a plan B for future exigencies by involving regulators, universities, educational experts and professional associations.

CONCLUSIONS

How do we choose to see the glass: half full or half empty? Our optimist's mind tells us that this period of 'no teaching' can be the period of 'greatest learning'. Medical students are watching first-hand the principles of epidemiology in practice and are more aware of the dynamics of a pandemic, use of PPE, and importance of hand hygiene. Additionally, many students have the time now to catch up on their previous studies. Medical

educators have been provided with the perfect opportunity to develop and evaluate the suitability and application of technology-based learning. Medical regulatory bodies and associations have the most important reason to connect and integrate education materials and methodologies. And humanity has rediscovered the value of enjoying the little things in life!

Pedagogically speaking, this time is likely to bring out medical ingenuity. Whether online teaching becomes a standard mode of pre-clinical education, and virtual and simulation technology an integral part of clinical education is for time to see, but the seeds for a paradigm shift already seem to be have been sown.

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Using Telemedicine During the COVID-19 Pandemic

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Telemedicine is the delivery of health care services using information or communication technology. In the current pandemic scenario, telemedicine can supplement health-care delivery in the absence of in-person visit. The Government of India has recently launched the e-sanjeevani OPD, a National teleconsultation service, which has been adopted by many state governments as mandatory for health-care providers. With Indian Medical Association issuing an advisory against the use of telemedicine except in few situations, a lot of confusion exists in the mind of a pediatrician. Despite the uncertain situation, we have to remember that other diseases shall not stall in the face of a pandemic. Since telemedicine is an evolving subject, training of medical professionals, clear guidelines and good quality internet service systems will go a long way in increasing the acceptability of telemedicine in the Indian population. We herein discuss issues related to using telemedicine during the SARS-CoV-2 pandemic.

Keywords: *Guidelines, SARS-CoV-2, Telecommunication, Teleconsultation.*

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In the face of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the Indian government has proactively taken multiple measures to slow down disease progression. This includes converting some hospitals to dedicated COVID-19 hospitals, and shutting down many routine hospital services including outpatient departments and elective operation theatres, while emergency services have continued. However, the patients face a tough dilemma of risk of infection during hospital visits *vis-a-vis* denial of adequate care because of these measures [1].

To ensure continued health services, the government has given guidelines for practicing telemedicine to aid continuous delivery of healthcare services to the public. Telemedicine is defined as the delivery of health care services, where distance is a critical factor, by all healthcare professionals using information or communication technology. It serves the purpose of exchange of valid information for diagnosis, treatment and prevention of disease and injury, research and evaluation, and lessens overcrowding in hospitals, especially in the time of a pandemic [2,3]. Telemedicine aims to ensure equitable services to everyone, is cost-effective, provides safety to both patient and doctors during pandemics, and offers timely and faster care. Since children represent a vulnerable population, detailed guidance on the delivery of primary and emergent care *via* telemedicine services is the need of the hour.

Telemedicine can be classified on the basis of mode of communication as (*i*) audio, video or text-based (video mode is preferred as it allows limited examination as well); (*ii*) timing of information transmitted as real time or asynchronous exchange; (*iii*) purpose of consult as first time or follow up (in non-emergent cases or emergency consultation); and (*iv*) according to individuals involved as patient to medical practitioner, caregiver to medical practitioner, medical practitioner to medical practitioner or health worker to medical practitioner [2]. The use of telemedicine ranges from educational purposes such as teleconferencing and tele-proctoring, health care delivery, screening of diseases, and disaster management [3]. Telemedicine is widely used in areas of radiology, dermatology and pathology; but has had a limited role in other branches in the past. In 2018, the Bombay High Court had convicted a doctor couple who were guilty of criminal negligence and death of a lady after delivery because the doctor had not come and physically examined the patient. The attending doctor directed her staff telephonically for patient management. The Supreme Court at that time had advised doctors to limit the use of telemedicine and to use it only in emergencies [4]. This will now change with the latest guidelines [2]. Despite all its advantages, practicing telemedicine poses several challenges to clinicians as it is an evolving tool (***Fig.*** **I**).

Following are some of the issues that need to be addressed by pediatricians in the current setting of the

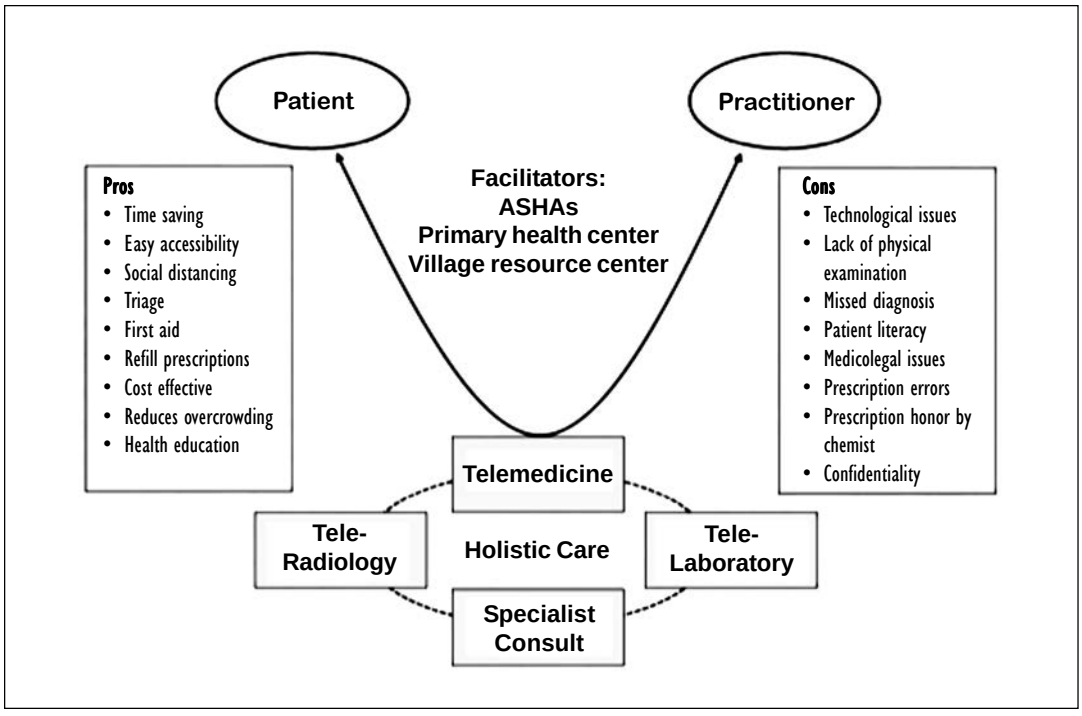

***Fig.* 1** *Pros and cons of telemedicine during the SARS-CoV-2 pandemic*.

COVID-19 pandemic in an Indian scenario and their possible solutions.

Lack of Physical Examination

Telemedicine has an inherent drawback since the patient is not actually present and a thorough physical examination is not possible. The limited examination, which is possible only through inspection, might be hampered by low video quality or lack of video facilities altogether. The younger the child (especially below 2 years), the more difficult it is to make a diagnosis based on history alone because of overlapping and nonspecific symptoms in children. This can often lead to underestimation or misinterpretation of the disease. To overcome this we can ask the patients to give a detailed description about their complaints and not merely state the issues. We can employ the use of peripheral examination devices like electronic stethoscope, electronic blood pressure apparatus, pulse oximeter and ultrasonography. However, accuracy and effectiveness of these devices needs to be ascertained before recommendations can be made. One way to partially overcome this challenge is to encourage telemedicine between a health worker and pediatrician to facilitate a rudimentary examination [5]. The pediatrician may need to have a low threshold for ordering basic investigations because of the limited examination possible. The health care worker can certainly assist in triaging patients and identifying sick children requiring an urgent inpatient visit. If no hospital is available nearby, telemedicine might be the only option available *e.g.* in a case with trauma, pediatrician can advise appropriate first aid which may be lifesaving after which the patient can visit the nearest hospital for assessment of the extent of trauma and stabilization.

Medico-legal Considerations

With the issue of telemedicine practice guidelines under the Indian Medical Council Act, 1956, medical practitioners are now empowered and legally protected to provide telemedicine services according to guidelines stated [2]. Clinicians may face difficulties in providing telemedicine services in medicolegal cases as detailed documentation is required. Doctors should avoid giving advice in such cases and the patient must be referred for an urgent in-person visit to the nearest hospital.

Informed Consent

In cases where patient initiates the conversation, the consent is implied, but if a doctor initiates the conversation an informed consent should be taken and documented. For a minor seeking health care, child assent

is also required. The patient and the parent can send an email, text or an audio/video message. Wherever in doubt, consent must be documented/ recorded.

Prescription and Liability

The doctor is liable for any advice he gives. In case the physician takes advice from another doctor, the liability lies on the primary physician and it is his discretion whether or not to follow the other doctors' advice. He can give a list of probable or differential diagnosis and can advise the patient to visit the nearest hospital. Unless the physician is sure of the diagnosis, no prescription should be given – rather, patient should be advised to visit the nearest health facility. Age and weight are important parameters in children for dosage calculation. Hence we must avoid giving prescriptions if these parameters are not known. For patients with chronic diseases, assessment of disease activity becomes difficult and certain medications *e.g.* narcotics, psychotropic drugs etc. are prohibited for telemedicine use by the authorities. The prescriptions when given should be in the specified format [2] and can be counter checked at any point.

Proper record-keeping is essential for first time and refill prescriptions (allowed for a maximum 6-month period without onsite visit). A screenshot record of whatsapp chats, emails texts and video recording can be kept. The pediatrician can also ask the caregiver to call back when he feels the symptoms are in evolving phase. Documenting the call-back instructions given to parents is often as important as documenting the reported symptoms to cover liability risks. Prescriptions for common symptoms can be easily copied by quacks in large numbers leading to irrational drug use and quackery. For this we should have stringent laws and any defaulter should face vigorous punishment.

Confidentiality

The practitioner can choose his telemedicine consultation timings as per convenience. It is his choice to accept or decline a consultation at any time. It is duty of the doctor to maintain patient confidentiality and not to share patient details without consent. Patient images should be sent *via* secure, encrypted means of communication [6]. However, in case either party records conversation there can be a breakdown of the doctor-patient relationship. This relationship has multiple cultural influences. The patient's trust in his/her doctor is not acquired in a moment, but in long coexistence, especially in situations of risk [9]. The government guidelines are not very explicit on how to address any barriers or chinks in doctor-patient relationship. However, the practitioner is not liable if the patient information gets shared due to technological issues [2].

Fee

A similar fee structure as applied for inpatient visits is applicable here as well. Telemedicine is much more economical both for the patient and physician as it reduces cost of travel and stay (during out-station consultations). The Indian Academy of Pediatrics has recently introduced an app for its members, which can be used for telemedicine consultation and payment services.

Holistic Care

Using telemedicine, it is possible to provide a more holistic care faster *e.g.*, we can take advice from the expert in a shorter duration without referring the patient for expert opinion. Services such as tele-radiology, tele-pathology will also aid us in faster diagnosis. Common procedures (such as use of metered dose inhalers, technique of giving insulin injections) can be shared with the patient/caregiver *via* YouTube links, pre-prepared videos or live demonstrations. Needless to say, this would be possible on a case-case basis depending on the literacy and understanding of the patient/caretaker. We can also screen patients through telecommunication. In case we find a disease suspect we can refer the patient for urgent testing, isolation and management. However, certain issues like child abuse and/or sexual abuse remain outside the purview of telemedicine in India currently and a hospital visit would be required.

Technological Issues

Lack of widespread access to telecommunication facilities to the wider public leads to inequitable access to health services *via* telemedicine. For example, if there is a transient error in voice transmission the patient might receive incomplete information which can be hazardous and may have medico-legal implications. Any breakdown in technology should preferably be documented by the provider.

Communication

The primary person of contact in the pediatric age group is usually not the patients themselves, but the parents or the caregivers. The already difficult doctor-patient communication is further compounded with telecommunication. Moreover, patient literacy and socio-economic factors might pose challenges in communication during telephone or video calling. Prescriptions *via* this mode can also be incorrectly interpreted, either by the patients themselves or the chemists, which can lead to disastrous results. The solution is to have good quality internet connections, uninterrupted power supply,

workshops on telecommunication, and designated centers such as post offices, dispensaries and primary health care centers where good internet services and trained facilitators like Accredited Social Health Activists (ASHAs) are available (***Fig.* 1**). The staff should be trained in performing video calls and explaining prescription to the patients. We should avoid providing telemedicine by telephonic conversations and should encourage video calls and provide prescriptions in the fixed format *via* email. We should have a better liaison between tertiary care hospitals and primary heath care centers, as has been done with the Village resource centers developed by Indian Space Research Organisation in October, 2018 [8]. If the practitioner still faces communication glitches, he can record the issue and terminate the conversation [2].

We as physicians have become comfortable with the traditional method of providing treatment but in the current scenario of the COVID-19 pandemic, a temporary change is required [9]. With more and more healthcare professionals getting affected, the doctor-patient ratio will further deteriorate. Telemedicine might be the only promising solution available. However as the usage of telemedicine will increase in India, more issues regarding medicolegal aspects might emerge, which should be deliberated among the medical fraternity *a priori*. Although caution is necessary on the part of a pediatrician, given the benefits of telemedicine we must welcome it. We may find it as an important adjunct to the traditional way of practicing medicine.

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ERRATA

Please note that information on ethics clearance for the study was missing from the article titled "Acute peritoneal dialysis in premature infants" published in Indian Pediatr. 2020;57:420-22. The information is as follows: "Ethics Clearance: Clinical Research Ethics Committee of Zeynep Kamil Maternity and Children's Training and Research Hospital; No. 122 dated August 4, 2017." Appropriate corrections have already been done in the web version at *https://www.indianpediatrics.net/may2020/420.pdf.*

Please note that affiliation of Dr. Anupam Das was wrongly attributed to RG Kar Medical College, Kolkata, West Bengal, India in the article titled "Traumatic anserine folliculosis" published in Indian Pediatr. 2020;57:597. The correct affiliation is: "KPC Medical College, Kolkata, West Bengal, India." Appropriate corrections have already been done in the web version at *https://www.indianpediatrics.net/june2020/597.pdf.*

REVIEW ARTICLE

Autoimmune Encephalitis in Children: An Update

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Context: Autoimmune encephalitis has acquired immense significance as a treatable cause of encephalopathy, epilepsy and movement disorders in children. In this review, we discuss the various clinical syndromes, diagnosis, treatment and prognosis in children.

Evidence acquisition: A MEDLINE search strategy using the following terms (1998-2019) was adopted for this review. Limits of 'Human' and 'English' were applied. Search terms included: "autoimmune encephalitis", "autoimmune encephalitis AND epidemiology", "pathophysiology", "diagnosis" and "treatment" for studies in children. Review articles, practice parameters, guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case series and case reports were included.

