



A Brief Review on Covid-19 Effects in Children and Treatment Methods

Vaishnavi Tammishetty*¹, Sravika Nagamalla², Pravalika Sakilam³, Hyma Ponnaganti⁴

1,2,3: Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Hyderabad, Telangana, India.

4: Associate Professor, Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Hyderabad, Telangana, India.

*Corresponding author's E-mail: vaishnavivaishnavi694@gmail.com

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ABSTRACT

As there is an outbreak of novel corona virus in 2019 it has spread globally that resulted in severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic and mostly there is limited data provided on children. The main aim of this review is to provide a knowledge on introduction, epidemiology, pathogenesis, transmission, clinical manifestations, laboratory findings, treatment of COVID-19 in children. And it also includes latest statistical data of children prone to COVID-19. Besides respiratory and GI symptoms atypical features such as chilblains and multi-inflammatory system are also reported. pathophysiology gives information regarding the life cycle of virus in hostcell and epidemiology explains the different types of viruses affecting the respiratory system. The clinical signs and symptoms are almost similar to the adults but they are in mild, and most of the children affected with Covid-19 are asymptomatic. This review study makes a medical practitioner to have a quick, practical approach to the disease to use in different scopes, especially in pediatric medicine.

Keywords: Covid-19, epidemiology, transmission, treatment methods.

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INTRODUCTION

Background:

The first outbreak of corona virus has started in Wuhan, city of Hubei province in China 2019. Many cases have been reported for pneumonia, the reason for many cases is unknown initially later on the etiology of the causative organism is corona virus is known by the health commission of Hubei^{1,3}. There are further studies had done and it's confirmed that main causative organism is novel corona virus with almost 85% of genomic identity of bat SARS like virus^{4,5}. This coronavirus has spread worldwide and became a pandemic on march 11 2020, it is officially declared as pandemic by World health organization^{1,2}.

SARS-cov2, mainly belongs to a Beta-coronaviruses and it belongs to family coronaviridae. There are few viruses like Hcov -229E, -HLCU1, -NL63, -OC43 these virus has ability to circulate in body and it causes mild respiratory infections whereas the SARS cov-2 it undergoes few mutations, and change in its structure and undergoes recombination's all this had led to the development of novel corona virus it can easily transmitted from animals to humans that causes severe respiratory diseases.³

Most of the children's who are affected with covid have shown symptoms or asymptomatic and mild symptom like nearly, less than 10% to 20% have shown symptoms for corona virus and requirement of hospitalization. Whereas 1-3% of children are affected more and the requirement of intensive care to children. And few children have shown multi-inflammatory syndrome.⁶

Structure of coronavirus:

1. They are large, enveloped, RNA viruses.¹
2. Coronavirus-Its structure is a member of coronaviridae, nidoviral.
3. Subfamily-Coronavirinae also called as corona viruses.⁷
4. The virus is spherical elliptic consisting of 60-140nm in diameter mainly it is pleomorphic.¹
5. This type of viruses mainly consists of mRNA as genome with 26-32 kilobases. The mRNA has 5'cap and 3'poly(A) tails the main use of it is for translation of polyprotein replica.⁷
6. Virus genome is mRNA it consists of 6-11 open reading frames (ORF).
7. The genome or virus consists of ORF 1a/b it nearly codes for 16 non-structural proteins but mainly S, N, M, E are considered as essential structural and they encode the remaining of genome.
8. In this protein the S protein binds to the ACE2 receptors of the host cell and N, E proteins mainly interfere with the immune response of the host.



9. M protein it mainly helps in the transferring of the transmembrane nutrients⁸
10. S proteins consists of subunits like S1 and S2. The main function of S1 is to interact with ethe ACE2 receptors for the entry in to the host cells and the function of the S2 is to involve the fusion of the membrane through the HR1 and HR2 (heptad repeat).^{9,10}

