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COVID-19 SEVERITY AND TREATMENT STRATEGIES AMONG THE PEDIATRIC AGE GROUP

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ABSTRACT

In December 2019, novel coronavirus infected pneumonia (NCIP) occurred in Wuhan, China. Since then it has become a global health crisis. As of 15th May, 2020, the coronavirus disease had resulted in > 4 million confirmed Coronavirus disease -19 (COVID-19) cases. Pediatric coronavirus has shown a relatively milder course when compared to adults. Though children may withstand the outbreak of the novel coronavirus pandemic, they have been proven to be a major link in the transmission of this infection. The objective of this article was to provide a comprehensive review on the epidemiological aspect of COVID-19 in children. It additionally considers the reasons for the uneventful course of this infection in children along with providing a summary of latest pharmacological therapies available. More than 200 clinical trials for COVID-19 have been carried out on a variety of drugs. However as of date, there are no randomized clinical trial data to guide treatment of children with life-threatening COVID-19 symptoms. With no clear treatment guidelines for children, clinicians are left in the difficult scenario of deciding which treatment strategy to adhere to. Understanding the gravity of this current situation, the article provides a detailed analysis of the various experimental therapies available for COVID-19 patients, emphasizing on their usefulness in the pediatric age population.

KEYWORDS: COVID-19, SARS-CoV-2, Pediatric coronavirus, Management, Treatment strategies.

INTRODUCTION

Coronavirus disease -19 (COVID-19) is a global health crisis. As of 15 May 2020, more than 4 million confirmed cases of COVID-19, including 285,000 deaths have been reported to the World Health Organisation (WHO).[1] The impact of COVID-19 infection is seen to be less aggressive in the pediatric age group in comparison to adults. The clinical characteristics, disease progression and mortality outcome in children and young adults all appear significantly milder. The preliminary data of this outbreak have been focused on severe respiratory manifestations, which are more predominant in adults, as compared to the pediatric age group.[2] With limited initial data on the burden of COVID-19 in children, this review was aimed to provide a comprehensive observational view on the epidemiological aspect in children, along with reasons for their uneventful course of COVID-19. An attempt to provide an overview of latest pharmacological therapies available, based on the publications reported till date has also been made.

One of the initial statistics in children has been reported by Dong et al,[3] who had reported a series of more than 2000 children with suspected or confirmed COVID-19. The authors found that 4% of virologically confirmed cases had asymptomatic infection. As many children who are asymptomatic are not going to be tested, this certainly understates the true rate of asymptomatic infection. Among children who were symptomatic, 5% had dyspnea or hypoxemia (a substantially lower percentage compared to 31% reported in adults), Also 0.6% progressed to acute respiratory distress syndrome or shock (less than the 19.6% & 8.7% respectively seen in adults). Preschool-aged children and infants were seen to have more severe clinical manifestations as to older children.

Evaluation of a similar study report from the United States of America was done. In this study the percentage of pediatric patients was only 1.7% of the total number of 2,572 COVID-19 positive cases. The survey suggested that in adults aged between 18-64 years, 93% of patients complained of symptoms like shortness of breath, cough

along with fever. This number is higher in comparison to 73% of pediatric patients, aged between 0-17years, showing these similar symptoms. Furthermore, only 5.7% of all pediatric patients had to be hospitalized, again a lower number than the percentage needing hospitalization in the adult age group, that was 10%. All these figures reinforce the findings from the earlier studies, which indicated that children with COVID-19 might not show symptoms of fever or cough as often as adults.[4] Whereas most COVID-19 cases in children are not severe, serious COVID-19 illnesses resulting in hospitalization have been reported in this group. Information on the hospitalization status among pediatric patients showed that infants aged less than 1 year accounted for the highest percentage of hospitalization, which was 15-62% of the total hospitalizations occurring in this age group.[5]

A study of 345 pediatric cases confirmed with COVID and having additional information on underlying conditions was also analyzed. It was observed that, 80 (23%) of the children had at least one underlying condition. The most common underlying conditions were chronic respiratory diseases including asthma (50%), cardiovascular disease (20%), and immunosuppression (12.5%).[5] These findings are largely consistent with a report on pediatric COVID-19 patients aged <16 years in China, which found that only 41.5% of pediatric patients had fever, 48.5% had cough, and 1.8% were admitted to an ICU.[4] A second report additionally suggested that although pediatric COVID-19 patients infrequently have severe outcomes, the infection might take a more severe course among children below 1 year of age.[3]

Recently, reports from Europe and North America have described clusters of children and adolescents requiring admission in intensive care units with a multisystem inflammatory condition having features similar to Kawasaki disease & toxic shock syndrome.[1] Preliminary hypotheses are that this syndrome may be related to COVID-19, based on the initial laboratory testing. The collection of standardized data is essential to characterize this syndrome, its risk factors & causality features. In order to do so, the WHO has established an online clinical database platform. The valuable information, from this database will provide a beneficial understanding of this new syndrome.