Conclusions: Autoimmune encephalitis is being increasingly recognized in children. Anti-NMDAR encephalitis is the most common form. Children present with a polysymptomatic presentation including behavioral changes, psychosis, sleep disturbances, mutism, seizures, movement disorders, memory impairment as well as other neurocognitive deficits. Diagnosis is based on suggestive history and ancillary investigations including magnetic resonance imaging, cerebrospinal fluid analysis, and serology for autoantibodies. Treatment is based on immunomodulation of the acute episode followed by maintenance therapy, with earlier initiation being associated with better outcomes. Prognosis depends on the type of clinical syndrome.

Keywords: *Anti-NMDAR encephalitis, Autoimmune epilepsy, Limbic encephalitis, Movement disorders.*

Autoimmune encephalitis (AIE) is being increasingly recognized as a significant as well as frequent cause of encephalopathy in the pediatric age group. Despite a plethora of antibodies being described against the central nervous system, a significant proportion of childhood autoimmune encephalitis do not exhibit detectable known antibodies, spawning a diagnostic challenge [1]. These children may have as yet unidentified antibodies or other immune mechanisms. AIE incorporates proven syndromes based on clinical phenomenology and based on autoantibody associations. Of these, syndromes with antibodies to cell surface antigens have evidence to suggest pathogenicity. Rarely, antibodies to intracellular antigens can be a biomarker but their role is unproven.

The most common antibody associated with AIE in children is anti-NMDA receptor (NMDAR) antibody. Unlike adult AIE, association with cancer is less frequent in children [2]. Early diagnosis and treatment leads to better neurocognitive outcomes. Pediatricians and intensivists need to be aware of this entity so that they can ensure timely and appropriate diagnosis and treatment. This review will provide readers with an updated account of clinical presentation, diagnosis and treatment options in autoimmune encephalitis in children, with discussion of future priorities and challenges.

METHODS

A MEDLINE search strategy using the following terms (1998-2019) was adopted for this review. Limits of 'Human' and 'English' were applied. Search terms included: "autoimmune encephalitis", "autoimmune encephalitis AND epidemiology", "pathophysiology", "diagnosis" and "treatment" for studies in children. Review articles, practice parameters, guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case series and case reports were included.

EPIDEMIOLOGY

Data on the epidemiology of pediatric AIE is limited. A retrospective study of anti-NMDAR encephalitis conducted over seven years in Hong Kong estimated an incidence of 2.2/ million children per year [3]. This disorder likely accounts for a large number of cases of encephalitis in children. Anti-NMDAR encephalitis may also contribute to recurrence of encephalitis following herpes simplex virus encephalitis in both children and

adults [4]. Other non-herpes viruses may also act as triggers for anti-NMDAR encephalitis [5]. Anti-NMDAR encephalitis accounts for 4% of all encephalitis and is the most common cause of seropositive AIE in children. Almost 40% of all reported cases are below 18 years of age [6]. Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's encephalopathy has a prevalence of 2/100,000 in adults but its frequency in children is much less [7]. Anti-thyroid antibodies may be detected in up to 10% of normal children, entailing caution while interpreting these in the presence of neurological impairment in children [8].

PATHOGENESIS

Autoimmune encephalitis can be categorized as per antigen location into two groups. In one group, antibodies target intracellular antigens, and in the second, antibodies target cell surface antigens. This categorization has clinical relevance as well. Intracellular antigen-based diseases are usually paraneoplastic and are mediated by cytotoxic T-cells [9]. These syndromes respond poorly to immunomodulatory therapy with poorer outcomes [10]. Cell surface antigen-based diseases have a lower association with malignancy and are mediated by the humoral immune system [11]. These have a better response to immunotherapy and a more favourable outcome [12]. AIE may also be paraneoplastic or non-paraneoplastic, based on the presence or absence of an underlying neoplasm, respectively - although, this is less relevant in pediatric AIE.

Paraneoplastic syndromes: These result when tumor antigens are shared by neuronal cell antigens, leading to antibody-mediated immunological destruction of neural tissue [13,14].

Infections: Another mechanism is post-viral autoimmune encephalitis. This was first highlighted in a study that reported the development of anti-NMDAR antibodies in 30% of patients with HSV encephalitis based on CSF PCR studies [15]. It is now known that relapsing symptoms following HSV encephalitis that lack viral antigen positivity may be attributable to anti-NMDAR antibodies in 20% of the cases, with a higher frequency in children [16]. These relapses improve dramatically with immune therapy. A putative mechanism involves the release of brain-specific neo-antigens caused by viral toxicity that trigger development of pathogenic antibodies. Another mechanism may be the non-specific stimulation of a range of antibodies following viral inflammation. In children, these relapses frequently take the form of choreo-athetosis and diminished consciousness. Even the viral phase of herpes virus encephalitis may have immunological basis, supported by the occurrence of less severe disease in immunocompromised individuals [17], as well as the beneficial role of steroid therapy in this condition [18]. Although less frequently documented, other viral infections such as varicella zoster, Epstein Barr virus (EBV), Human herpes virus-6 (HHV-6), Cytomegalo-virus (CMV), adenovirus, rickettsial infection as well as HIV are also known to predate AIE [19]. Non-NMDAR antibodies have also been reported after viral encephalitis, including anti-D2 receptor, anti-GABA-A/B, anti-AMPAR antibodies [20].

Post-vaccinal: Several cases of anti-NMDAR encephalitis have been reported following vaccination with influenza (H1N1), diphtheria, tetanus, pertussis, polio and Japanese B encephalitis vaccination [21].

CLINICAL FEATURES

Pediatric autoimmune encephalitis clinically manifests as various clinical syndromes dictated by the type of antibody. Both paraneoplastic and non-paraneoplastic syndromes are associated with the following broad type of antibodies: (*i*) antibodies directed against cell-surface antigens, (*ii*) antibodies directed against intracellular antigens, and (*iii*) antibodies directed towards synaptic antigens present on the extracellular surface. The clinical syndromes are summarized in ***Web Table* I**.

Anti-NMDAR Encephalitis

Anti-NMDAR encephalitis accounts for 4% of all encephalitis and is the most common cause of seropositive AIE in children. This entity was first described in 2007 as a paraneoplastic syndrome in adult females in association with ovarian teratomas [22]. Since then, it has been described in men, women and children of all age groups, with and without teratomas. Almost 40% of all reported cases are below 18 years of age [6]. Pathogenic IgG1 antibodies bind to the GluN1 subunits of the N-Methyl-D-aspartic acid receptor leading to their internalization. Clinical features include a prodrome in 50% of cases lasting weeks to months comprising fever, malaise, headache, gastrointestinal or respiratory complaints followed by neurological (abnormal behavior, cognitive deterioration, short-term memory loss, seizures, movement disorders, central hypoventilation syndrome), psychiatric (delusions, hallucinations, catatonia) and autonomic dysfunction [23,24]. Younger patients tend to present with seizures and movement disorders compared to adults who present with psychiatric abnormalities [22]. Children with anti-NMDAR encephalitis have multiple symptoms, and monosymptomatic cases are present in only 1% of patients which is why, anti-NMDAR encephalitis is unlikely to be a cause of isolated psychosis and is usually

accompanied by seizures [23]. Seizures, seen in up to 80% of patients, may be focal or generalized, including status epilepticus, and may occur in any stage of the disease [23]. In a study from New Delhi of 15 patients with AIE (age range 2-64 years), seizures were reported in 100% patients [24]. Movement disorders include orofacial dyskinesias, chorea-athetosis, ballismus, rigidity, opisthotonus and tremors [25]. Advanced disease is characterized by stupor, coma, periods of agitation alternating with catatonia as well as autonomic dysfunction. In younger children, behavioral changes may be difficult to discern as they present with temper tantrums, irritability and hyperactivity as opposed to frank psychosis. Unlike adults, the first symptoms are non-psychiatric, ranging from dystonia and seizures to mutism. In a study from Chandigarh that studied patients below 12 years of age with anti-NMDAR encephalitis, the presence of extreme irritability, insomnia and mutism were reported in all the children [26]. Three clinical phenotypes have been described *viz*., the classic form and the psychiatric form (associated with good outcomes) and the catatonia-predominant form (associated with poor outcome) [27].

Atypical forms have also been described with children presenting with dominant autistic regression [28], catatonia and neuroleptic malignant syndrome [29] and gait disorder [30]. The presentation of pediatric anti-NMDAR encephalitis differs from adult AIE in several respects and these are summarized in ***Table* I**.

Overlapping Encephalitis

A recent study showed that some patients with anti-NMDAR encephalitis had an overlap in terms of clinical features or magnetic resonance imaging (MRI) findings with neuromyelitis optica (NMO) [31]. Syndromes with dual-positive antibodies have also started to be recognized, for *e.g.* anti-NMDAR and anti-MOG or anti-AQP4 or anti-D2 receptor positivity, anti-GAD and anti-GABA-A etc [32]. The proportion of anti-GABA-B antibodies with overlap seem to be more. Among 20 patients with anti-GABA-B receptor encephalitis, seven showed overlap with other antibodies [33]. Anti-NDMAR encephalitis may also overlap with opsoclonus syndrome [34].

Seronegative Autoimmune Encephalitis

Only up to 44% of patients with AIE have an antibody-positive status [1]. 'Seronegative but suspected autoimmune encephalitis' has received a consensus definition [1]. The definition includes rapid progression of symptoms, along with exclusion of well-defined AIE syndromes such as typical limbic encephalitis, absence of serum and CSF antibodies along with two of: MRI abnormalities suggestive of autoimmune encephalitis, CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index or brain biopsy showing inflammatory infiltrates, along with exclusion of other causes [35].

When to Suspect Autoimmune Encephalitis?

The diagnosis of AIE should be suspected in all children who develop a polysymptomatic syndrome encompassing encephalopathy, seizures, movement disorders, psychiatric features, gait disturbances and autonomic disturbances. The clinical features suggestive of autoimmune encephalitis include:

- Abrupt onset / rapid decline
- Autonomic instability
- Delirium slipping into catatonia and vice versa
- Urinary/ faecal incontinence
- Cognitive slowing
- Gait and balance disorder
- Relapse after treatment for viral encephalitis
- Seizures that may be in the form of status epilepticus or multifocal drug resistant epilepsy or seizure clusters
- Involvement of multiple domains *eg*. Cognition and

Table I Clinical Features of Anti-NMDAR Encephalitis in Children and Adults

Clinical features	*Adults*	*Children*
Initial feature	Change in mood and behavior, psychosis	Seizures, movement disorders, speech abnormalities, sleep problems
Features at nadir of	Seizures, impaired memory, movement disorders, impaired consciousness	Seizures, movement disorders, change of behavior
Autonomic dysfunction	Arrhythmia, central hypoventilation	Tachycardia, hyperthermia, hypertension
Association	Tumors, post-infective	Post-infective

NMDAR: *N-methyl D-aspartate receptor.*

extrapyramidal system etc.

- CSF may also reveal features of inflammation in the absence of infection.

Features that point away from the diagnosis of AIE include:

- A very chronic or indolent course
- Plateauing of symptoms
- No impairment in activities of daily living
- Cognition remaining intact
- Purely psychiatric symptoms

***Table* II** depicts some differentiating features between autoimmune and infective (viral) encephalitis.

DIAGNOSIS

The diagnosis of AIE is based on the presence of an appropriate clinical syndrome supported by various ancillary investigations. All other possible etiologies should be ruled out along with confirmatory antibody testing. The common differentials include CNS infections, toxins, CNS vasculitis, inborn errors of metabolism, neoplasms and a primary psychiatric disorder. The features supportive of an autoimmune etiology include evidence of CNS inflammation (CSF pleocytosis, elevated IgG index or oligoclonal bands, elevated CSF neopterin), MRI abnormalities and a response to immunosuppressive treatment. Criteria for the diagnosis of anti-NMDAR encephalitis have been proposed by Graus, *et al*. [35]. As per this criteria, probable anti-NMDAR encephalitis can be made if all three of the following criteria have been met: (*i*) Rapid onset (less than three months) of at least four symptoms among psychiatric/behavioral dysfunction, speech abnormalities, seizures, movement disorders, decreased consciousness or autonomic dysfunction; (*ii*) Abnormal EEG/CSF; and (*iii*) Exclusion of other causes. A study evaluating the reliability of these criteria found them to be 90% sensitive and 96% specific for the diagnosis of anti-NMDAR encephalitis in children [36]. Diagnostic evaluation includes the following:

Magnetic Resonance Imaging of Brain

Classic neuroimaging abnormalities in AIE include unilateral or bilateral T2/ FLAIR signal hyperintensities involving the mesial temporal lobe. The large majority of patients (66%) with anti-NMDAR encephalitis do not exhibit neuroimaging abnormalities [37]. Abnormalities in the form of signal hyperintensities may be seen throughout the brain. Transitory cortical enhancement in the absence of restricted diffusion or hemorrhage may also be seen [37]. In patients with normal MRI and typical clinical and EEG picture, positron emission tomography may be useful to highlight involvement of the mesial temporal lobes [38]. In contrast to NMDAR encephalitis, the large majority of patients with limbic encephalitis such as anti-Lgi1 antibodies exhibit mesial temporal hyperintensities and may go on to develop mesial temporal sclerosis on follow-up imaging [39]. The presence of restricted diffusion and contrast enhancement correlated with the development of mesial temporal sclerosis [39]. MRI is mostly abnormal in anti-GABA-A receptor and anti-D2 receptor encephalitis. Most patients with anti-GABA-A receptor encephalitis show MRI abnormality in the form of extensive, multifocal or diffuse cortical and subcortical T2/FLAIR signal alterations. Rapid progression from frontal and temporal T2/FLAIR abnormalities to atrophy and extensive bilateral lesions has been reported in some patients. Majority of patients with anti-D2 receptor encephalitis exhibit bilateral basal ganglia T2/FLAIR signal abnormalities.

Electroencephalography

EEG may show focal or diffuse slowing as well as epileptiform discharges. 30% of anti-NMDAR encephalitis patients may exhibit a typical pattern called 'extreme delta brush' [40].

