Review Article

COVID-19: A review of drugs and therapies for children

***Patel Zeeshan Jameel[1], Amar M Taksande[1]**

Sri Lanka Journal of Child Health, 2020; **49**(3): 210-217
DOI: http://dx.doi.org/10.4038/sljch.v49i3.9136
(Key words*:* Paediatrics, COVID-19, coronavirus, chloroquine, azithromycin, vitamin supplementation, interferons)

Introduction

The World Health Organisation (WHO) has declared the disease as Corona Virus Disease (COVID-19) due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Coronavirus infection was restricted to animals but gained importance in medicine as it acted as the aetiological factor responsible for the SARS epidemic in 2002 in the Guangdong province of China[1]. WHO reported its spread to over 26 countries, causing infections in 8096 individuals and 774 deaths[2]. This group of viruses caused another outbreak in 2012 as Middle Eastern Respiratory Syndrome (MERS)[3]. Since December 2019, a strain of novel coronavirus has wreaked havoc in the Hubei province of China and has caused severe pneumonia[4]. On March 11, the WHO declared it a 'pandemic'. More than 1.5 million cases of COVID 19 have been reported with a mortality of over 85,000 across 212 countries[5]. The largest study on children with COVID 19 to date includes an analysis of 2143 children documented from 16th of January, 2020 to 8th of February, 2020. This study showed that only 1 child had died while 5.9% were critical or had severe pneumonia, the majority having mild to moderate illness[6]. Although pneumonia remains the chief cause of death among the under 5 year age category, the features of COVID-19 pneumonia were relatively milder compared to pneumonia of other aetiologies and the prognosis was better with deaths being extremely rare[6-8].

Clinical presentation in infants and children

Since the outbreak of the pandemic, 9 infants were reported to be positive till 6th February, 2020 in China with the youngest being 1 month old and the oldest being 11 months old[9]. In older children, clinical presentation varied from asymptomatic to symptoms of mild upper respiratory tract infection in the majority[6], 22% manifesting with pneumonia, and some children having gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhoea[10]. The first paediatric case of severe pneumonia in China due to SARS-CoV2 requiring mechanical ventilation was reported by Chen F, *et al*[11]. Thus SARS-CoV2 can cause a severe form of pneumonia in the paediatric age group and there is a dire need for efficient management strategies. To date, no definitive treatment strategy has proven efficacious for SARS-CoV2 infection. Table 1 lists all possible management strategies in children.

Triage

A pre-defined, devoted area for triage of patients is essential for all children suspected of having COVID-19. Use of Personal Protective Equipment (PPE) is mandatory for the attending paediatrician. It must be ensured that the child and accompanying parents/ relatives are using a 3-ply surgical mask[12].

Respiratory support

Oxygen support is required in a child with oxygen saturation (SpO_2) less than 90% and/or with signs of respiratory distress[13]. The British Paediatric Respiratory Society (BPRS) has advised that hypoxic children should initially receive low flow nasal cannula (LFNC) oxygen rather than high flow nasal cannula (HFNC) oxygen as HFNC is associated with an increased risk of aerosol spread[14]. HFNC may be the next step if the child continues to be hypoxic[14]. Improvement is indicated by reduced heart and respiratory rates by 10-20%, reduced fraction of inspired oxygen (FiO_2) requirements to less than half and improved SpO_2[13].

Both the European Society of Intensive Care Medicine and the American Association for Respiratory Care have advised against usage of non-invasive ventilation (NIV) in acute respiratory failure in H1N1 influenza as it is a high risk procedure which should be cautiously used due to the high probability of spread of infection[13,15].

[1]*Jawaharlal Nehru Medical College, Wardha, India*
**Correspondence:* zeeshan1311@gmail.com
orcid.org/ 0000-0002-8040-4835
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

Bubble continuous positive airway pressure (Bubble CPAP) is an alternative procedure which may be used for newborns and children with hypoxia when both NIV and mechanical ventilation are not available[13]. Lung protective mechanical ventilation is a recommended strategy for treatment of acute hypoxic respiratory failure[16].

Table 1: ***Management strategies of possible implication in paediatrics***

• ***Triage***
• ***Respiratory support***
Low flow nasal cannula (LFNC)
High flow nasal cannula (HFNC) / Heated high flow nasal cannula (HHFNC)
Non-invasive ventilation (NIV)
Bubble continuous positive airway pressure (Bubble CPAP)
Mechanical ventilation (MV)
• ***Nutritional supplementation***
Vitamin B complex
Vitamin C
Zinc
• ***Immunotherapy***
Interferons
Convalescent plasma or intravenous immunoglobulin (IVIg)
• ***CoV specific therapy***
CoV protease inhibitors like Cinanserin
Spike(S) protein ACE 2 Blockers like Griffithsin, ACE2 binding Ab or peptides
• ***Chloroquine / Hydroxychloroquine (CQ/HCQ)***
• ***Antiviral therapy***
Ribavirin
Lopinavir / Ritonavir
Remedesivir
• ***Antibiotics***
Azithromycin
Teicoplanin
• ***Anti-parasitic drugs***
Ivermectin