Microbiology & pathology

Coronaviruses are a family of enveloped, single stranded, zoonotic RNA viruses which rapidly mutate, leading to infections that can spread from animals to humans.[6] Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is transmitted through inhalation of respiratory droplets of an infected person and from touching surfaces contaminated with fomites.

The SARS-CoV-2 virus utilizes the Angiotensin Converting Enzyme2 (ACE2) receptors as its cell surface receptor,[7] similar to the SARS 2002-3 virus. ACE2 is predominantly present on ciliated epithelial cells in the human lungs and the intestines.

The clinical spectrum of SARS-CoV-2 disease (COVID-19) as reported can be classified as mild asymptomatic infection, mild upper respiratory disease with fever and cough, and severe pneumonia that can lead to ARDS, as reported in 15% of the hospitalized cases in a study done in China.[8]

In Severe COVID-19 disease there are three phases: the first being the viral phase; the second being the cytokine storm; and the third encompassing acute respiratory distress syndrome (ARDS), impaired cardiac function and death.[9] The cytokine storm appears to be driven by a dysregulated host immune response,[10] consequently contributing to mortality.[8] The cytokine storm resembles secondary hemophagocytic lymphohistiocytosis.[10] It is characterized by fulminant and fatal hypercytokinemia, multiorgan failure, lower CD4 and CD8 T cell counts, higher levels of interleukin 6 & 10 along with higher D-dimer and fibrin degradation products levels. All these result in increased thrombosis with multiorgan injury,[11] as found in a recent study in Northern Italy. This study reviewed autopsies and observed fibrin thrombi of the small arteries. It supported the hypothesis proposed by recent studies, that COVID-19 is related to coagulopathy and thrombosis. As a result, the use of anticoagulants in patients suffering from severe COVID -19 has been recently suggested.

Perspective of milder coronavirus disease in pediatric age group

As discussed above multiple reports have demonstrated that children and young adults have a milder form of the disease as compared to adults.[3] Asymptomatic, mild and moderate infections comprise over 90% of all children who have tested positive for COVID-19 with fewer severe and critical cases (5.9%) compared to adults (18.5%).[3] Various reasons for lower number and milder infections in children have been suggested.

Children could have lower exposure with the coronavirus along with pollution and cigarette smoke, all contributing to healthier respiratory tracts. Physiologically a higher frequency of beating of lung cilia in children has been documented,[12] which will hinder the entry of the virus into lung pneumocytes. Apart from that, children have low risk for COVID-19 associated acute respiratory distress syndrome (ARDS) due to reduced production of fibrin and thrombin.[13,14] Another explanation for the preservation of the lungs and airways, are lack of co-morbidities detected in the pediatric age group.[15] Moreover the distribution, maturation and functioning of ACE2 may play an important role in age dependent susceptibility to severe COVID-19 infection. It has been observed that children have a stronger innate & weaker adaptive immune response,[15,16] which help them to escape the cytokine storm and its fatal complications.[16, 17] Further, in children various viral co- infections may

cause limited replication of the SARS-CoV-2, due to direct virus to virus competition. In addition, exposure of the pediatric population to various vaccines carried out as per the Universal immunization program,[18] enhances the activation of their immune system.[19,20] An absence of physical and mental stress in children may eventually give them additional protection *via* psychoneuroimmunology. All these factors help children to withstand the outbreak of the novel coronavirus pandemic.

Transmission

As discussed earlier, reporting and testing of children for COVID-19 are less, which lead to under-sampling and under-reporting of the disease.[3] It has been further indicated that children may be a link in transmission of the virus, due to the possibility of underreporting of cases, subclinical syndrome and longer shedding period of virus by them. Available data suggest that children can shed COVID-19 virus through stools for several weeks after diagnosis. Additionally, leading to concerns about fecal-oral transmission of the virus along with the viral replication in the gastrointestinal tract via ACE2 receptors.[21] All these insights indicate that children play a major role in community based viral transmission.