Pathophysiology:^{6,11}

Mainly the pathogenesis of covid-19 involves 4 stages like entry of virus and attachment, expression of the protein replicase, replication of the virus and transcription, and assembly of the virus and release. For the attachment of the virus to the receptors mainly there is an involvement of the S-protein to the receptor site it causes the first attachment of virus to the receptor site. After the attachment of protein, the protease in host cells gets cleaves that leads to the activation of protein attached to

the receptor. This type of activation mainly depends on the availability of the protein. For the attachment there is a requirement of peptidase for binding to receptor for protein. once the virus enters in to the host cell the virus gets uncoated and the genome of virus enters in to the cytosol of the host cells. The virus genome is RNA it is 5’Methylated caps and 3’poly adenylated tail. These RNA’s are translated by the ribosomes of the host cells. The genetic variability is the main part of the genetic recombination. The more no. of the proteins is released by the cells due to translation of mRNA of virus by the ribosome of the host cells. Usually, the viruses consist of the S, E, M proteins. The virus along with the proteins enters in to Golgi apparatus and the M protein involves in the initiation of the protein-protein interaction for the assemblage of the viruses. And its binding to the nucleocapsid then the viruses are released by exocytosis by the vesciles. Once the viruses are released and next, they infect other fresh host cells.

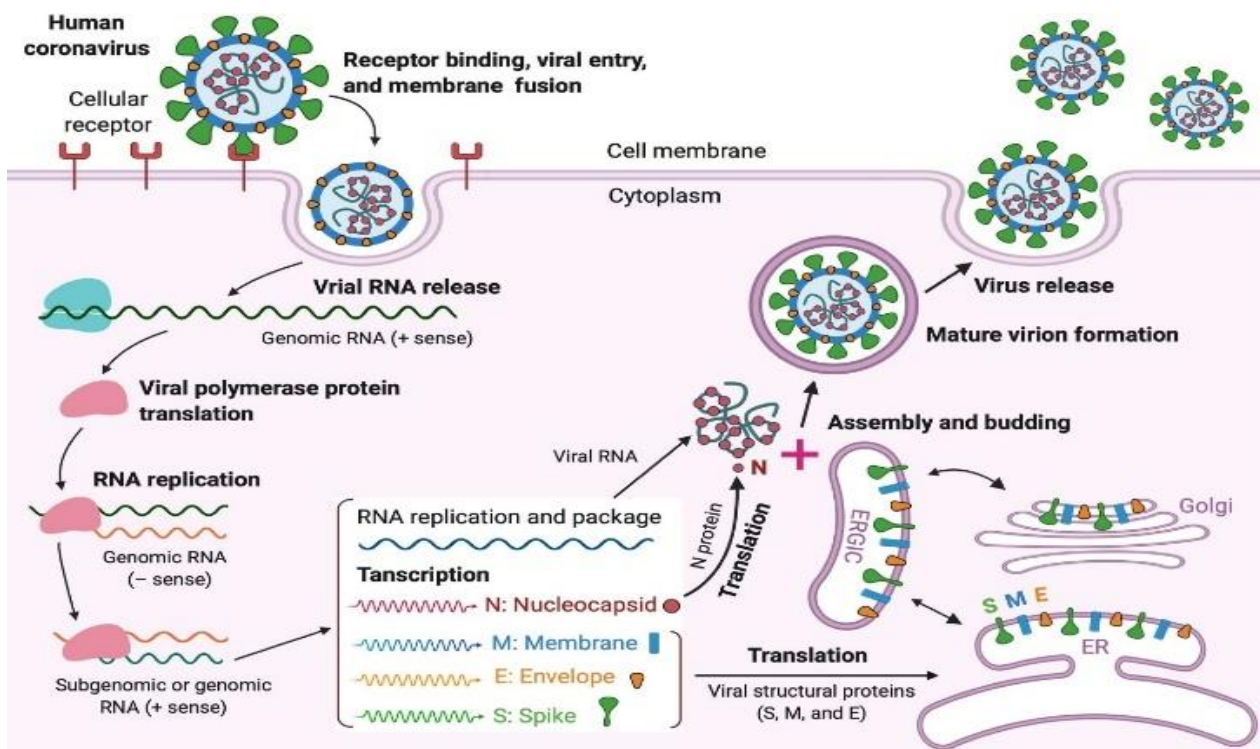


Figure 1: Pathogenesis of sarscov²

Epidemiology:¹²

1.Common circulating HCOV:

It occurs mainly in the children with 4 to 6% with acute respiratory syndrome. And, mostly children are hospitalized and 8% of children in outpatient’s department. These types of viruses are seen in a child with the heart disease under the age of 3. And even children with 11-46% are affected with the co-infections with the other virus which affect the respiratory system like adeno, Rhino, influenza, RSV. The infection in children with chronic conditions have shown more effect compared to the coinfection in children.