Table II Differentiating Features Between Autoimmune Encephalitis and Infective Encephalitis

Feature	*Autoimmune encephalitis*	*Infectious encephalitis*
Clinical presentation	Psychosis, language dysfunction, autonomic instability, movement disorder; around 50% may have fever. Rash is not seen	Fever, altered sensorium, seizures; most patients have fever. Rash may appear in HSV/ VZV encephalitis
CSF findings	CSF lymphocytic pleocytosis milder	More severe lymphocytic pleocytosis
MRI findings	MRI may be normal in anti-NMDAR encephalitis.The lateral temporal lobes and insula are less commonly involved; basal ganglia often involved.	Characteristic mesial temporal involvement; Lateral temporal lobe and insula may also be involved, basal ganglia spared.
Treatment	Immunotherapy (+/- tumor removal)	Antiviral agents (acyclovir)

Antibody Testing

Confirmation of the pathogenic antibody forms the basis for diagnosis of autoimmune encephalitis. Those testing positive are deemed 'definite' cases, while those who do not are labelled 'suspected'. These antibodies bind to conformational extracellular epitopes of proteins on the cell surface like receptors, synaptic proteins or ion channels. Their shape and conformation determine antibody binding. Therefore, cell-based assays with live or fixed eukaryotic cells should be used. The importance of the same was highlighted in the false positivity associated with voltage gated potassium channel (VGKC) complex radioimmunoassay because it not only precipitates the target antigens: leucine rich glioma inactivated (LGI1) and contact in associated protein 2 (CASPR2) but also other intracellular antigens [41]. Serum testing for these antibodies is non-inferior to CSF testing, except in the case of anti-NMDAR encephalitis, where CSF testing is more sensitive [42] with CSF sensitivity being 100% (versus 85.6% in serum). In addition, commercial anti-NMDAR testing should be done using assays that test IgG antibodies to the extracellular domain of the NR1 subunit of the receptor. Antibodies such as serum IgA or other antibody types other than IgG, or antibodies to the NR2 subunit, do not necessitate treatment as these are not clinically relevant.

Testing both serum and CSF should be done whenever possible. The utility of follow up evaluation of these antibodies has not yet been ascertained and is therefore not indicated as of now. If diagnosis is delayed or patients have received treatment with plasma exchange or IV immunoglobulin, antibodies might be detected only in CSF. Patients with a protracted clinical course or persistent symptoms might be sero-negative and have persistently raised CSF titres until symptoms improve [43]. Less frequently, long-term follow-up reveals patients who, after recovery, still have high serum titers and absent or barely detectable titers in the CSF. Findings are consistent with a disease in which the immune response is initially triggered systemically by a tumor or other unknown causes and is reactivated and expanded in the CNS.

TREATMENT

Basic tenets that guide the treatment of autoimmune encephalitis are that patients treated with immunotherapy fare better than those not given immunotherapy. Earlier initiation of immune therapy is associated with better prognosis. Lastly, if the patient does not respond to first line therapy, or if the disease is severe or relapsing, treat-ment with a second-line agent improves prognosis [44].

The primary immunomodulation options include steroids, intravenous immunoglobulins or plasma exchange. This may be followed by maintenance therapy in the form of oral steroid taper, monthly pulse steroids or pulse IVIG therapy. Azathioprine and mycophenolate mofetil are often used in maintenance therapy as steroid-sparing agents. Usual duration of maintenance therapy ranges from 6 to 12 months but is individualized. Second line therapy in case of non-response to first line agents includes rituximab. Cyclophosphamide is another second line agent. Third line agents include bortezomib and tocilizumab. Another important tenet is to screen for tumours, especially in adolescent females, due to the association with ovarian teratomas. Additionally, clinicians must consider Subacute sclerosing panencephalitis (SSPE) in the differential as it is a close mimic of AIE, presenting as cognitive decline, seizures, myoclonic jerks, ataxia and extrapyramidal disorders.

First-line Therapy

Corticosteroids form the cornerstone of treatment. They have good penetration across the blood brain barrier and have a broad spectrum of anti-inflammatory activity. They are usually given as a pulse therapy with methylprednisolone (30 mg/kg/d for 3-5 days, maximum 1g/d), followed by sustained oral steroids according to bodyweight (prednisolone 1-2 mg kg/day) followed by slow taper over 6-12 months (in severe syndromes like anti-NMDAR encephalitis), determined by case-based scenario. Intravenous immunoglobulin (IVIG) (2 g/kg given over 5 days) or plasma exchange (PLEX) (5 to 7 exchanges of 50 mL/kg every alternate day) are commonly used as alternatives and occasionally, concomitantly. Evidence, although scarce, has found early PLEX along with corticosteroids to have better outcomes than either alone [45]. No evidence exists regarding the superiority of PLEX *versus* IVIG. However, considering that patients with autoimmune encephalitis are commonly agitated, IVIG might be easier to administer. In a study from Bangalore, 13 children with anti-NMDAR encephalitis were followed up for a mean duration of 10.3 (6.7) months [46]. All patients were administered intravenous methylprednisolone followed by monthly pulses of methyl prednisolone. IVIG and PLEX were administered during the acute phase for inadequate response to methyl prednisolone. The study concluded that Anti-NMDAR encephalitis required prolonged immunomodulatory therapy and methylprednisolone was effective for this purpose [46].

If AIE is suspected, empirical therapy has to be initiated immediately. Waiting for the results of antibody tests is not an essential pre-requisite. If resources are a

constraint, CSF is the preferred sample for antibody testing because it is more sensitive than serum, especially for anti-NMDAR encephalitis [42]. If the patient is unable to afford antibody testing altogether, empirical therapy should be initiated after reasonably excluding alternate causes. ***Fig.* 1** depicts a diagnostic and therapeutic algorithm in children with suspected AIE.

Second-line Therapy

A significant proportion of patients respond to first line therapy, showing benefit of treatment within the first 1-2 weeks of treatment initiation. Non-responders are treated with 2nd line agents *viz*, rituximab or Cyclophosphamide. Rituximab is a chimeric monoclonal antibody against CD20 resulting in B-cell depletion, which leads to reduced pro-inflammatory CD4+ and CD8+ T cell responses [47].

B-cell measurement should be done 2-4 weeks after dosing to check for B-cell depletion (some children may be resistant which entails a substitute treatment) and 3-6 monthly thereafter to look for B-cell repopulation, that may assist redosing, if clinical symptoms persist or a relapse is suspected [48]. Although well tolerated, infusion reactions occur in approximately 12% individuals, and serious adverse events are rare. Dale, *et al*. reported serious adverse events in 4 children out of the 144 treated with it, including two deaths [49].

Cyclophosphamide is the other alternative and has broad cellular immune suppression effects. Monthly intravenous infusions of 500-1000 mg/m^2 body surface area for 6-9 months is the usual course of treatment. The risks of infertility and secondary malignancies are the major limitations to its use. However, these are dependent on the cumulative dose received and doses <7.5 g/m^2 are justified in sick patients. In the case series of Dale et al [49], 58 of the 144 patients received concomitant rituximab and cyclophosphamide without any increase in the adverse effect profile. This provides re-assurance for using both together, if the need arises.

Third-line Agents

Third line agents are needed when both 1st and 2nd line agents fail. Literature regarding their use is limited to general recommendations. Behrendt, *et al*. [50] showed benefit of Bortezomib (protease inhibitor which inhibits the pro-inflammatory signalling cascade) in two adults with severe refractory anti-NMDAR encephalitis. Tocilizumab, an anti-IL6, has also been tried [51] based on the observation of elevated levels of IL6 in the CSF of patients with anti-NMDAR and anti-MOG associated disease [52]. Tatencloux, *et al*. have used intrathecal steroids and methotrexate in pediatric patients with refractory anti-NMDAR encephalitis.

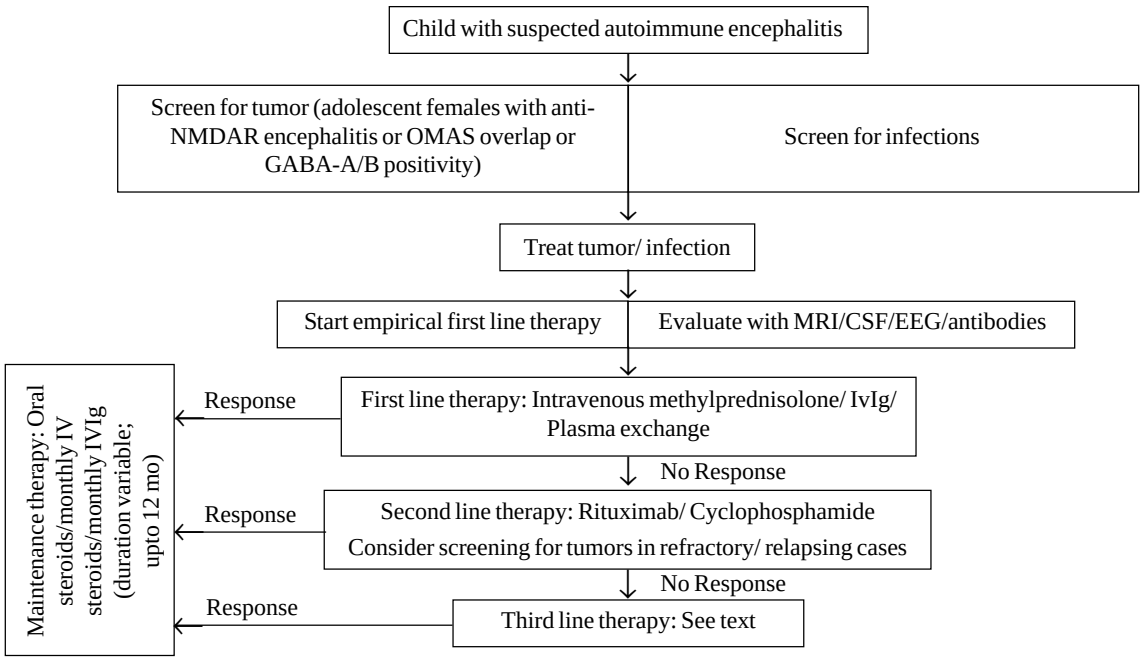

Fig. 1 *Suggested management algorithm for a child with suspected autoimmune encephalitis.*

KEY MESSAGES

- Pediatric autoimmune encephalitis forms a group of acquired disorders with antibodies targeting cell-surface antigens or intracellular antigens that are treatable.
- Pediatric disease manifests differently from adults, with less frequent association with neoplasms and predominance of movement disorders, behavioral abnormalities and seizures.
- Anti-NMDAR encephalitis is the most common pediatric autoimmune encephalitis. It exhibits typical clinical features (limbic encephalitis) as well as imaging abnormalities (mesial temporal signal change) although these may be seen in only 30-40% of patients. Hence, clinical recognition is the key. It responds well to early therapy.
- Treatment involves immunomodulation which should be initiated empirically as soon as the diagnosis of autoimmune encephalitis is suspected, even prior to the availability of antibody test results.

Maintenance Therapy

Mycophenolate mofetil (MMF), methotrexate and azathioprine have been used as steroid-sparing agents in paediatric anti-NMDAR encephalitis. In a systematic review of retrospective cohort data, MMF/ methotrexate/ azathioprine used individually or in varying combinations were associated with a reduced risk of relapse if started after the first event rather than after subsequent ones, and were reasonably safe [54].

Other Measures

Symptomatic therapy: Symptomatic management should be given along with immunosuppressive treatment. Sedating agents are used to induce and maintain sleep, relieve agitation and emotional imbalance. Benzodiazepines, anti-epileptics, clonidine and chloral hydrate are commonly used for this purpose. Neuroleptics are best avoided due to the high incidence of adverse effects like rigidity and neuroleptic malignant syndrome.

Management of relapses: Relapses tend to be uncommon in AIE. However, when they do occur, they are managed with repeat dosing of the first line agents. In these cases, there is concern of ongoing inflammatory activity, and hence, chronic immunosuppressive therapy such as azathioprine, mycophenolate or repeated dose of rituximab may be considered.

PROGNOSIS

Most patients with anti-NMDAR encephalitis respond to immune therapy. A study with a median follow up of 24 months showed that 94% patients responded within four weeks to first line immunotherapy/ tumour removal [23]. Of the patients who failed first line therapy, 57% underwent second line therapy and had better outcomes. At 24 months follow up, 81% patients had a good outcome, with mortality in 6%. Outcomes continued to improve up to 18 months following treatment. Predictors of good outcome included early treatment and lack of intensive care unit admission.

Relapses in AIE tend to be uncommon and the approximate percentage varies according to the subtype being dealt with. Approximately 12% of patients with anti-NMDAR encephalitis were found to relapse in initial descriptions [42]. However, this has reduced, probably due to the use of second line therapies and chronic immunosuppression, which lead to the alteration in the natural history of disease. The patients that do relapse tend to be mono-symptomatic, presenting with seizures or movement disorders commonly, unlike the initial presentation which almost always tends to be polysymptomatic. Chronic immunosuppression with mycophenolate, azathioprine or re-dosing with rituximab is done in this scenario.

FUTURE DIRECTIONS

Pediatric autoimmune encephalitis is a challenging condition to diagnose and treat and these are suffers from several lacunae in evidence. More literature is required on the diagnosis of suspected autoimmune encephalitis in children with seronegativity as well as on overlap syndromes. Duration of optimal therapy in children is also not clear. Another challenging aspect of therapy that demands research is the management of refractory autoimmune encephalitis. However, it is heartening that with the current status of knowledge, appropriate and timely management can ensure satisfactory outcomes in the majority.

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Web Table I Features of Autoimmune Encephalitis in Children

Antibody syndrome	*Antigen*	*Clinical features*	*Evaluation*	*Additional findings*	*Tumor-association*
Antibodies to cell surface antigens					
Anti-NMDAR	Amino terminus of NR1 subunit of NMDA receptor	Seizures, encephalopathy, dyskinesias, autonomic dysfunction, mutism.	Mesial temporal hyperintensity on MRI; Extreme delta brush on EEG	May follow herpes simplex encephalitis	Present Ovarian teratoma
Limbic encephalitis	Component proteins of the VGKC complex, leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (Caspr2)	Limbic encephalitis, fever-related epileptic encephalopathy, status epilepticus and drug-refractory epilepsy.Caspr2-encephalitis includes features of peripheral nerve hyperexcitability including neuromyotonia and Morvon syndrome.	Mesial temporal/ basal ganglia hyperintensity, white matter signal changes on MRI.	Typical facio-brachial dystonic seizures in anti-LGI1.Antibodies to VGKC complex may be positive in the absence of antibody positivity or LGI1 or CASPR2	Rare- thymus, lung
Anti-GABA-A receptor	Anti-gamma -amino butyric acid type A (GABA-A) receptor	Seizures and status epilepticus, movement disorders and memory impairment.	Mesial temporal hyperintensities on MRI.	A few cases described in children	Rare- thymus, Hodgkin lymphoma
Anti-GABA-B receptor	Anti-gamma -amino butyric acid type B (GABA-B) receptor	Limbic encephalitis or seizures.	Mesial temporal hyperintensity, cortical-subcortical hyperintensities on MRI.	Few reports in adolescent females	Lung, thymus
Anti-Glycine	Alpha-1 subunit of the receptor	Progressive encephalomyelitis with rigidity and myoclonus, as well as optic neuritis.	MRI usually normal	Reported in only a few cases of pediatric AIE.	None
Anti-D2 receptor	Amino terminus of dopamine D2 receptor	Parkinsonism, dystonia, lethargy, psychiatric intensities symptoms.	Bilateral basal ganglia hyper- may be seen.	Rare	–
Anti-AMPA receptor	Target the glutamate receptor (GluR1) or (GluR2) subunit of the AMPA receptor	Limbic encephalitis		Extremely rare in children	–
Anti-mGluR5	Anti-metabotropic glutamate (mGluR5) receptor	Limbic encephalitis	May exhibit hippocampal hyperintensity on MRI.		Hodgkin lymphoma (Ophelia syndrome)
Anti-Neurexin-3 alpha	Neurexin-3 alpha	Anti-NMDAR like syndrome, orofacial dyskinesias, seizures, encephalopathy		After the initial report, findings not replicated	
Anti-DPPX	Dipeptidyl peptidase-like protein	Stiff-person syndrome, myoclonus, ataxia, tremor,		Diarrheal symptoms may be present	–

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Antibody syndrome	*Antigen*	*Clinical features*	*Evaluation*	*Additional findings*	*Tumor-association*
		parkinsonism, opsoclonus myoclonus			
Anti-glutamate receptor	Glutamate receptor delta 2	Opsoclonus-myoclonus-ataxia syndrome (OMAS)	–	–	–
Antibodies to intracellular antigens					
Anti-Hu	Anti-neuronal nuclear antigen 1	Limbic encephalitis, drug refractory epilepsy	–	–	Paraneoplastic (neuroblastoma) and non-paraneoplastic
Anti-Ma2	Intracellular onconeural protein	Limbic encephalitis/ brainstem or diencephalic dysfunction	–	Infrequent in children	Testicular tumors in males (young adults)
Anti-GAD	Glutamic acid decarboxylase (responsible for GABA synthesis)	Neuropsychiatric and memory impairment, focal seizures, pediatric stiff-person syndrome	MRI usually normal. May have hyperintensities in hippocampus, cerebellum.	Infrequent in children	Not described

International Guidelines 2020 for the Management of Septic Shock in Children

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The recent version of pediatric septic shock guidelines, 2020 have addressed practical issues pertaining to pediatric septic shock management, which can be applicable to resource-limited setting as well. Supportive aspects in management of septic shock such as ventilation, antibiotic stewardship, and nutrition are addressed compared to previous guidelines that concentrated more on first-hour management. The current guideline needs to be adapted to local clinical practice cautiously in the light of experience, clinical acumen and judgement.