Management of pediatric covid-19

The four principles of "early identification", "early isolation", "early diagnosis", and "early treatment" should be emphasized in pediatric COVID-19 patients.[22]

Strict isolation strategies comprising of medical isolation should be carried out once the suspected cases are identified. Immediate Infection Prevention Control (IPC) measures must be instituted. Standard precautions such as hand hygiene, use of Personal protective equipment (PPE), must be followed as per the guidelines issued by the Ministry of Health and Family Welfare (MoHFW).[23] Viral screening is a must to rule out any other cause of symptoms. The confirmed cases should be admitted only to the designated COVID-19 hospitals.

The cornerstone of management in pediatric patients is supportive therapy including adequate nutrition and calorie intake, fluid and electrolyte management and oxygen supplementation. Communication with parents is an essential part of management.

There are no randomized clinical trial data to guide treatment of the very few children that present with life-threatening COVID-19 symptoms like severe pneumonia, ARDS, sepsis and septic shock. The WHO has also not recommended any specific treatment for children.

As a result clinicians may be left in the difficult scenario of deciding whether to pursue treatment with antiviral drugs or immunomodulatory agents for children with severe COVID-19. Also children with underlying health conditions such as leukemia, tumor or other immune deficiencies along with COVID-19 will have more severe complications and their treatment prognosis may be unpredictable.

Pharmacological therapies

The treatment guidelines are very cautious about recommending antiviral drugs for children. Almost all guidelines highlight that there are no effective antiviral drugs for children at present. Based on available evidence, the use of IFN-α2b, lopinavir/ritonavir and ribavirin in children have been recommended according to a study in China.[24] Unfortunately the dosage of ribavirin infusion varies in different medical literatures. Some suggest intravenous infusion of ribavirin administered at a dose of 10 mg/kg every time (maximum 500 mg every time) 2–3 times daily,[22] whereas others recommend 10–15 mg/ kg per day, divided into 2–3 times daily.[25] In the absence of adequate evidence for its efficacy and safety, experts have not reached on an agreement for the usage of ribavirin in the pediatric population.

There is also lack of data on the safety of using lopinavir/ritonavir for children under 2 years of age. Oral lopinavir/ritonavir together with corticosteroids for complications and intravenous immunoglobulin for severe cases has been recommended in one report in China.[24] Improved outcomes were only observed when they were used as initial therapy. They were not useful as rescue therapy in other studies, therefore it is not recommended in serious COVID-19 patients.

On the other hand, Interferon α-2b can be used in children, as it has shown good safety profile in one report from China.

The MoHFW has allowed off label use of hydroxychloroquine in combination with azithromycin in adults with severe disease and requiring intensive care.[23] However, these treatments are not currently recommended in children below the age of 12 years, as children are particularly sensitive to the accumulation of chloroquine phosphate in the body, which could possibly induce severe retinopathy, ototoxicity and cardiotoxicity. Corticosteroids too are not routinely recommended as they might exacerbate COVID-19 associated lung injury.[26] However they can be provided to patients who have indications for its use like septic shock, asthma & COPD.

A study of a PICU, in the children's hospital in Philadelphia, USA, broadcasted that antiviral use in children should be on a case to case basis. According to their study most of the pediatric patients recover with supportive care. The doctors noted that as of now no antivirals have shown any proven efficacy for treating COVID-19. Out of all antivirals, the panel concluded that the relatively new antiviral Remdesivir, has been found to inhibit SARS-CoV-2 growth in vitro.[27] Also, in

preclinical trials it has shown significant activity against coronavirus.[28,29]

Due to the occurrence of cytokine storm syndrome in COVID-19, there is a potential role of immunomodulators in the treatment of patients with severe infections. These drugs have shown to decrease pulmonary inflammation and thereby reduce the mortality rate. Anakinra (IL-1 blockade) has established a vital role in survival benefit of patients with hyperinflammation. Safety concerns should be evaluated in patients with thrombocytopenia, neutropenia along with its own infusion-related reactions that can occur.

A multicenter randomized control trial (RCT) of the IL-6 receptor inhibiting Monoclonal Antibody, Tocilizumab was undertaken for adults who had COVID-19 pneumonia along with raised IL-6 levels. The preliminary data suggest it may be clinically beneficial as an adjunctive therapy.[30]

There may also potentially be a role of Janus kinase inhibitors like Baricitinib since these drugs block downstream inflammatory pathways and reduce the cellular entry of the virus.[31] Though again there are some safety concerns like thrombosis, risk of GI perforation, patients with neutropenia, lymphopenia, anemia & elevated liver function tests. Data regarding clinical efficacy for use in COVID-19 patients are being evaluated.