2.SARS-COV-MERS-COV:

- i. SARS-COV: It belongs to the novel group of 2b bacteriovirus it is firstly seen in the Guangdong province in south China in 2002, from their it eventually Spreaded to many countries.it mainly infects the lower respiratory tract mostly 50% of people above 60 years of age are infected. And it is easily transmitted from person to person. Nearly 29 countries had affected.
- ii. MERS-COV: It belongs to the bacteriovirus occurred first in Saudi Arabia in 2012. It is easily transmitted from person to person. And mainly it affects the lower respiratory tract wit 20to20% of cases are reported it

was an endemic in the middle east region. later years in 2014 it has seen in south Korea infected with 186 patients later it is infected to many people nearly 27 countries had affected.

- iii. SARS-COV-2: Its outbreak has caused transmission of virus from person to person. And its incubation if for 5-6 days. When outbreak had occurred, there were numerous cases of pneumonia had been reported in China, Italy, Iran. By august, 2020 there were severe cases in southern states of India nearly millions of cases had been reported there was a high risk of transmission among children and young adults. The R_0 indicates the number of people infected can infect other persons. The reproductive number of people who are affected with corona virus can infect approximately with 2.2. this number indicates the virus is transmitted from person to person. Recently it has shown there are increased cases due to increase in infectious nature of virus. And lack of testing kits and lack of awareness.

Transmission in children:

After the respiratory tract infection children are more prone to hospitalize mainly, they are affected due to influenza, syncytial virus. In children there is no proper development of the respiratory system and the immune system it is thought that there is a high risk of infections.¹³

In Wuhan there was their pediatric series are reported 171,20 and 10 children after the incubation period of 2-14 days the children had become symptomatic. In 171 children's series with RT-PCR they have confirmed to SAR COV-2 it has shown with signs and symptoms like cough, diarrhea, vomiting, fatigue etc. asymptomatic infection, pneumonia, upper tract infection has shown and one child had died.

There are 72% children with mild symptoms, and upper respiratory syndrome and positive PCR test. And 22% of children with moderate symptoms associated with fever, cough, fatigue, headache, myalgia. The persons with diabetes, hypertension, chronic respiratory disease, aplastic anemia they are more risk to infection. 73% of pediatric patients have shown fever, cough, dyspnea and 5.7% are hospitalized according to US CDC.¹

CLINICAL MANIFESTATIONS

There is a systemic organ involvement in children with COVID-19. It includes the following:

Signs and symptoms.

1. In Case of Neurological Issues in Children:

Headache, altered mental status and weakness are the most common.

Demyelinating disease, stroke and encephalopathy.

Multi inflammatory syndrome (MIS), seizure, coma, aseptic meningitis.¹⁴

2. In Case of Cutaneous Manifestations in Children:

Macules and papules, vesicles/varicelliform like eruption.

Urticarial eruption, acral pseudo chilblain.

Erythema multiform, MIS in children.

3. In Case of Cardiac System:

Raised troponin / brain natriuretic peptide (BNP).

Myocarditis / pericarditis, valvulitis.

Pericardial effusion, coronary artery dilation / aneurysm.

Shock (requiring inotropic support).

4. In Case of Respiratory System:

Pneumonia, Acute respiratory distress syndrome (ARDS), pleural effusion.

5. In Case of Dermatologic manifestations:

Kawasaki like eruption.

6. In Case of Ophthalmics:

Conjunctivitis, non-suppurative / non purulent.

7. In Case of Renal System:

Acute kidney injury, proteinuria, hematuria.

8. In Case of Hematologic manifestations:

Coagulopathy (including thrombosis), leukocytosis, raised inflammatory markers (ferritin).

9. In Case of Gastrointestinal Tract:

Children with COVID-19 can be asymptomatic or present with fever, dry cough, fatigue and sometimes GI symptoms such as Diarrhea, vomiting, nausea.