Keywords: *Fluid resuscitation, Golden hour, MODS, PARDS*.

Recently the society of critical care medicine (SCCM) has published evidence-based guideline of management of pediatric septic shock and multi-organ dysfunction in children [1]. This guideline is an update to the previously published version in the year 2017 [2] and the scope of guideline includes all term neonates (>37 wks) till end of childhood up to 18 year. Due to complex and different pathophysiology of shock in preterms, the guideline has not particularly looked for evidence pertaining to shock in preterm neonates. In general, the words 'suggested for' or 'suggested against' have been used to denote 'a weak recommendation' emerging from very 'low to low-quality evidence' for or against certain practice, respectively; while the words 'recommended for' or 'recommended against' have been used to denote 'strong recommendation' for or against certain practice arising from 'moderate to high quality evidence'. However, some of the recommendations in all the above mentioned categories have also emerged as best practice statement, based on the consensus opinion of experts when adequate evidence is not available.

KEY CHANGES

As compared to previously published guideline the current guideline is more extensive and detailed which covers supportive and ancillary management of pediatric septic shock which were henceforth not covered in the previous version. These include details of evidence-based recommendation on antimicrobial therapy, source control of infection, nutrition, ventilation, prophylaxis against bedsore, deep vein thrombosis and ulcer. As compared to previous guidelines, the current guideline has de-emphasized the role of lactate in hemodynamic monitoring. Similarly, it promotes restrictive fluid up to 40 mL/kg (previously up to 60 mL/kg) and each bolus of 10-20 mL/kg (previously 20 mL/kg) during resuscitation in settings where there is no support of intensive care facility to avoid fluid overload. As is the case in many health care facilities in lower-middle income countries, where prevalence of malnutrition in children is very high, unsupervised administration of high volume of fluid can actually increase mortality. Hence the current guideline has been more conservative in these scenario. Further, it has set a time frame of 3 hour for initiation of antibiotics in children with sepsis but without septic shock. In light of recent emerging evidence the guideline has replaced epinephrine or nor-epinephrine in place of dopamine as first choice inotrope. However, its applicability in resource-limited setting may remain an issue where these two drugs are not easily available and dopamine may have to be used as first line drug in these situations. As the recent guideline has not mentioned exact cut-off of blood pressure for hypotension, normal range of blood glucose or hemoglobin level cutoff for transfusion in unstable children, for point of care issues related to these topics, the readers still have to either refer the previous version or other published guideline. The summary of 2020 surviving sepsis campaign guideline in contrast with 2017 guideline has been provided in ***Table* I.**

THE WAY FORWARD

The current version addressed practical issues pertaining to pediatric septic shock management, which can be applicable to resource-limited setting as well. Supportive aspects in management of septic shock such as ventilation, antibiotic stewardship, and nutrition are addressed compared to previous guidelines that concentrated more on first hour management. Like with any other International guidelines, the current guideline also needs to be adapted to local clinical practice cautiously in the light of experience, clinical acumen and judgment for its maximum benefit/utilization.

Table I Comparison of the 2020 Surviving Sepsis Campaign Guideline With 2017 Guideline for the Management of Children With Septic Shock or Sepsis Associated Organ Dysfunction

Steps	*2020 Recommendation [1]*	*2017 Guideline [2]*	*Implications for resource-limited setting*
Screening, diagnosis and management	Suggested for • Systematic screening for timely detection	Same	• In our setup, thorough and repetitive clinical examination should be done to identify children with septic shock in time.
	Recommended • Protocol/guideline-based management	Same	
	• Obtaining blood culture before initiation of antimicrobial therapy	Same	• Facility for blood lactate estimation is not easily available in majority health facilities in India
	No recommendation • Blood lactate values for categorizing children	Did not mention	
Antimicrobial therapy	*Recommended* • In children with septic shock, give antibiotics in the first hour of shock recognition	Same	• In our setup, strict hospital driven antimicrobial stewardship program along with written antibiotic policy needs to be implemented for timely de-escalation of antimicrobials
	• Give empiric broad-spectrum antibiotics while awaiting culture report and narrow down or stop subsequently as per culture and sensitivity	No mention	
	• Use pharmacokinetic/ pharmaco-dynamic based antimicrobial dosing	No mention	• Every attempt should be made to obtain blood culture before initiation of antibiotics where ever possible.
	• Daily assessment for timely de-escalation of antimicrobials	No mention	
	• Duration of antimicrobials as per site, etiology, treatment response and control of source	No mention	• Due to serious risk of misuse, multiple antibiotics therapy solely based on immunocompetent status should be discouraged.
	Suggested for • In children without septic shock but with other organ dysfunction starting antimicrobials within 3 hr	No mention	• Decision for continuation, de-escalation, or stoppage should be made on clinical basis taking consideration of site of infection, agent, host risk factors
	• In immunosuppressed or high-risk children use of multiple empiric anti-biotics to expand coverage, evade resistance or achieve synergy	No mention	
	Suggested against • In immunocompetent children routine use of empiric multidrug therapy	No mention	
Source control	*Recommended for*		
	• Implementation of source control strategy for prevention of infection as early as possible • Removal of intravascular line which are confirmed source of infection after establishing alternative vascular access	No mention	In Indian setting where aseptic maintenance of central lines is an issue, the emphasis should be on timely removal as soon as possible (when they are no more required)
Fluid therapy	*Suggested*		

Contd....

Steps	*2020 Recommendation [1]*	*2017 Guideline [2]*	*Implications for resource-limited setting*
	• Using 40-60mL/kg of fluid (10-20 mL/kg per bolus) in first hour with appropriate clinical titration • Fluid bolus up to 40mL/kg may be given in first hour in case of hypotension in health facility without support of intensive care • Use of crystalloids as compared to colloids in first hour fluid resuscitation • Use of balanced/buffered crystalloids rather 0.9% saline	• Fluid volume up to 60 mL/kg (each bolus of 20mL/kg) in first hour resuscitation • Either crystalloid or colloids can be used for fluid resuscitation	In Indian set-up where pediatric intensive care facilities are not widely available, aggressive fluid resuscitation (more than 40mL/kg) needs to be avoided especially in absence of hypotension as per age
	Recommended against • Bolus fluid in the absence of hypotension in a health facility without support of intensive care • Use of starch/gelatin for resuscitation	• No mention • No mention	
Hemodynamic monitoring	*Suggested for* • Use of advanced hemodynamic variables (*e.g* cardiac output/ cardiac index, central venous oxygen saturation, systemic vascular resistance) where ever available in addition to clinical parameters • Use of serial trends of lactate rather single isolated value *Suggested against* • Isolated use of clinical signs in categorising warm or cold shock *No recommendation for or against* • Whether to target a MAP 5th centile or 50th centile for hemodynamic stability	• Frequent re-evaluation of hemodynamic parameters for choosing the appropriate vasoactive/ inotropic drug • Provided a range of normal heart rate as per age as well as mean arterial pressure(50th centile) as per age • Provided age wise targets for perfusion pressure (MAP-CVP)	• Interpretation of advanced clinical condition of the child, hemodynamic parameters should be in context with not just numbers. • Though serial blood lactate value provides idea about microcirculation during resuscitation, it may remain elevated even after correction of microcirculation if associated with hepaticor renal dysfunction. Hence in these situation, lactate levels should be interpreted cautiously • There is no consensus whether to target 5th centile, 10th centile or 50th centile MAP for critically ill children during resuscitation. MAP-CVP target provided by previous guideline may be used
Vasoactive medications	Suggested for • Epinephrine or norepinephrine in place of dopamine as first-line • Dopamine may be substituted as first line when epinephrine or norepinephrine are not available • May add vasopressin or titrate catecholaminesby clinician to achieve target *No recommendation for or against* • Use of vasoactive agents in peripheral line • Specific first-line vasoactive agent one above the other • Adding inodilator in children with cardiac dysfunction despite addition of vasopressors	• Dopamine, dobutamine, or epinephrine can be used as first-line inotropic support. • Low-dose epinephrine as the first-line choice for cold hypotensiveshock • Vasopressin as rescue therapy • Epinephrine may be infused through a peripheral IV route or through an intraosseous needle while attaining central venous access • Milrinone is first-line	• It is reasonable to initiate vasoactive agent after a fluid resuscitation of 40-60mL/kg and first line vasoactive agents may be administered by a peripheral venous route till the time central venous line is inserted • Usual recommended doses (IV/IO) of commonly used vasoactive drugs (as infusion)(3) 1. Epinephrine 0.1 to 1 mcg/kg/ min (higher doses may be considered in case to case basis) Norepinephrine 0.1 to 1 mcg/kg/ min 2. Dopamine up to 10 mcg/kg/min infusion 3. Dobutamine up to 10 mcg/kg/ min infusion

Contd....

Steps	*2020 Recommendation [1]*	*2017 Guideline [2]*	*Implications for resource-limited setting*
		inodilator in patients with epinephrine-resistant shock with normal blood pressure.	4. Milrinoneup 0.75mcg/kg/ min. 5. Vasopressin up to 0.002 units/kg/ min
Ventilation	*Suggested for* • A trial of NIV over invasive ventilation in children with PARDS • High PEEP in sepsisinduced PARDS • Trial of prone positioning in PARDS • Use of iNO as rescue therapy • Use of neuromuscular blockade *Suggested against* • Use of etomidate for intubation • Routine use of iNO *No recommendation for or against* •Intubation of children with fluid refractory, vasopressor resistant shock • HFO over conventional ventilation • Recruitment maneuvers	• High-flow nasal cannula /non-invasive respiratory support can be given to selected patients • Etomidate to be avoided • Those with persistent or worsening shock should be considered as high risk for deterioration and should receive ventilatory support	Although the current guideline has not mentioned exact value for defining high PEEP in PARDS, the readers may go through pediatric acute lung injury consensus conference group (4) (Generally a PEEP up to 10-15 cmH2O may be needed in severe PARDS and occasionally upto >15 15 cmH2O)
Steroids	*Suggested against* • Use of IV hydrocortisone for treating children with septic shock who are stabilized by adequate fluid resuscitation and vasopressor therapy *Suggested for* • Use of hydrocortisone in treating septic shock children where hemodynamic stability is not achieved with fluid resuscitation and vasopressors	In a child at risk of adrenal insufficiency with shock even after epinephrine or norepinephrine infusion, injection hydrocortisone should be given after obtaining sample for serum cortisol level	• Serum cortisol level may not be available at all facilities. • IV hydrocortisone can be considered at dose of 100 mg/ m^2 stat dose followed by100mg/m^2 /d in 4 divided doses in children who remain hypotensive despite adequate fluid resuscitation and vasopressor
Endocrine and metabolic	*Recommended against* • Routine insulin therapy to achieve normoglycemia (< 140 mg/dL) *No recommendation* • Range of blood sugar levels as target, but suggested to target <180 mg/dL as consensus • Whether to target normal calcium levels *Suggested against* • Routine use of levothyroxine *Suggested for* • Either antipyretic therapy or permissive approach for fever control	• Maintaining glucose range of 80-150 mg/dL by appropriate titration of glucose/ insulin infusion and avoiding use of lesser glucose (5% D or lower volume of 10% D) in hyperglycemic patient • Thyroxine in catecholamine resistant shock with underlying thyroid insufficiency • Maintenance of normal ionized calcium level by calcium replacement	As calcium is required for cardiac contractility, targeting normal ionic calcium levels for these children as per previous guideline seems rational in current scenario.
Nutrition	*Suggested against* • Withholding enteral feeding solely based on ionotropic support • Supplementing with specialised lipid emulsion • Routine measurement of gastric	No mention in previous version	Early trophic feeds are to considered and may increase feeds further provided no increment in vasoactive support or decreasing the vasoactive drug support

Contd....