Convalescent Plasma is the therapy where the plasma is collected from persons who have recovered from COVID-19. The plasma contains antibodies to SARS-CoV-2. Antibody (IgG) titer should be greater than 1:1,000. In one study, two successive transfusions of 200 mL to 250 mL of convalescent plasma was given. Patients had severe pneumonia and were on mechanical ventilation. Three days after plasma infusion, a reduction of pyrexia was observed. In 4 of 5 patients, overall improvement was seen; viral loads had also decreased and had become negative within 12 days of the transfusion. The neutralizing antibody titers also increased after the transfusion. The John Hopkins University, Baltimore is conducting various trials on plasma therapy. Their suggested fifth trial will be done in the pediatric population. Aim of the study will be to evaluate the safety and pharmacokinetics of convalescent plasma in high risk Pediatric patients.[32] This data will provide useful insight on the potential benefit of this therapy in children.

Anticoagulants for venous thromboembolism (VTE) prophylaxis with LMWH or fondaparinux are recommended for all hospitalized patients with COVID-19 infection. Elevated D-dimer has been associated with increased fatality. Evidence from trials indicate an improvement in patients, when LMWH or heparin were administered for VTE prophylaxis.[33]

The window of anti-inflammatory treatment is of great importance in a COVID-19 patient. Acetaminophen is the only anti-inflammatory drug that should be provided for temperature control. The use of other non-steroidal anti-inflammatory drugs (NSAIDs) in these patients, have been indicated to potentially worsen their symptoms, but evidence based data from clinical trials are lacking at this time.[34] An association between ibuprofen and increased ACE2 expression that may lead to serious outcomes in COVID-19 patients has also been debated.[35]

Most patients with COVID-19 have not shown the need of inhaled bronchodilators, unless the patient has an underlying respiratory condition like asthma or chronic obstructive pulmonary disease. Metered-dose inhalers (MDI) are preferable, as with nebulization the potential generation of aerosols may enhance the risk of spreading of the virus.[36,37]

The capability of nutritional supplements in the treatment or prevention of COVID-19 is also being explored. Several supplements like zinc, vitamin C, vitamin D are under investigation, in combination with other treatment modalities, for both treatment and prophylaxis.[38,39,40] In addition, the adverse events from excessive use and their potential for drug interactions are too being evaluated.[41,42]

Also several vaccines against SARS-CoV-2 are under research across the globe. It is important to mention that a vaccine fit for humans usually takes years to develop as it goes from preclinical studies to phase IV trails to test its efficacy and safety. The first upcoming vaccine is the Oxford university vaccine which has been developed in three months.[43] It is currently undergoing Phase I clinical trial. Serum Institute of India is also collaborating with Oxford University to boost the production of these vaccines. Other potential vaccines are Massachusetts, US based Moderna company vaccine & China based CanSino Biologics vaccine.[43] In India, the Indian Council of Medical Research (ICMR) has also teamed up with Bharat Biotech International limited for developing a COVID-19 vaccine. Data from these trials will provide useful insight about their capabilities of inducing protective immunity from COVID-19 along with information on vaccine related adverse events. Clinical trials of the above mentioned COVID-19 vaccines are emphatically essential in children as well.

DISCUSSION

At present, all the above drugs are being currently evaluated in adult patients. Their efficacy, safety, appropriate dosage, course of treatment and mechanism of action need to be studied in children with special attention to adverse drug reactions and drug interactions.[22,25]

The guidelines for clinical trials of pediatric drugs, has declared that it is not suitable to perform extrapolation on

drug efficacy from adults to children. Therefore, comprehensive and systematic clinical trials for drug safety and efficacy in pediatric population should be planned and conducted, once the data of preliminary safety and efficacy of the drugs, has been acquired from the adult population.[44]

Although the proportion of infected children in the pediatric population to the whole population is relatively low, children are still at high risk of infection and should not be neglected. Precautions must be taken beforehand while carrying out the clinical trials of pediatric drugs for the treatment of COVID-19. Not to say the least, emphasis has to be given on the ethical principles of pediatric clinical research, which must be abided during the entire course of clinical trial. The clinical trials designed for pediatric population need to follow the principle of "minimum sample size, and minimum pain" as much as possible.[45,46]

CONCLUSION

In the end, SARS-CoV-2 infected "COVID-19" is a new pandemic disease. There are differences in clinical manifestations between children and adults. It is imperative for the governments, pharmaceutical industries and medical institutes all over the globe to be prepared to conduct clinical trials for evaluating the safety and efficacy of pediatric medications. The data from these clinical trials will yield important insights into disease management and the development of therapeutics for COVID-19 disease in the future.

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