Nutritional supplementation

Riboflavin supplementation has been reported to effectively scale down the titres of MERS-CoV in the human plasma products[17]. Treatment with nicotinamide was able to significantly repress neutrophil infiltration into lungs during ventilator induced lung injury but had no effect on cytokine production or protein leakage and was also found to paradoxically lead to hypoxaemia[18]. Pyridoxine plays a vital role in antibody production and immune system regulation[19]. Thus, B complex vitamins are a valuable adjunct in COVID-19 therapy.

Five trials found preventive or therapeutic benefits of vitamin C against pneumonia with the overall quality of the studies being good[20]. Thus, Vitamin C supplementation is a potential therapy in the treatment of viral pneumonias. Because of this, a triple blinded randomised controlled trial (RCT) is being carried out by Peng *et al*[21] evaluating the role of intravenous ascorbic acid for treatment of severe pneumonia due to COVID-19. Results of this trial are awaited.

Velthuis *et al*[22] determined in their study that zinc and pyrithione when administered at low concentration inhibited the replication of SARS-CoV in Vero-E6 cells by RdRp template binding and inhibition of its elongation. Therefore, zinc supplementation may be a useful treatment for this novel coronavirus.

Immunotherapy

Interferons (IFNs) restrict virus replication before adaptive immune responses develop[23]. Ian Hall, a molecular medicine professor at Nottingham University stated, "The idea behind the trial is that by giving more of this molecule to the lung, it could help reduce the severity of infection with COVID 19, especially in those people who have reduced immune responses to the virus. If the trial shows that interferon beta is a useful treatment for COVID 19, it would provide a way to reduce the severity of disease and potentially reduce death rates"[24]. Ströher *et al*[25] found that the SARS-CoV is inhibited in tissue culture by IFN-α2b at concentrations of ≥1000IU/ml. Another study concluded that early intervention with the use of exogenous IFNs only or along with direct antivirals prior to complete subversion of the host's immune response may provide a viable treatment option[26]. In an observational cohort study comprising 36 children, an aerosolized form of interferon alpha was used for all patients with no adverse outcomes or mortality[10]. A study by Chen *et al*[27] found that both leucocytic IFNα and IFNβ1a were more active and ribavirin was determined to have highly synergistic action with either of the two IFNs. The study concluded that ribavirin combined with either IFN must be considered for SARS therapy.

On the basis of experience of using INFα as well as clinical research in the treatment of bronchiolitis, viral pneumonia, acute upper respiratory infection and SARS in childhood, Shen *et al*[28] recommends the use of IFNs in the following dosages:

- INFα nebulization: INFα 200,000-400,000 IU/kg in 2ml sterile water, twice a day for 5-7 days.
- INFα2b spray for high risk population with close contact with suspected SARS-CoV2 infected patients or those in early phase with only upper respiratory tract symptoms. Use 1-2 sprays in each nostril with 8-10 sprays in oropharynx, 1-2 hourly, 8-10 sprays/day for 5-7 days (Dose of INFα2b per injection – 8000IU).

Convalescent plasma or immunoglobulins can be considered in SARS patients who continue to deteriorate in spite of treatment[29]. Furthermore, numerous studies suggest that testing the efficacy of therapy with convalescent plasma or SARS specific hyper-immune immunoglobulin in the early phase of SARS could be rewarding[30]. Hung *et al*[31] showed a substantial decrease in the relative risk of death in patients being treated with convalescent plasma during the H1N1 influenza A pandemic in 2009. The WHO recommended use of convalescent plasma from recovered patients as an empirical therapy in the 2014 Ebola outbreak[32]. The meta-analysis by Mair-Jenkins *et al*[33] concluded that the use of convalescent plasma may decrease mortality and appears to be safe. However, it also concluded that this therapy should be studied with a well-designed clinical trial for therapy of CoV infections. Shen *et al*[34] treated 5 critically ill adults with COVID-19 and ARDS with convalescent therapy containing neutralizing antibody and results showed decreasing Sequential Organ Failure Assessment Score (SOFA) in all 5 of them, decreased oxygen demand and weaning of 3 adults from ventilator within 14 days with all 5 surviving the serious illness. Thus, literature shows that convalescent plasma from recovered patients is a management strategy with some potential at this time but it is yet to be tried in the paediatric population.

Intravenous immunoglobulins (IVIg) may be used in severe cases or critically ill patients but requires further validation. The recommended dose in children is 1g/kg/day for 2 days or 400mg/kg/day for 5 days[35]. In a single centre observational study by Dan Sun *et al*[36], immunoglobulin therapy was administered to 4 patients with 2 children getting discharged while the other 2 were still in the intensive care unit at the time of publication of the study.