Steps	*2020 Recommendation [1]*	*2017 Guideline [2]*	*Implications for resource-limited setting*
	residual volume routine prokinetic agent • Use of micronutrient selenium, glutamine, arginine, zinc, thiamine, vitamin D as immunomodulators *Suggested for* • Enteral nutrition as preferred to parenteral nutrition and withholding parenteral nutrition till 7 days of PICU admission • Orogastric feed as compared post pyloric feed *No recommendation* •Early trophic/hypocaloric feed vs full early enteral feed		
Blood products	*Suggested against* • Transfusion of PRBC with Hb ≥7g/dL for stabilized children •Prophylactic platelet transfusion (based on platelet levels) or plasma transfusion in nonbleeding cases *No recommendation* •Hb transfusion threshold for unstable children	Transfuse to maintain Hb ≥7 g/dL for stable children and ≥10 g/dL for children with septic shock	During resuscitation phase of shock one may target Hb ≥10 g/dL
Extracorporeal therapy	*Suggested against* • Routine plasma exchange • Routine high-volume hemofiltration over standard hemofiltration *Suggested for* • Early renal replacement therapy for prevention and treatment of fluid overload • VV ECMO (VA in case VV fails) in PARDS and refractory hypoxemia	Individualized approach while using extracorporeal therapies such as ECMO, CRRT, and blood purification (hemofiltration, hemoperfusion, and therapeutic plasma exchange [TPE]) in pediatric septic shock	
Routine IVIG	*Suggested against**	No mention	
Routine prophylaxis for critically ill children	*Suggested against** • Routine stress ulcer prophylaxis • Routine deep vein prophylaxis	No mention	

*Information extracted from Weiss, et al. [1] and Davis, et al. [2]; MAP: Mean arterial pressure; NIV: Non-invasive blood pressure; VV: Venovenous; VA: Venoarterial; PARDS: Pediatrics acute respiratory distress syndrome; *Selected cases may be benefitted on a case-to-case basis; HFO: High frequency oscillation; iNO: Inhaled nitric oxide.*

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Modified Antibiotic Regimen for Pediatric Complicated Appendicitis to Reduce Infectious Morbidity in Taiwan

We compared our previous hospital-based antibiotic protocol and an optimum modified one by reviewing hospital records of children younger than 18 years with complicated appendicitis between 2010-2016. The modified protocol showed no infectious morbidity, which is significantly different from that of our previous protocol (mortality rate, 21.4%). An optimum hospital-based antibiotic protocol for complicated appendicitis can reduce the infectious morbidity rate without increasing hospital cost.

Keywords: *Abscess, Cost, Emergency, Management*.

The infection rate of appendicitis may increase to up to 23% when perforation occurs [1]. A 3-antibiotic regimen (cefmetazole, gentamycin, and metronidazole) was in use in our hospital to decrease postoperative infection. However, wound infection and intra-abdominal abscess were noted in some cases of complicated appendicitis (perforated or gangrenous appendicitis). We found that 29% of our patients had a positive *Pseudomonas sp.* culture of the appendix that was not covered by the above three antibiotics. We switched our antibiotic regimen to piperacillin and tazobactam and metronidazole, based on bacterial cultures sensitivity tests of all complicated appendicitis cases in our hospital. This new regimen, followed by oral ciprofloxacin, has been in use in our department since April, 2013. Standardized guidelines for patient care can help reduce infectious morbidity [2]. We assumed that this protocol would decrease the infectious complication rate. However, its net cost is higher than that of the old protocol. Thus, we aimed to investigate the differences in hospitalization duration and cost between the previous and new antibiotic protocols.

This study was approved by the Research ethics review committee of our hospital. Charts of all patients (aged younger than 18 years (n=87) who presented to our department from January, 2010 to August, 2016 with complicated appendicitis were reviewed retrospectively. Laparoscopic appendectomy was performed with a 7-mm Jackson-Pratt drainage tube in all patients. A 3-antibiotic regimen, followed by an oral antibiotic, was employed before April, 2013, thereafter, pipiracillion- tazobactam and metronidazole, and subsequent oral ciprofloxacin were used. Patients were divided into two groups according to their antibiotic regimen *viz.* Group 1 patients received three antibiotics (cefmetazole 25 mg/kg 6-hourly, gentamycin 2.5 mg/kg 12-hourly, and metronidazole 10 mg/kg 8-hourly). Group 2 patients received piperacillin-tazobactam 112.5 mg/kg and metronidazole 10 mg/kg 8-hourly, followed by oral ciprofloxacin. Antibiotics were administered intravenously until patients were afebrile for >24 hours and their appetite had recovered. All patients were followed up in our outpatient department until full recovery.

Hospital costs in this study are estimates based on the current pricing in our institution. The expense excluded the cost of emergency room (ER) services and imaging studies performed in the ER, and was calculated in United States dollars. Unpaired 2-tailed Student t-test and chi-square test were used to compare data between both groups. P <0.05 was considered significant. All analyses were performed using SPSS version 20.0. (IBM Corp., Armonk, NY).

The patient demographics and clinical outcomes are presented in ***Table* I**. The durations of intravenous and oral antibiotics in group 2 were 3.95 and 5.8 days, respectively. Nine patients in group 1 developed postoperative complications, including 7 wound infections and 2 intra-abdominal abscesses (P<0.0001 when compared to group 2). Three of these patients visited the ER because of a wound infection or postoperative fever. The two patients with intra-abdominal abscess were re-admitted. Therefore, the total admission duration ranged from 4-16 (mean, 8.89) days. The total cost increased significantly to $3613.34 (mean, $1824.00; P=0.03) in patients with infectious

Table I Characteristics of Children With Complicated Appendicitis

Characteristics	*Group 1 (n=42)*	*Group 2 (n=45)*
Age, y	11 (4.13)	11 (3.87)
Weight, kg	42.49 (18.72)	42.78 (16.64)
Males	57%	64%
CRP, mg/dL	13.81 (11.26)	12.78 (10.14)
Admission, d	7 (1.93)	6.84 (1.25)
Total cost USD*	1507.5 (498.7)	1579.09 (457.3)
Infection[#]	9 (21.4)	0

*CRP: C-reactive protein; *Cost per patient; all P>0.05 except [#]P<0.0001.*

complications compared to patients who recovered uneventfully.

The study limitations were the retrospective, single-centre design and small sample population. Piperacillin-tazobactam has been recently demonstrated to be as efficacious as traditional 3-antibiotic therapy [4,5].

The daily costs of receiving intravenous antibiotics in our hospital in group 1 and 2 were $18.27 and $88.73, respectively, for a child weighing 40 kg. However, we found no difference in cost with the optimum regimen, which is mainly related to the significant decrease in infectious morbidity. Group 2 patients did not require further antibiotic treatment and hospitalization. Generally, the cost of managing infectious complications was significantly higher in our study than in previous studies [6]. Therefore, we have improved the quality of our medical care by the decreasing infection rate without increasing cost.

It is important to use an effective empirical antibiotic to control severe infection, but at the same time, we should prevent antibiotic resistance. Therefore, our principle is to monitor the duration of antibiotic use, which can reduce the possibility of resistance [7]. Therefore, piperacillin-tazobactan was not used for >7 days in our patients.

We suggest that bacterial culture and sensitivity tests should be performed for every case of complicated appendicitis, and antibiotic protocol guided by these reports. Reducing postoperative infectious morbidity in complicated appendicitis using an optimum hospital-based antibiotic protocol can reduce hospital stay without increasing expenses.

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Medical Education During the COVID-19 Pandemic: A Single Institution Experience

Social distancing to curb the COVID-19 pandemic has caused suspension of classroom teaching in all educational institutions. We implemented a novel online classroom platform at our institute to continue medical education. The program attracted encouraging feedback from the students. It may serve as a model for uninterrupted teaching and training during times of crisis.

Keywords: *COVID-19, G Suite for Education, Online classroom*.

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The novel coronavirus (SAR-CoV-2) pandemic has disrupted medical education worldwide [1]. Most of the medical schools have quickly adapted to the online classes with shifting of live clinical exposure with the virtual one. Some schools also echoed concerns over clinical clerkships and assessment during these times. The COVID-19 pandemic represents a transformation in medicine with the advancement of telehealth, adaptive research protocols, and clinical trials with flexible approaches to achieve solutions [2-4]. We herein share our early initial experience of online training of medical students in the setting of COVID-19.

In wake of impending restrictions, we explored available options for online classes and adopted G Suite for Education using Google Classroom coupled with Google Meet for Video-conferencing (*https://edu.google.com/products/gsuite-for-education/?modal_active=none*). A schedule was made and messages were sent to students by email and short messaging service (SMS) to join their respective classes. An orientation program was conducted to familiarize the faculty to this platform. A team of trained faculty members was deputed at the lecture venues to assist and troubleshoot technical issues, if any. Additionally, training videos were shared with faculty members.

In order to minimize excessive data usage by students and preventing high screen time, a four-hour teaching schedule, ensuring a judicious mix of lectures and practical demonstrations/case discussions were employed with a break of 10-15 minutes between sessions. To promote student engagement, and to closely replicate laboratory and clinical environment, short videos on lab procedure and case based clinical examination were prepared and shared on the virtual classroom. To make the session interactive, students were encouraged to use chat-box and switch on their microphones, wherever feasible. Assignments were administered through inbuilt plugins.

A questionnaire was prepared and administered *via* Google forms to the students belonging to different semesters of the MBBS course. The questionnaire was reviewed and validated by the involved faculty members. Participation was voluntary and complete anonymity was ensured. Data was compiled using spreadsheets. Gaussian fit of data was assessed using Kolmogorov-Smirnov test.

Across four batches from second to eighth semester, 398 medical undergraduate students were enrolled in the classes; 208 provided their responses to the questionnaire, with similar proportion across various semesters (44-61%). The detailed responses are depicted in ***Table* I**. The students, based on their quantitative (***Fig.* 1**) and qualitative feedback, appreciated the online platform. Large number of students had not attended any online classes previously. Majority of the students stated that they were given the opportunity to ask questions (92.3%). They believed their interaction with the teacher was better than (27%) or as good as (27.8%) that during physical classroom. The responses across semesters were also uniformly similar.

Interestingly, innovative solutions have emerged whenever such problems have set in during SARS and MRES outbreaks using telephone and virtual environment [5,6], and other adaptations during COVID-19 [7]. While Moszkowicz, *et al.* [8] implemented Google Hangouts for a similar purpose but with only 10 students,

Table I Feedback on Online Teaching by Medical Undergraduates (*N*=208)

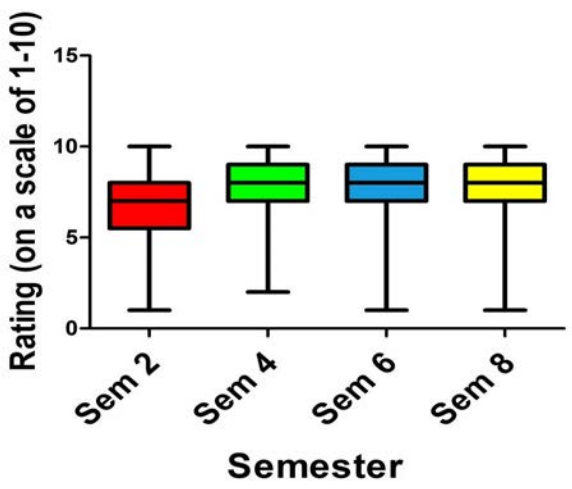
Feedback question	*No. (%)*
Previously attended any online classes	73 (35)
Given the opportunity to ask questions during the e-classes?	192 (92.3)
The material shared before/after e-classes was useful	191 (91.8)
*How do you rate your interaction with the teacher during e-classes?**	
As good as physical classroom	58 (28.0)
Better than physical classroom	58 (28.0)
Poorer than physical classroom	91 (43.9)
Select the statement that applies best to you:	
Physical classes are better than e-classes	106 (50.9)
E-classes are as good as physical classes	56 (26.9)
E-classes are better than physical classes	46 (22.1)

**One student did not reply.*

we conducted concurrent sessions for a large number belonging to four different semesters. Our platform also supported flipped classroom to some extent by providing learning material in advance and promoting student discussion during online sessions [9].

Student feedback revealed some interesting paradox. While appreciative of the platform, nearly 50% of the students still believed that physical classroom was better than e-classroom. However, the reasons for this perception could not be assessed. The study was based on a small sample of students who have anonymously volunteered to provide feedback. Secondly, we had very short time to implement and hence a well-structured training program for faculty could not be done. This was; however, circumvented to some extent, by the ease and self-explanatory nature of the platform, a short explanatory video and provision of technical support at lecture venues. Furthermore, majority of our teachers got adapted to this forum after taking a couple of classes.

The novelty of the initiative lies in the swift implementation of this program on a large scale both for the students and for faculty members. Another study from India has previously reported using the same platform, but restricted to a single specialty [10]. We believe our early experience can serve as a model for educational institutes looking for continuing medical education in situations that disrupt traditional teaching.



Number of students in II, IV, VI and VIII semesters was 61,47,44 and 56, respectively.

Fig. 1 *Rating of online classes during COVID-19 pandemic by medical graduates of different semesters on a Likert scale of 1-10.*

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Incomplete Kawasaki Disease in a Child with COVID-19

We report a case of incomplete Kawasaki disease in a child who also tested positive for COVID-19. This case brings attention to the diverse presentation of coronavirus disease (COVID-19) disease in children.

A 5-year-old previously healthy African American male was admitted to the Pediatric inpatient floor with daily fever up to 39.4°C for 8 days. He had a history of rash, swelling (palms and soles), conjunctivitis, decreased appetite, diarrhea, dysuria, and abdominal pain. He had been treated with cefdinir for positive rapid streptococcal antigen test four days before, without clinical improvement. Physical examination showed dry, cracked, erythematous lips, non-exudative conjunctivitis, and bilateral shotty cervical lymphadenopathy but no rash. He had right scrotal edema and hydrocele suggestive of epididymo-orchitis on ultrasound. Clinically, he met the criteria for incomplete Kawasaki disease (KD).

Initial laboratory workup was significant for leukocytosis (white blood cells 40,000/cumm), anemia (hemoglobin 8 g/dL), thrombocytopenia (platelet count 104,000/cumm), elevated inflammatory markers (ESR 72 mm, CRP 25.6 mg/dL, procalcitonin 27 ng/mL, ferritin 1030 ng/mL), hyponatremia (serum sodium 121 meq/L), pyuria, hypoalbuminemia (2 g/dL), elevated liver enzymes (ALT 55 U/L), elevated troponins (0.06 ng/mL) and negative rapid influenza A/B antigens. Chest *X*-ray showed an enlarged cardiac silhouette (***Fig.* 1**). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was detected on RT-PCR from his nasopharyngeal swab. Echocardiogram showed a small global pericardial effusion but no ectasia, dilation, or aneurysm formation of coronary arteries (***Fig.* 2**).