Abdominal pain / discomfort, transaminitis, ascites.

Hepatosplenomegaly, colitis / ileitis.¹⁵

Laboratory Findings:

- In case of cutaneous manifestations:

Histopathologic analysis of the erythema multi form like eruptions revealed a superficial and deep perivascular and peri eccrine inflammatory infiltrate with immune histo chemistry (IHC) demonstrating cytoplasmic granular positivity to the SARS-COV / SARS-COV 2 spike protein in endothelial epithelial eccrine glands.

Pediatric patients presenting with cutaneous manifestations of COVID-19 may also have a false negative PCR nasopharyngeal / oropharyngeal swab, yet are harboring COVID-19.¹⁵

- In case of hematological manifestations:

Laboratory findings from children are similar with infections caused by different novel COV's. The WBC count is typically normal or reduced with decreased neutrophil and lymphocyte count. Thrombocytopenia may occur.



In severe cases, elevated liver enzymes, lactate dehydrogenase levels, as well as an abnormal coagulation and elevated D – dimers have been reported.¹⁶

Radiological Findings:

CT changes observed in children infected with SARS-COV 2 include bilateral multiple patchy, nodular ground glass opacities, speckled ground glass opacities and / infiltrating shadows in middle and outer zone of the lung or under the pleura. These findings are unspecific and milder compared with those in adults.¹⁷

Statistical data of children prone to covid-19:

Over 7,100 children and adolescents died from COVID-19, which is 0.3 percent of the 2.4 million COVID-19 deaths in 78 countries.

The 2.4 million COVID-19 deaths in 78 countries account for 68 percent of the total global deaths reported by Johns Hopkins University. COVID-19 data were collected from January 2020 to present and country data were updated on different dates.

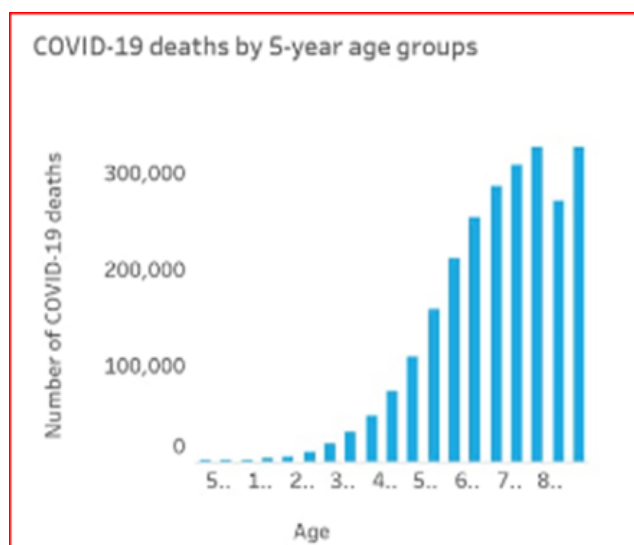


Figure 2: Covid-19 deaths by 5 year age groups

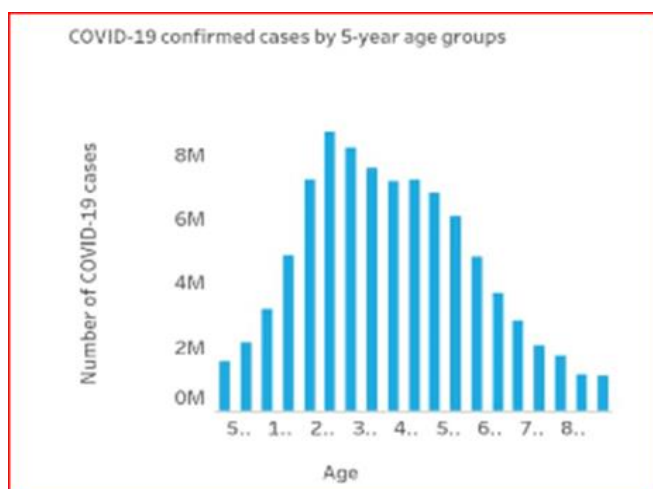


Figure 3: Covid-19 confirmed cases by 5year age groups

Around 12 million COVID-19 cases occur in children and adolescents, which is 13 percent of the 88 million COVID-19 cases in 100 countries.