CoV specific therapy

CoV protease inhibitors

Cinanserin is a drug well-known for its antagonistic action on serotonin receptor. In the study by Chen *et al*[37], cinanserin inhibited the 3-chymotrypsin-like protease of SARS-CoV and also inhibited replication of SARS-CoV. In a study by Parks JY, *et al*, diarylheptanoids inhibited the papain-like protease of SARS-CoV[38].

Spike (S) protein ACE 2 blockers

Griffithsin, a lectin, binds to oligosaccharides present on the surface of some viral glycoproteins, including SARS-CoV spike glycoprotein and HIV glycoprotein 120[39]. *ACE2* is a receptor for SARS-CoV virus and mediates its entry into the cell by binding with S protein[40]. Blocking the binding of S protein to ACE2 is an important therapeutic option which could be used for treatment in the form of mAb[41]. Sui *et al*[42] have developed an anti-S1 human monoclonal antibody 80R which neutralizes SARS-CoV infection with a strong nanomolar affinity and also efficiently inhibits formation of syncytia by receptor binding blockage. The data in this *in vitro* study also suggested that the monoclonal antibody may be further developed and tested in *in vivo* animal studies to determine its clinical utility as a potent inhibitor of viral entry for use in prophylaxis and treatment of SARS.

CoV specific treatment is yet to be evaluated in the paediatric population.

Chloroquine/Hydroxychloroquine (CQ/HCQ)

Wang *et al*[43] tested 5 FDA approved drugs *in vitro* to reduce the viral infection Vero E6 cells and found CQ to be effective against 2019-nCov(EC_{90} – 6.90μM). Numerous trials have been started already evaluating the role of CQ in COVID-19 infection. Interim results of these trials may be available by April 2020. An expert consensus comprising multicentre collaboration group of the Department of Science and Technology of Guangdong province and Health Commission of Guangdong province have published a paper regarding the use of CQ phosphate. Although, there was no information on the methodology utilized to achieve this consensus but based on multiple *in vitro* studies and clinical experience which are yet to be published, the panel recommends CQ phosphate in a dose of 500mg twice per day for 10 days for diagnosed cases of SARS-CoV2 pneumonia in the absence of any possible contraindications to this drug[44]. WHO has still not recommended CQ or HCQ as a treatment modality for COVID-19.

Anti-viral drugs

Ribavirin, Remdesivir, Galidesivir, Tenofovir and *Sofosbuvir* are potent drugs against SARS-CoV2 as they tightly bind to its RNA dependent RNA polymerase[45]. There is no consensus on the use of these drugs in children. *Lopinavir* (LPV) is a protease inhibitor of HIV-1 which is combined with *Ritonavir* (RTV) in order to increase its half-life. Combination of LPV/RTV has shown efficacy against the SARS-CoV in tissue cultures as well as in patients with estimated EC_{50} being 4 mcg/ml in foetal rhesus kidney-4 cells[46]. A randomized clinical trial in China, comparing the use of LPV/RTV to the prevailing care in 199 admitted COVID-19 patients, concluded that LPV/RTV did not significantly decrease the 28 day mortality or the time to clinical improvement and that this drug regimen was associated with more adverse events[47].

Antibiotics

Teicoplanin, a glucopeptide antibiotic usually used for treatment of bacterial infection, was found to be active against SARS-CoV *in vitro*[48]. A recent non-randomised clinical trial in France showed that hydroxychloroquine could reduce the viral load and also that addition of azithromycin had increased its efficiency significantly[49]**.** Azithromycin is thus a potential therapeutic agent which could be exploited further in paediatric clinical trials for COVID-19 pneumonia.

Anti-parasitic drugs

Ivermectin, FDA approved for parasitic infections, is an inhibitor of SARS-CoV2 *in vitro* and a single treatment can effect a 5000 fold reduction in virus at 48 hours in cell culture[50]. Thus, it merits further study for treating COVID-19 infection in children.

In conclusion, Anti-CoV drugs need to be further evaluated and studied for their mechanism of action, appropriate dosing regimen as per body surface area or body weight, and efficacy with special consideration being given for adverse reactions and possible drug interactions in children. Although COVID-19 has been relatively less severe in children, there is a dire need to come up with a definitive treatment protocol for children.

Keeping this in mind, this article reviews all possible beneficial therapeutic agents in the paediatric population. Ascorbic acid and zinc supplementation may be useful as preventive measures as well as in asymptomatic patients. Interferons, SARS- CoV-2 specific antivirals, HCQ/CQ, Azithromycin and Ivermectin present the best available therapeutic agents for symptomatic children. However, a series of clinical trials are required at the earliest to evaluate their efficacy and safety in the paediatric population.

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