He was transferred to the pediatric intensive care unit because of hypotension. He received fluid boluses and intravenous immunoglobulin (IVIG) therapy was begun, which had to be discontinued because of recurring hypotension. He was briefly supported with high flow nasal cannula up to 10 liter for tachypnea and increased work of breathing, which was weaned-off. Once he was hemodynamically stable, IVIG infusion was resumed slowly at 5 grams over 10 hours (2-5 mL/minute) for 6 doses for a total dose of 30 grams (1.8 g/kg) [1] with a

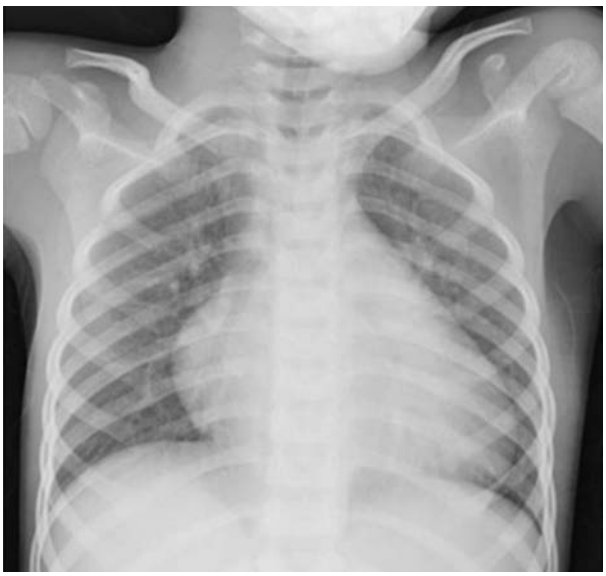

Fig.1 *Chest radiograph showing enlarged cardiac silhouette.*

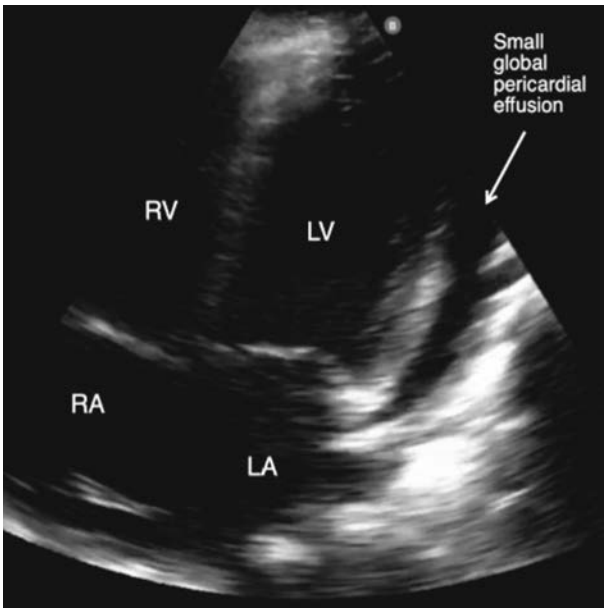

Fig. 2 *Apical four chamber view of a two dimensional echocardiogram of the patient showing a small global pericardial effusion. LA-Left Atrium; LV-Left ventricle; RA-Right atrium; RV-Right ventricle.*

different formulation, after pre-medicating with diphenhydramine and methylprednisolone (only for the first dose) and started on medium-dose aspirin (~39 g/kg/day).

The patient recovered on the pediatric floor with supportive therapy for COVID-19 [3] and was discharged after 6 days in the hospital. Hypotension with elevated inflammatory markers in patients with KD are the manifestations of KD shock syndrome (KDSS) [4]. Association between COVID-19 and KDSS [5] has been speculated, but warrants further investigation.

Adverse effects to IVIG infusion commonly include hypotension and anaphylactic reactions. This can be treated with steroids and antihistamines as pre-medication. However, there is a weak recommendation regarding avoidance of steroids in patients with COVID-19, with some indirect evidence of disease worsening [2]. Readers need to be aware of co-occurrence of Kawasaki disease with COVID-19, and the associated management issues.

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Hyper-inflammatory Syndrome in a Child With COVID-19 Treated Successfully With Intravenous Immunoglobulin and Tocilizumab

Coronavirus disease (COVID-19) in children appears to be largely a benign condition. However, there are reports of children presenting significantly unwell across Europe and USA in the last couple of weeks with a new multisystem inflammatory syndrome [1]. We report a child with COVID-19 who had overlapping features of Toxic Shock Syndrome (TSS) and Kawasaki disease (KD).

A previously well, eight-year-old boy presented with fever, cough and throat pain. He was admitted to a local hospital on day 4 of illness in view of high-grade fever spikes. Investigations showed neutrophilic leukocytosis (total white blood cell count 23,000/µL, Neutrophils 89%) with raised acute phase reactants (C-reactive protein, CRP 120 mg/L). Chest *X*-ray showed right upper and middle lobe infiltrates. Reverse transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory illness novel coronavirus 2 (SARS-CoV-2) was negative. Treatment was empirically started with ceftriaxone and azithromycin. Despite treatment for three days, he continued to have high fever, worsening respiratory symptoms and was referred to our hospital.

On arrival, he was alert, had respiratory rate of 50/min, intercostal retractions and was maintaining SpO_2 in room air. He was febrile with tachycardia (HR 160/min), hypotension (80/31 mm Hg), warm extremities and a capillary refill time of 3 seconds. He was also noted to

have a generalized non-pruritic erythematous skin rash, non-purulent bulbar conjunctivitis, cracked lips, strawberry tongue, edema of limbs, tender hepatomegaly and abdominal distention. Investigations in our hospital showed haemoglobin of 8.9 g/dL, neutrophil predominant leukocytosis (total count 17,600/µL, 86% neutrophils), platelet count 3,95,000/µL, markedly raised CRP (317 mg/L), raised erytherocyte sedimentation rates (115 mm/h), hyper-ferritinemia (Ferritin 1,496 ng/mL), hypoalbuminemia (2.6 g/dL), hyponatremia (133 mEq/L), normal kidney and liver function, and 2+ proteinuria. He was given a fluid bolus and treatment empirically started with piperacillin-tazobactam and doxycycline. When reassessed after 30 minutes, he was febrile, hypotensive and had increased work of breathing. He was shifted to the pediatric intensive care unit. The initial differential diagnoses were pneumonia with septic shock, COVID-19 penumonitis, KD and TSS. High-flow nasal cannula (HFNC) support was started and antibiotics were modified to meropenem, vancomycin and clindamycin. The blood pressure was stable and urine output was normal. Intravenous Immunoglobulin (IVIG) was given (2 g/kg) with aspirin (75 mg once-a-day). Echocardiogram did not show any abnormalities and repeat chest *X*-ray showed increased right-sided infiltrates. Repeat nasopharyngeal COVID-19 RT-PCR was positive. Multiplex PCR of nasopharyngeal aspirate (BioFire FilmArray) detected Coronavirus OC43 and Human Rhino/Enterovirus. As he improved, he was gradually weaned off HFNC. Blood cultures showed no growth and antibiotics were changed to ceftriaxone. In light of the persistent high-grade fever and elevated CRP (121 mg/L), 72 hours after IVIG infusion, he was given tocilizumab (8 mg/kg IV over 2 hours). Twelve hours later, his fever spikes settled, and inflammatory parameters rapidly decreased to baseline (***Fig.* 1**). He was noted to have periungual peeling of skin and recovered completely after two weeks of illness.

The clinical characteristics of COVID-19 disease progression and outcome in children and young adults appear significantly milder compared to older individuals [2]. However, there is now a growing recognition of a small number of children presenting with a multisystem inflammatory syndrome. This rare syndrome shares common features with other pediatric inflammatory conditions, including KD, Staphylococcal/streptococcal toxic shock, bacterial sepsis and macrophage activation syndrome. It can also present with unusual abdominal symptoms with elevated inflammatory markers. Recently 8 children have been reported to present with hyper-inflammatory shock [3]. This has been labelled as Pediatric multisystem inflammatory syndrome temp-orally associated with COVID-19 and a case definition has been suggested [1]: a child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features, which may include fulfilling full or partial criteria for KD; exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes; and SARS-CoV-2 PCR testing may be positive or negative

Our case fulfils these criteria. It is likely that cytokine storm (CS) is one of the major causes of acute respiratory distress syndrome (ARDS), multi-organ dysfunction and possibly pediatric multisystem inflammatory syndrome [4]. IL-6 is a key cytokine in this process and few studies suggest that CS is positively correlated with disease severity [5]. Various immunomodulators have been discussed and tried for controlling the inflammatory response [6]. Tocilizumab, an IL-6 receptor antagonist approved by the US FDA for treating of Cytokine release syndrome (CRS), is now in clinical trials for treating severe COVID-19 pneumonia [7]. Tocilizumab blocks downstream signal transduction by binding membrane IL-6 receptor and soluble IL-6 receptor and plays a role in the treatment of CS in COVID-19 [8]. High CRP levels seen in our case shows that this inflammatory syndrome is likely mediated by IL-6. Our case suggests that immunomodulation with IVIG and IL-6 blockade can be an effective therapeutic strategy, which has a scientific rationale. It is clear from Europe and the USA that appearance of this syndrome in children follows the peak of infections in affected areas. The immunopathology behind this phenomenon is yet to ascertained. We believe that children across India may present with this inflammatory syndrome related to COVID-19 in the weeks ahead and would like to highlight this to pediatricians across India. Tocilizumab may prove to be an effective second line agent in IVIG refractory children with COVID-19 hyper-inflammatory syndrome

Though most SARS-CoV-2 infections in children are likely to present with mild features, some may develop a hyper-inflammatory syndrome, which may require treatment with IVIG and Tocilizumab. Pediatricians should be aware of such presentation and immunomodulatory treatment modalities.

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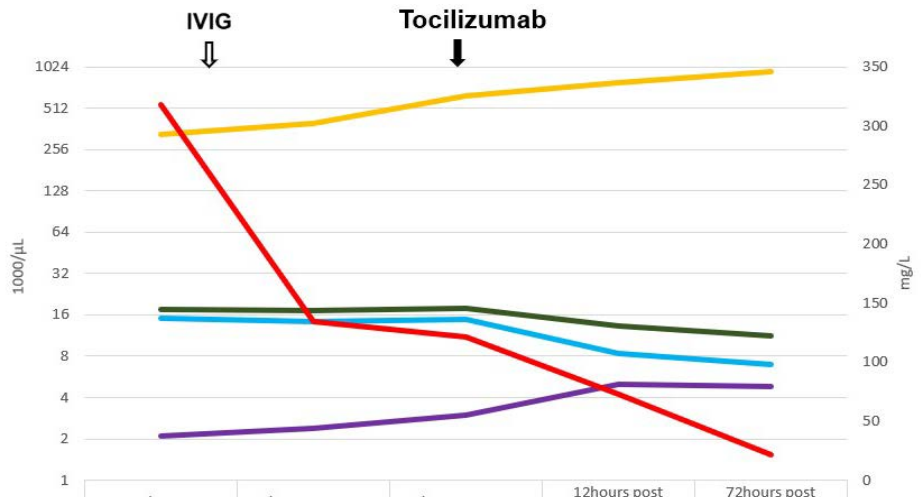

	At admission	24hours post IVIG	72hours post IVIG	12hours post Tocilizumab	72hours post Tocilizumab
TWBC(1,000/µL)	17.6	17.3	17.8	13.2	11.2
Lymphocyte(1,000/µL)	15.1	14.2	14.8	8.3	7
Neutrophil(1,000/µL)	2.1	2.4	3	5	4.8
Platelet(1000/µL)	333	400	630	780	950
CRP(mg/L)	318	134	121	73	22

Fig. 1 *Trend of inflammatory markers in a child with hyper-inflammatory syndrome and COVID-19.*

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Management of Asthma in Children during COVID-19 Pandemic

Coronavirus disease (COVID-19), an acute respiratory infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is presently affecting children and adults worldwide [1]. Asthma is a common respiratory disease in children and may be a co-morbidity in some affected children; we, herein, highlight a few related issues.

Moderate to severe, especially uncontrolled asthma, is considered as an increased risk for SARS-CoV-2 infection, though not reported initially as one of the co-morbidities amongst COVID- 19 patients [2]. However, the data from United States and United Kingdom shows asthma as one of the prevalent underlying conditions in patients with COVID-19 [3,4]. Nonetheless, the evidence is still evolving and is primarily from adults. Experimental studies have revealed that inhaled corticosteroid (ICS) and/or bronchodilator can suppress SARS-CoV-2 replication and cytokines synthesis [5], but its therapeutic implications are still unclear. In children, asthma flare up is usually due to viral infections, and clinically, it is difficult to differentiate these viral infections from SARS-CoV-2 infection [5]. At present, there is no evidence that asthma medications *viz*. bronchodilators, corticosteroid (inhaled, intranasal or oral) or antihistamine can lead to increase risk of severe disease from SARS-CoV-2 infection. Therefore, asthmatic children should continue their maintenance therapy in the same dose, as proper asthma control can prevent unnecessary hospital visits [6].

Spirometry and peak expiratory flow meter (PEFR) should be better avoided during the COVID-19 pandemic, due to the risk of transmission to healthcare staff or other children. If these are essential for some reason, then full infection control should be followed as per the standard guideline [6].

There is tremendous scope of telemedicine in the management of asthmatic children, particularly in follow-up patients. The compliance and technique of a child can be checked and corrected through video conference, and health education provided about the asthma action plan for the worsening of the symptoms, which can reduce non-urgent health care visits to a great extent [7].

Nebulization is considered as a potential risk for aerosol generation and transmission of SARS-CoV-2 infection. Thus, if a child presents with asthma exacerbation, it is recommended to use a pressurized meter dose inhaler (pMDI) with a spacer with a tightly fitted mask for rescue medication. Though there may be concern regarding the use of systemic steroids in the COVID-19 pandemic, Global Initiative for Asthma (GINA) 2020 guideline clearly stated that systemic steroids, if required, should be given in asthma exacerbation for a shorter duration [8].

Emphasizing general precautions to all asthma patients and their caregivers should, of course, continue during outpatient visits or telemedicine consults.

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COVID-19: Important Issues for Pediatricians

Choudhary and Goyal [1] have raised important issues regarding issues affecting children during the SARS-CoV-2 pandemic. We wish to highlight two additional issues related to the pandemic and the resultant lockdown.

A large number of children are likely to miss out on vaccinations due to postponement of campaigns and interruptions in routine vaccinations [2]. The Strategic Advisory Group of Experts (SAGE) on immunization recommended that all mass vaccination campaigns should be discontinued but routine immunization should continue where possible [3]. In keeping with this, the Indian government has issued guidelines advising continuation of routine immunization activities and the Indian Academy of Pediatrics – Advisory Committee on Vaccines and Immunization Practices (IAP-ACVIP) has issued guidelines for pediatricians in private practice [4,5].

The immunization activities are mainly being carried out in fixed facilities with strict guidelines on hygiene and social distancing. Reduction in outreach immunization activities is likely to have an immediate impact on vaccine coverage. Health workers are involved in COVID-19 pandemic management, with decreased manpower available for routine immunization. The supply chain is also under strain due to transport disruptions. As immunization campaigns have been suspended, there will be a need for 'catch-up' campaigns, to identify those who missed their immunizations, as soon as the campaign is restarted.

The private sector is an important provider of immunization services in India. Reasons for the impact on immunization in private practice are lack of PPE for clinic staff, unavailability of vaccines and parent's inability to travel to clinic due to lockdown. Apart from the suggestions given by IAP-ACVIP [5], establishing a common 'community clinic' run by practicing pediatricians by rotation to offer vaccination and other services may also be explored. Moreover, electronic media and social media can be used to highlight the importance of continuing routine immunization services.

Another important issue is child abuse identification and prevention during the lockdown. During lockdown, children do not have access to any outside person to talk about the abuse that they face. They may be denied access to phone or any other mode of communication. Child Line services reportedly have a 50% increase in calls, many of them reporting child abuse [6]. The government has made efforts to ensure access to critical services such as healthcare, nutrition, food security, mental health and psychosocial support and protection against violence. Pediatricians need to be alert to the increased possibility of child abuse during the lockdown, and should report and liaison with the government authorities.