The 88 million COVID-19 cases in 100 countries account for 51 percent of the total global cases reported by Johns Hopkins University. COVID-19 data were collected from January 2020 to present and country data were updated on different dates.¹⁸

Definitions:

Clinical syndromes associated with covid-19 in children were defined based on WHO classification as follows^{19,20}

1) Asymptomatic case- The infection is identified during screening without any symptoms.

2) Mild Case- Fever or fatigue or upper airway symptoms without any radiological findings.

3) Moderate Case-Fever/fatigue/upper airway symptoms like mild respiratory distress/pneumonia identified with chest x-ray.

4) Severe Case-It is associated with fever and cough, along with one of the following:

- Oxygen saturation level (SpO₂) < 92%
- Severe respiratory distress (grunting, severe chest indrawing, cyanosis, intermittent apnea.
- Fast breathing (regardless of fever and crying)
Respiratory rate (RR) in breaths/minute > 60 if < 3months; > 50 if 3–12 months; 40 if 1–5 years; > 30 if > 5 years of age.
- Systemic symptoms: drowsiness, lethargy, seizures, dehydration.

5)Critical Case-It is seen in case if the child is associated with

- Pediatric acute respiratory distress syndrome
- Sepsis-associated organ dysfunction
- Septic shock
- Coma.

TREATMENT

Treatment Approaches Based on Different Scenarios

- 1) Asymptomatic Cases-No Specific Treatment Is Required. These cases can be treated at home. They should be isolated to prevent transmission and monitored for clinical deterioration. The patient should have enough calorie and water intake.²¹
- 2) Mild and Moderate Cases: Mild cases could be symptomatically treated at home and be assessed for vital signs and oxygen saturation. Moreover, CBC, CRP, blood chemistry, myocardial and liver enzymes, kidney function, and coagulation test results should be assessed if needed, but

Antipyretic Therapy Is Required. It is preferred to use paracetamol (10–15 mg/kg every 4–6 h) in case of fever > 38.5 °C. Avoid ibuprofen in case of dehydration, vomiting and diarrhoea, as it is associated with an increased risk of kidney failure. For Cough Throat soothing agents like warm saline gargles can be used.²²

Children with moderate Covid-19 diseases should be administered:

- i. For fever: Paracetamol 10-15 mg/kg/dose. May be repeated every 4-6 hours.
- ii. Amoxicillin to be administered, if there is evidence/strong suspicion of bacterial infection.
- iii. For SpO₂ below 92-94%, oxygen supplementation is required.
- iv. Corticosteroids may be administered in rapidly progressive disease. It is not required in all children with moderate illness, specifically during first few days of illness.
- v. Supportive care for comorbid conditions, if any.⁶

3) Severe and Critical Cases: children with spo₂ levels less than 90% are considered to be having severe degree of infection. Therefore, Different Therapies and Various Drugs Are Used for children associated with this are-

Anti-viral Therapy:

Remdesivir: It is one of the drugs approved by the FDA for the treatment of covid-19 in both hospitalized adult and pediatric patients for emergency use as it is not evaluated in clinical trials that include children. It is a nucleotide analogue that is incorporated into viral RNA chain leading to premature termination.

Dosage: If body weight > 40 kg: 200 mg on 1st day then 100 mg once daily for 4 days. If body weight is between 3.5 kg to 4 kg: 5mg/kg on 1st day, 2.5 mg/kg once daily for 4 days.^{23,24}

Hydroxychloroquine (HCQ): It is an antiviral drug where in vitro studies suggest that it could act by increasing the endosomal pH required for virus / host cell fusion and interfering with the glycosylation of the SARS-Cov-2 cell receptor. In particular, hydroxychloroquine appears to have better in vitro activity towards SARSCoV-2. The anti-inflammatory activity of these molecules, through the inhibition of the production of Interleukin (IL) -6 and Tumor Necrosis Factor (TNF)- α , could contribute to their effectiveness. In addition, this molecule has been in use for decades, showing a good safety profile.