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Renal Complications in Children with Hematotoxic Snakebite: More Information Needed

We read with interest the recent article on renal complications in children with hematotoxic snakebite by Islam, *et al*. [1]. We herein wish to raise some pertinent issues to assist in better understanding of this article.

(*i*) Though the aim of the study was to ascertain clinical and laboratory indicators predicting acute kidney injury (AKI) "early" in children with snakebite envenomation; these predictors have neither been mentioned in the results nor in tables, unlike an earlier study [2], where various clinical and laboratory parameters were reported as predictors.

(*ii*) There is no mention of baseline hemoglobin, maximum fall in hemoglobin, serum lactate dehydrogenase, evidence of myoglobinuria, hemodynamic status, cardiac dysrhythmias, cardiac dysfunction, evidence of adrenal hemorrhage, blood pressure, creatinine etc. which would have helped interpret the results better. These would have looked at creating a list of predictors of renal complications too [2]. Similarly, AKI could have been due to numerous other confounders like shock, dehydration, nephrotoxic antibiotics adminis-tration etc., which have not been detailed. Similarly, whether drug dose adjustments were made in those with AKI has also not been mentioned.

(*iii*) AKI was appropriately defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [3]. However, these patients were then followed up for 6 months [1], the reason for which is not clear, because for labelling chronic kidney disease, a 3-month follow-up would have been enough.

(*iv*) Though one of the criteria for dialysis mentioned in this study was hyperkalemia, but the reason why medical management was not considered as an option is not apparent. Similarly, other reasons for dialysis like uremia, refractory metabolic acidosis too may have been indications for dialysis in these patients, which probably have not been included.

(*v*) It was mentioned in the methodology that "peritoneal dialysis was done in the institution and hemodialysis in a referral hospital". Whether these children were excluded or followed up is not clear. Details of how these children were followed up are missing. How many of these children who underwent dialysis developed 'permanent renal damage' at the 6-month follow up too has not been mentioned by authors, which could have been new information for the readers.

(*vi*) Similarly, it is not clear as to whether the authors had taken the AKI stage at presentation or the maximum AKI stage as per the KDIGO guidelines during the hospital stay.

(*vii*) What were the indications and timing for the renal biopsy? Was doing a renal biopsy in the setting of an AKI reasonably justified and ethically correct? Snake-bites being medicolegal cases, it looks improbable that a renal biopsy was possible in 100% of the children who died but in only 81.4% of those who survived.

(*viii*) It is mentioned that 59 out of 364 children (16.2%) had "permanent renal damage" [1]. This is inappropriate as the denominator should exclude the deaths as permanent renal damage can be assessed only in those who survived the episode. So, we feel that the 16 children who succumbed should have been excluded, thus increasing the percentage of children with permanent renal damage to 16.9%.

(*ix*) We presume that the median number of vials of anti-snake venom (ASV) used in both groups have been mentioned in Table I [1]. It may have been appropriate to have also mentioned the mean value, which would have added more clarity to the renal outcomes.

(*x*) In the results, the authors state "our model can correctly predict 67.2-78.9% variation in AKI and 53.1-61.7% variation in mortality." However, it is unclear which model they are referring to?

(*xi*) The authors have mentioned mean "bite to ASV administration time" as 36.4 (5.9) minutes which seems practically difficult as their study population included patients from faraway places like the neighboring states of Bihar and Jharkhand. Besides, the whole blood clotting time itself takes 20 minutes to process after which the ASV must have been administered as per standard practice, which further delays the time to ASV administration. Hence, the mentioned time does not appear to be possible in these settings, as also seen in a previous study from the same region where this interval was 270 minutes [4].

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AUTHORS' REPLY

We thank the readers for their interest in our study [1]. Our replies to the queries are as under:

(*i*) Different clinical and laboratory parameters were already described in table I and II of the article, and some of the determinants are similar to previous reports [2]. Reasons for discrepancy with published literature were mentioned in the discussion section of the article.

(*ii*) Detailed baseline data were collected, but all of it could not be presented due to limitation on the size of the manuscript. Serum LDH and adrenal hemorrhage were not assessed in our study. We appreciate your concern about cardiac dysfunction, hemodynamic status etc, but different parameters (requirement of ventilation, serum potassium level, requirement of inotropes) mentioned in table I act as surrogate markers of them. We used logistic regression and adjusted odds ratio to remove confounders. Nephrotoxic drugs are avoided in viper-bite patients according to unit protocol in our set-up.

(*iii*) In a previous research project in the same setting, the investigators noted some long-term toxicity of snakebite, as also previously reported [2]. Hence we decided on a follow-up period of 6 months.

(*iv*) In the paper, we had mentioned the unit protocol for dialysis. Opinion of a nephrologist was sought before starting dialysis in all patients.

(*v*) All study patients were followed up at our nephrology specialty clinic after discharge from hospital.

(*vi*) If at any point of time during the hospital stay, the children developed AKI, we included them in the AKI group. The initial version of the manuscript had information on AKI grades, but it was later edited out on the suggestion of reviewers.

(*vii*) We did not perform renal biopsy in AKI settings. We considered renal biopsy in the children who developed permanent renal damage, as per opinion of nephrologist. Before doing renal biopsy, we took informed written consent from parents.

Snake bite, being a medicolegal case, autopsy is done in every death. Samples from viscera are also routinely collected by forensic expert. We could convince parents of all such children for consent for renal histopathology examination.

(*viii*) We used the study population as denominator because we want to identify renal complication in children with hematotoxic bites, not in the surviving children.

(*ix*) As the data are skewed, we had summarized it as median and interquartile range [1]. The mean (SD) number of vials required were 12.3 (9.1) and 21.5 (18.9) in AKI and no AKI groups, respectively.

(*x*) It is the regression model used in the study.

(*xi*) The mentioned time is only for those who did not develop AKI; it was higher for those who developed

AKI (74.5 minutes) [1]. If we consider all children, mean time between bite and ASV administration was 51.2 minutes. Moreover, many of the children received the first dose of ASV at the place of initial medical care, before referral to our center. The study referred to by the readers was conducted in 2012-2016 and included both children and adults [3]. Due to the sustained awareness campaigns and easy availability of ASV, bite to needle time is gradually decreasing. Transport vehicles are also easily available for children under different government schemes. Moreover, our study included children with viper-bite only, which is symptomatic at early stage leading to early seeking of healthcare.

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Response to Journal Club: Cluster Randomized Trial Evaluating Impact of a Community-based Microfinance Scheme on Childhood Nutritional Status: Evidence-based Medicine Viewpoint

We read, with interest the Evidence-based medicine viewpoint [1] on our recent publication [2]. The author of the viewpoint has made some notable points about the methodology, most of which were already acknowledged in our paper. The viewpoint includes some interesting observations that appear to be based on selective use of the data and has some key errors, which we wish to highlight.

(*i*) *"Although a research question was not articulated…"* The study hypothesis is clearly stated in the last sentence of the introduction.

(*ii*) *"The investigators chose a cluster RCT design… It is difficult to judge which of the two designs is superior to compare community effects through individual empowerment of some members…"* A cluster randomized design is the appropriate approach when the intervention is delivered at the level of the local population (*tola*). Individual randomization is not possible when the intervention is delivered to a group (the self-help group).

(*iii*) *"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 allocation concealment…"* There was complete allocation concealment as the *tola*s were assigned a code number and randomization took place in Nottingham with the local trial team informed only after randomization had taken place. Having the local team toss a coin would of course prevent allocation concealment.

(*iv*) *"It is also unclear what proportion of the children whose baseline data were collected, underwent data collection at the end of the study."* This is stated in table 2 of the paper *e.g.* of 1377 children with baseline data for WHZ, 559 were followed up longitudinally with further data at 18 months [2].

(*v*) *"First, it assumes that under natural circumstances, children's nutritional status declines over time. However, the authors showed no data supporting this presumption."* Nutritional indices deteriorated amongst children in both arms of the trial and this is a large sample. In these rural communities in Bihar, we have shown that nutritional status does decline over time.

(*vi*) *"…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)."* On referring to figure 3 of the paper [2], we see that two of the top three reasons for taking loans were medical expenses and working capital for agriculture. Both of

these expenditures will have increased resilience to food insecurity.

(*vii*) *"It should be remembered that children in the Intervention arm had superior HAZ than those in the Comparison arm."* Nutritional disadvantage was seen in both the intervention and control groups at baseline - significantly more children were wasted in the intervention arm (20%) *versus* controls (15%).

(*viii*) *"However, the proportion of participating women in each tola were not described, hence this assumption could be too simplistic."* This is clearly stated in the online supplement (which is signposted in the main manuscript). *"In the intervention group, 35% of women overall (median by tola 37%, IQR 8% - 59%) reported being members of a Rojiroti SHG. In control tolas, 29% of women overall (median by tola 24%, IQR 0% - 54%) reported being a member of a non-Rojiroti SHG."*

We acknowledge that childhood malnutrition is a multi-factorial problem but the link between social and economic well-being and health is well documented. A multi-sectoral approach that addresses all the determinants (such as social, economic, cultural, and commercial) of child health and wellbeing is key to the integrated approach to health as promoted by the UN Sustainable Development Goals [3]. Our study is the first randomized controlled trial that focused on the effect of microfinance on child health [4]. Despite its limitations, it is a vital step toward achieving this joined-up thinking. The abovementioned shortcomings in the viewpoint [1] undermine the assertion that *"…it is difficult to draw firm conclusions from this trial or recommend further similar studies."* On the contrary, we believe the time is now right for scaling up the program within Bihar and neighboring states, whilst evaluating the intervention in settings where cultural practices, climate and agriculture differ.

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AUTHOR'S REPLY

I thank the authors of the article [1] for their interest in our journal club discussing the same [2]. The points raised by the authors are based on selective interpretation of their own data [1] and selected quotes from the Evidence-based viewpoint [2]. Hence, none of the points change anything in the critical appraisal commentary [2]. Responses to specific points in the correspondence are as follows:

(*i*) 'Study hypothesis' is not synonymous with 'Research question'. Besides the fact that the latter includes five elements of the PICOT frame-work, it starts from a position of clinical equipoise (*i.e.* the investigators do not pre-assume that the intervention will be beneficial). Thus the 'Research question' sets the tone for the methods used in a study, and is a touchstone for readers/appraisers to judge its validity. It has been previously pointed out that the "science of evidence-based medicine hinges on the art" of framing appropriate questions [3].

(*ii*) It has already been emphasized [2] that a cluster RCT is the ideal design when either the intervention or outcomes or both, are expected to spill over into/onto those who are not randomized (but are present in the cluster). In this study [1], it is difficult to judge *a priori* whether the intervention (microfinance scheme support to individual women in certain households in a cluster) or outcome (nutritional parameters in their offspring) could have a spill-over effect on mothers (who did not receive the financial support) or their offspring, in which case an individually randomized trial would be more appropriate.

(*iii*) The study [1] mentioned that "*tola*s of similar size were paired" and those "in each pair were randomly assigned". For instance, if *tola*s 'A' and 'X' were paired and one of these was randomly assigned to a group, it follows that the other member of the pair would have to be assigned to the other group. This precludes any scope for allocation concealment. Thus one member of the pair would have a 50% chance of being assigned to either group, whereas the second member would have a 100% chance of being assigned to the other group. This is akin to using a coin-toss to randomize a pair of participants.

(*iv*) In this study [1], not all children who were present at

baseline were available for follow-up at 18 months; and not all children whose 18 month data were collected, had data collected at baseline. Thus, children whose data were collected at 18 months of age (presented in table 2 of the article) [1], comprised an unknown proportion of those who were present at baseline, plus an unknown proportion of those who were not present at baseline.

(*v*) The authors [1] found that children in the comparison group fared worse than children in the intervention group. Notwithstanding the methodological limitations compromising validity, they assumed this to mean that under natural circumstances, nutritional status of children would decline, and the intervention partially mitigated this. But they have not provided any data from any study, anywhere in the world, that can support this view. This suggests that the explanation offered for the unusual finding in this study [1] is erroneous. This view is strengthened by the other points mentioned in the commentary [2].

(*vi*) Figure 3 in the study [1] shows that only about 12% of the loans were for 'food and supplies' and the total amounted to less than Rs. 10,000 across the *tola*s. In the face of food insecurity (*i.e.*, starvation), one would expect people to take loans to purchase food (to tide over the immediate scarcity) rather than invest in capital for agriculture or medical supplies (that have no short-term impact on starvation).

(*vii*) The table of baseline characteristics in the study [1] showed statistically significant differences in three anthropometric parameters between the intervention and comparison groups. Two of these were better in the intervention group viz HAZ (*Z* score -2.00 *vs* -2.14) and proportion with MUAC <12.5 cm (13% *vs* 16%). In contrast, the proportion with wasting was higher in the intervention group (20% *vs* 15%). These data suggest that children in the intervention group had (statistically) better HAZ. Since height *Z* score is an indicator of longer-term nutritional status and does not decline immediately in acute malnutrition (unlike wasting or MUAC), it suggests that children in the interventional group had a statistically superior indicator of longer-term nutritional status (at baseline).

(*viii*) Since only one-third of the mothers in the intervention group actually received the intervention, it is difficult to believe that the comparable outcomes in offspring of those who did (and did not) receive the intervention was based on a spillover effect. The authors have not demonstrated how/why financial empowerment of a limited number of women in the community could create a spillover effect to other mothers and families.

In summary, methodological limitations compromise the validity of the trial [1], and the authors' recent comments do not change the viewpoint that this trial is insufficient to support further similar studies or launch a community-wide intervention with the specific microfinance scheme described (for the purpose of improving nutritional status of children). Whether the scheme could have any other positive social or cultural or health-related impact, is outside the scope of discussion.

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Acute Peritoneal Dialysis in Premature Infants: Few Concerns

We read with great interest the recent article by Okan, *et al*. [1] published in *Indian Pediatrics* which concluded that peritoneal dialysis (PD) is technically feasible in very low birthweight (VLBW) and extremely low birthweight (ELBW) neonates despite a high mortality rate in the studied population (81%). We also agree that peritoneal dialysis in neonates, and particularly in preterm neonates, is challenging and is still evolving with only few anecdotal case report and case series till date indicating its feasibility in preterm neonates. Further, due to the physiological compromise (small size, poor hemodynamic stability and tendency of coagulopathy), overall prognosis in preterm neonates undergoing peritoneal dialysis is grimmer as compared to their term counterparts as well as older

children. This study was need based and addressed a very important and clinically relevant issue. However, we have few concerns related to the article which we would like to get the clarification from the author.

1. In Table I of the article, we were intrigued to note that patent ductus arteriosus (PDA) led to acute kidney injury on day 1, and that too requiring PD [1]. We would like to know the exact clinical/ laboratory criteria for doing peritoneal dialysis in that baby.