Dosage: 6 mg/kg (maximum: 400 mg/dose) twice a day on day 1, followed by 3 mg/kg (maximum: 200 mg/dose) twice a day for up to 5 days. HCQ solution preparation is mostly recommended for children.²⁵

Favipiravir: Favipiravir is an antiviral drug authorized for the treatment of flu. It works by inhibiting RNA polymerase which is RNA-dependent and seems to show a better efficacy compared to lopinavir/ritonavir. Still clinical trials

are undergoing to evaluate the efficacy of Favipiravir in SARS-Cov-2 infection in children.²⁶

Steroids:

At present, there are no clear evidences to support the use of steroids during Covid-19 infection unless specific needs in children. The COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone for children who require high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered.

Dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.^{27,28}

Inhalation therapy: If topical steroids and/or bronchodilators are needed (e.g., patient with recurrent wheezing undergoing exacerbation and suggestive symptoms or confirmed SARS-Cov-2 infection) the use of pressurized suspensions with spacer chamber is suggested. Conversely, the use of nebulisers is not recommended in order to avoid particles aerosolization and increased contagiousness. Ongoing steroid treatment should not be stopped once it is started.²⁹

Antibiotic therapy:

The choice to add empirical antibiotic therapy should only be made if there is reasonable evidence of bacterial superinfection.

- Amoxicillin 90 mg /kg/day in 3 doses,
- Ceftriaxone 80–100 mg/kg/day,
- Azithromycin 15 mg/kg the first day, then 7.5 mg/kg once a day for other 4 days.³⁰

Anti-SARS-CoV-2 Monoclonal Antibodies:

For Drugs like Bamlanivimab, Etesevimab, Casirivimab and Imdevimab EUAs have been issued for the treatment of hospitalized, high-risk patients aged ≥ 12 years and weighing ≥ 40 kg with moderate to severe COVID-19, there are currently no data available to determine which is causing high-risk to pediatric patients. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of monoclonal antibodies against different variants, may inform the choice of specific anti-SARS-CoV-2 monoclonal antibody therapy in the future.³¹

Multi System Inflammatory Syndrome in Children (MIS-C)

A small set of children and young adults with covid-19 infection developed MIS-C. This immune manifestation is also referred to as pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 (PMIS-TS), although the case definitions for the syndromes differ slightly. This syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified to have current or recent infection with SARS-CoV-2.^{32,33}



Clinical Manifestations:

- Fever >38.0°C for ≥24 hours,
- Laboratory Evidence of inflammation shows elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin (IL)-6, or neutrophils, or reduced lymphocytes or albumin levels,
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.³⁴

Treatment of MIS-C:

Drugs to be used in case of Multi System Inflammatory Syndrome in Children in case the child has cardiac dysfunction, shock, coronary involvement, multi organs dysfunction are:

- a. Steroids: Methylprednisolone 1 to 2 mg/kg per day.
- b. Intravenous Immunoglobulin 2 g/kg over 24 to 48 hours.
- c. Antimicrobials

The child needs appropriate supportive care, preferably in ICU. In absence of cardiac dysfunction, shock, coronary involvement, multi organs dysfunction, one may use steroids.

If the child does not improve with the above treatment the other alternative include:

- a. Repeat IVIg
- b. High dose corticosteroid (Methylprednisolone 10 to 30 mg/kg/day for 3 to 5 days)
- c. Aspirin: 3 to 5 mg/kg/day max 81 mg/day (if thrombosis or Coronary Aneurysm Score is >2.5)
- d. Low Molecular Weight Heparin: Enoxaparin: 1 mg/kg twice daily subcutaneously. Clotting Factor Xa should be between 0.5 to 1.³⁵

CONCLUSION

Although the numbers of infected children and the severity of illness are expected to be low, health professionals need to be prepared to face the situation. The impacts of COVID-19 in children may go far beyond health including psychological, economical, educational and others that are beyond the scope of this article. In most affected children the supportive care, oxygen therapy and antibiotics are adequate. Antivirals are not usually recommended but in case of severity used along with corticosteroids, immunoglobulins. This review applied a rigorous search strategy to retrieve relevant articles according to research objectives. This study may provide some evidence for future study.

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