2. Many babies (50% of the study population) had undergone PD due to necrotizing enterocolitis (NEC) as one of the underlying causes (***Table* I**) [1]. The result section also mentions that 5 (23.8%) of babies had perforated NEC (stage IIIb) [1]. As the presence of NEC, particularly perforated NEC is a contraindication to do PD [2], why was it carried out in these babies? This is important, as approximately 80% of the babies who had undergone PD with NEC as underlying cause, ultimately died [1].

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AUTHORS' REPLY

We would like to thank the authors for their interest in our article [1]. The comprehensive criticism of methodological and pathophysiological issues presented in their letters provides an illuminating framework for our study. We would like to offer some clarifications regarding the points they have raised.

Peritoneal dialysis was indicated according to the Neonatal RIFLE Criteria for acute kidney injury (AKI) [2] *i.e.*, oliguria/anuria (urine output of <0.7 mL/ kg/h for 24 h or anuria for 12 h), failure of conservative treatment (furosemide or water restriction in cases without hypovolemia), signs of uremia (impaired cardiac and respiratory functions, or seizures), refractory hyperkalemia, metabolic acidosis or fluid overload. In our study, the patient who was started peritoneal dialysis (PD) at the earliest time had a gestational age of 27 weeks and weighed 1060 g, with a hemodynamically significant patent ductus arteriosus (PDA) and history of anhydramnios. PD was initiated at the end of the first day of life for anuria, failure of conservative treatment, signs of uremia and was performed for four days. Urine output was obtained on the third day of life. The patient responded successfully to PD and survived thereafter. The literature on AKI in premature infants with a diagnosis of necrotizing enterocolitis (NEC) is limited. The incidence of AKI in NEC is very high and the mortality is two-fold higher than of infants with no AKI [3]. Downard, *et al*. [4] demonstrated in rat pups with NEC that the utility of direct peritoneal resuscitation (DPR) increases the intestinal blood flow significantly and speculated DPR may be a novel strategy to improve intestinal blood flow in NEC. Another study [5] reported that topical 1.5% dextrose solution enhanced significantly the blood flow in the terminal ileum to the same degree as 2.5% dextrose solution in Sprague-Dawley rats. Direct peritoneal resuscitation as a treatment modality is applicable in any disorder with decreased intestinal blood flow. The maintenance of intestinal blood flow takes control of the multisystem inflammatory response and decreases the overall risk of multiple organ dysfunction and death [5]. Peritoneal dialysis is also an alternative and rescue method to treat infants with NEC complicated with intestinal perforation. Peritoneal dialysis can be used as a type of peritoneal lavage in NEC for the removal of inflammatory cytokines, toxins, and may help in remodeling and healing of intestine [6]. We reiterate that initiation of early PD in sick extremely low birthweight infants with NEC and AKI may save lives [7].

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Effect of Rehydration Fluids on Serum Sodium Levels in Children With Acute Diarrhea

The recently published research article in the journal [1] on the above topic addresses an important 'felt-need' of the practicing pediatricians. We wish to seek clarifications on certain issues.

In this study the children of infantile age group, particularly those between 6 to 12 months, were excluded. This age group contributes to almost half of the disease burden of rotavirus associated diarrhea [2]. Further, severe dehydration is more commonly seen with cholera than rotavirus diarrhea [3]. Thus, stool culture for *Vibrio cholera* or a rapid card kit test for rotavirus could have been beneficial and would have added value to the present study.

Authors have mentioned that patients with systemic illnesses were excluded from the study, but the nature of these systemic illnesses was not clearly elucidated. Conditions like diabetic ketoacidosis, diabetes insipidus, burnsetc can also lead to dehydration in children. Whether diarrhea in these children was accompanied by any of the above mentioned conditions was not clarified [4].

Whether the mean duration of symptoms were considered from the beginning of the illness or after admission of the patient to the hospital needs to be elaborated as majority of the children enrolled in the study had acute asymptomatic hyponatremia [1].

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AUTHORS' REPLY

I thank the authors of this correspondence for the keen interest shown in our work [1]. Infants between 6-12 months were excluded in our study by trial design. The infants with severe dehydration in this age group would have required intravenous rehydration over 6 hours as per World Health Organization plan C of dehydration managemnt, and this would have created heterogeneity in terms of time to rehydration and the fluid calculations at time of analysis. Infants with dehydrating diarrhea are also deemed to be at higher risk for comorbid systemic illnesses like infections and dyselectrolytemia like hypernatremia, which necessitate individual fluid calculations and resultant exclusion of trial subjects.

Although, cholera leads to more severe dehydration compared to rotavirus diarrhea, the etiological agent of diarrhea does not determine the choice of fluid for the management of severe dehydration. We had hypothesized the equivalence of the two fluids *i.e.,* Normal saline or Ringer lactate in terms of electrolyte change, irrespective of the etiology.

A thorough history and detailed clinical examination was performed in all subjects to exclude cases with known renal, metabolic and endocrine disorders. The blood sugar, serum electrolytes, renal function tests and arterial blood gas sampling was done for all subjects. None of cases enrolled had hyperglycemia, persistent metabolic acidosis/alkalosis, severe dyselectrolytemia and continued need for intravenous fluids after the correction of diarrhea potentially excluding the renal, endocrine and metabolic disorders. No child with pancreatitis or burns was included in our study.

The duration of symptoms was from the time of onset of diarrhea and not time of hospitalization. A relatively high proportion of children with hyponatremia could be explained by the secretory diarrhea like presentation due to the referral pattern of the study site.

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KEY JOURNAL PAPERS RETRACTED

The paper published in the *Lancet* on May 22 which suggested that hydroxychloroquine may be harmful has been retracted by the journal. The paper was based on data from a multi-national registry collected by a less known company called Surgisphere. Sapan Desai, one of the authors of the paper is the chief executive of the company. *The Gaurdian*, Australia pointed out some discrepancies in the mortality data from Australia published in the paper. It had mentioned 73 deaths till 21 April while the John Hopkins database mentioned only 67 deaths.Following this, it came under further scrutiny by other researchers. Three of the lead authors asked for an independent review of the integrity of the data. However, Surgisphere refused to supply the raw data stating violation of client agreements and confidentiality agreements.

Subsequently, reviewers decided to withdraw from the peer review and three of the authors of the paper wrote to the *Lancet* requesting that the paper be retracted. Two other papers based on data supplied by Surgispherewere also affected. The *New England Journal of Medicine* has since retracted the paper analyzing the risk of COVID-19 infections in patients on angiotensin receptor blockers. The other paper was a preprint on the efficacy of ivermectin in SARS-CoV-2.
(Science 2 June 2020)

RESILIENCE DURING THE PANDEMIC

The stressors in this pandemic are multiple. There is the fear of an invisible enemy, the loneliness of quarantine and social distancing as well as economic anxieties. The European College of Neuropsychopharmacology has discussed the various strategies studied in literature to develop resilience in the face of stress. We must emphasize promoting social connectedness. Self-care including exercise and nutrition are paramount in reducing stress. Developing a daily schedule and taking regular media breaks will also help. Besides these evidence-based interventions to promote resilience at the personal and community level, attempts at an existential level to deliberately considering the future narrative of humankind is discussed in a thoughtful article in the *JAMA.*

Clear and consistent communication from the government, medical societies and scientific organizations will help to keep the society together.
(JAMA 3 June 2020; European Neuropsychopharmacology June 2020)

TELEMEDICINE GUIDELINES- INDIA

The Government of India has published telemedicine guidelines which will apply to all Registered Medical Practitioners (RMP). They will be soon developing an online program to help doctors become familiar with the procedure. It will be mandatory to undergo that training within 3 years of its development.

According to these guidelines all doctors can now practice telemedicine using chat platforms like WhatsApp or internet-based digital platforms or even email or Skype. The mode of communication may be video, audio or even text. An RMP may even provide emergency consultation to the best of his judgement but he must advise them to meet a doctor in person at the earliest. He/she must use his professional judgement to see whether a telemedicine consultation is appropriate in the given situation and not compromise on quality of care provided.

In every consultation he must verify the identity of the patient including his age, address, telephone number etc and must also display his own registration number. Patient consent is required for tele-consultation. The doctor can provide a prescription *via* teleconsultation, except forSchedule X drugs.The RMP is also to maintain a record of all teleconsultations including patient details and is free to charge an appropriate fee for the consultation.

The guidelines are timely and will be useful for all practitioners, especially during the current pandemic.
(https://www.mohfw.gov.in/pdf/Telemedicine.pdf)

POCUS- FOR RAPID DIAGNOSIS OF COVID19

Hand-held Point of care ultrasound devices (POCUS) are helping doctors to triage and monitor patients with SARS-CoV-2 pneumonia. Results are quick and there is no need to shift an infected patient through the hospital to the radiology department. These comprise of a small probe that sends ultrasound images to a phone or a tablet.

It was invented by a scientist and entrepreneur Jonathan Rothberg when his daughter needed regular ultrasound examinations for a renal mass. He invented the ButterflyiQ a POCUS device which connects the probe to the phone *via* an app. Today its use has spread to many ICUs and there is even a free online teaching course for lung ultrasounds in COVID-19 by an e-learning company called iTeachU. Normal lungs have horizontal 'A' lines which are a repetitive reverberating artefact of the pleura. In patients with interstitial edema,vertical pathological 'B' lines appear.

Its use in pediatrics in the current pandemic has also been described in a brief article in the Lancet. Its low cost and easy portability make it very attractive in today's time.
(Lancet Respiratory Medicine 1 May 2020; Scientific American 11 June 2020)

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Theme: Neurology and Development

Established status epilepticus treatment trial (ESTT) (*Lancet. 2020;395:1217-24*)

Currently, there is a lack of good quality evidence for the second line anti-seizure medications in the management of status epilepticus. The researchers of this multi-center, double-blind, response-adaptive, randomized controlled trial, done in 58 hospital emergency departments across the USA enrolled 462 patients (224 aged 2-18 years). Patients were eligible for inclusion if they had been treated for a generalized convulsive seizure of longer than 5-min duration with adequate doses of benzodiazepines, and continued to have persistent or recurrent convulsions in the emergency department for at least 5-min and no more than 30 min after the last dose of benzodiazepine. The primary outcome of absence of clinically apparent seizures with improved consciousness and without additional anti-seizure medication at 1-h from start of drug infusion was achieved in 52% (95%CI 41–62%) of children receiving levetiracetam, 49% (38–61%) receiving fosphenytoin, and 52% (41–63%) getting valproate. No differences were detected in efficacy or primary safety outcome (life-threatening hypotension or cardiac arrhythmia). Endotracheal intubation of children occurred more frequently in the fosphenytoin group (33%)than in levetiracetam group (8%) or valproate group (11%). Any of the three drugs can be considered as a potential first-choice, second-line drug for benzodiazepine-refractory status epilepticus.

Levetiracetam*versus* phenobarbital for neonatal seizures (NEOLEV2) (*Pediatrics. 2020;145:e20193182*)

Phenobarbital and phenytoin frequently fail to control neonatal seizures and there are concerns about the safety of these anti-seizure medications in the developing brain. Levetiracetamis increasingly being used in neonates without good quality evidence supporting its use. The researchers in this multicenter, randomized, blinded, controlled, phase IIb trial to study the efficacy and safety of levetiracetam (40 mg/kg) compared with phenobarbital (20 mg/kg) as a first-line treatment for neonatal seizures of any cause,analyzed 83 neonates who met the study criteria (53 received levetiracetam and 30 phenobarbitone). The primary outcome measure was complete seizure freedom for 24 hours, assessed by independent review of the EEGs by two neurophysiologists.In the phenobarbital group 80% patients remained seizure free for 24 hours, compared with 28% of patients inlevetiracetam (P=0.001). There appears to be a need for studies with higher doses of levetiracetam and with longer follow-up for adverse effects.

Drugs for acute attack of pediatric migraine (*Clin Neurol Neurosurg.2020;195:105853*)

To know the efficacy of the various drugs for the acute management of migraine in children, a network meta-analysis of high quality trials (6029 migraineurs) randomly assigned to 14 different drugs was done. The outcome measure used was pain-freedom and pain relief at 2 hours post-dose. Sumatriptan nasal spray and zolmitriptan nasal spray were superior to placebo in the two efficacy outcomes, whereas almotriptan, rizatriptan, sumatriptan with naproxen sodium, and ibuprofen were superior to placebo only in one of the efficacy outcomes. In network meta-analysis, the best three treatments for achieving freedom from pain were ibuprofen, sumatriptan with naproxen sodium and ibuprofen suspension. Meanwhile, the best three treatments for pain relief at 2 hours were ibuprofen suspension, ibuprofen, and rizatriptan. In conclusion, in acute treatments of pediatric migraine, most triptans and NSAIDs were effective to achieve pain-freedom or pain-relief.

Prednisolone in autistic spectrum disorder (*J Pediatr (Rio J). 2020:S0021-7557(19)30465-6*)

Autistic spectrum disorder may have an inflammatory or autoimmune etiology as supported by increased risk of ASD in children with a maternal history of rheumatoid arthritis or celiac disease. To study the role of immunomodulation using steroids, the authors designed a prospective, double-blinded, randomized, placebo-controlled clinical trial. Thirty eight boys aged between 3 to 7 years out of 40 enrolled (20 were randomized to the placebo group and 18 to the steroid group receiving prednisolone for 24 weeks, at an initial dose of 1 mg/kg/day and a tapering dose from the ninth week onwards) completed the study. Twenty out of 38 had history of language regression. Language was measured on four occasions over a 12-month period using standardized scales. Though there was no significant change in language score in both groups, there was change in the language scores in younger children and in those with language regression. More studies are needed to address the role of immunomodulation in children with autistic spectrum disorder.

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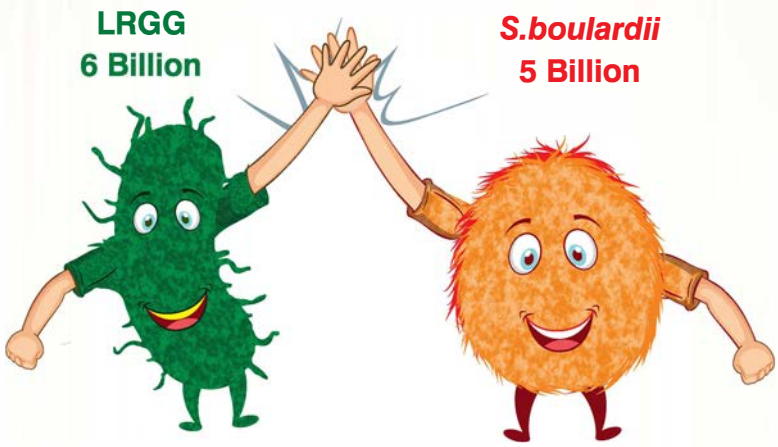

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