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Review Article

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COVID-19 in Children: A Narrative Review

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is the third known zoonotic coronavirus. It is a disease that does not spare any age group.

There has been a tsunami of information since January. This review aims to summarise pertinent information relating to COVID-19 in children.

Method: A literature search was conducted on the PubMed, MedLine, and Embase databases, with the keyword "COVID-19" and "children". Bibliographic search was also undertaken. The abstracts were scanned to assess their appropriateness to be included in this narrative review. This was updated on the 11th April.

Result: The aetiology, transmission, incubation, pathophysiology, clinical features and complications, and management are discussed.

Conclusion: Our understanding of COVID-19 is evolving, as more reports are published. Continued research to understand its effect in children is important to help us manage the disease in these vulnerable population in a timely fashion.

Keywords

COVID-19, Review, Children, Asymptomatic, Kids, Infants, Neonates, SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is the third known zoonotic coronavirus, after SARS-CoV-1 in 2003 and Middle East respiratory syndrome (MERS) in 2012. It is a disease that does not spare any age group.

There has been a tsunami of information since January. This review aims to summarise pertinent information relating to COVID-19 in children.

Method

A literature search was conducted on the PubMed, MedLine, and Embase databases, with the keyword "COVID 19" and "children". Bibliographic search was also undertaken. The abstracts were scanned to assess their appropriateness to be included in this narrative review. This was updated on the 11th April.

Results

Aetiology

SARS-CoV-2 is an enveloped single-stranded RNA virus, of subgenus Sarbecovirus of the genus β-coronavirus [1]. The RNA is 29 903 bp in length [1]. It is approximately 60-140 nm in size [1,2]. It has high sequence similarity to the Guangdong pangolin coronaviruses, which may be an intermediate host of the virus before transmission to human [1]. Tang, et al. found two subtypes: L (~ 70%) type, which is derived from the S (~ 20%) type [3]. L type is more prevalent, replicates faster and accumulates more mutations, resulting in a higher transmission rate, therefore is likely to be more aggressive [3].

SARS-CoV-2-S uses the SARS-coronavirus receptor, angiotensin converting enzyme 2 (ACE2) for entry into host cells, which is a surface molecule highly expressed in type 2 alveolar cells of lung, as well as the oesophageal upper epithelial cells, absorptive enterocytes of the ileum and colon [1]. The

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ACE2 expression is higher in the Asian population, and in the men [1].

Transmission

The transmission is reported to be between 1.5 and 4 cases per exposure [4-12].

Respiratory droplet (5-50 μm) is the main route of transmission, which is affected by gravity, and may cause direct transmission via close contact, or surface contamination [2,4,5,13-20]. Large droplets (> 5 μm) produced by coughing or sneezing fall rapidly to the ground [21]. SARS-CoV-2 can remain infectious on inanimate surfaces at room temperature for up to 9 days [22]. It is more stable on plastic and stainless steel than copper and cardboard [23]. It is detected up to 72 hours after application onto plastic, though the viral titre decayed exponentially [23]. The viral half-life was 6.8 hours on plastic, and 5.6 hours on stainless steel [23].

SARS-CoV-2 is highly contagious and can be transmitted via smaller aerosols with a droplet nuclei ≤ 5 μm, which can travel long distances and remain airborne for 2-4 hours, depending on the ambient conditions [8,21]. The particle size determines the location in the respiratory tract it is deposited when inhaled [21]. Certain events (e.g; coughing or sneezing, cardiopulmonary resuscitation) and aerosol generating procedures (AGP) (e.g; intubation, tracheostomy) can generate aerosols composed of smaller virus containing particles suspended in air [19]. Prolonged exposure to high concentrations of aerosols in a closed environment may facilitate transmission due to increased density of the viruses per unit volume [12].

Yung CF found no polymerase chain reaction (PCR) -detectable virus on the personal protective equipment (PPE) of the healthcare worker (HCW) caring for an asymptomatic infant with high viral load, with a total time spent of 15 minutes caring for the infant. The surrounding environment (bedding, cot rail and table one metre away) was found to have PCR-detectable virus [24].

Other mode of transmission reported include faecal-oral route as SARS-CoV-2 nucleic acid has been detected in the stool samples of COVID-19 patients with abdominal symptoms [4,20,25].

Currently there is no direct evidence of vertical transmission. Suspected vertical transmission has been reported in a 36-hour newborn who was delivered via emergency caesarean section to a COVID-19 mother who was wearing N95 respirator during the delivery and had no contact with the neonate [26]. In addition, Zeng L, et al. report of three infected neonates born to COVID-19 mothers [27]. The possibility further been raised as immunoglobulin M antibodies have been detected in newly born infants, although viral RNA has not been isolated [28]. However, several studies tested for the presence of SARS-CoV-2 in amniotic fluid, umbilical cord blood, breast milk samples at first lactation and neonatal pharyngeal swab but did not detect the virus.

Incubation

The incubation period is 3 to 7 days: The shortest being 1 day, and longest 24 days [11,12,29-33].

It is contagious during the latency period [8,15,16,34-38]. Shedding is greatest during the early phase of disease [16,39]. Viral load is highest in the first week (peaks at three to 5 days) after symptoms begin and decline over the second week, especially in the nose than throat [5,40-43]. The viral load in asymptomatic patients has been found to be similar to symptomatic patients [15,40,44,45].

Prolonged viral shedding after recovery has also been reported, with reports up to 22 days [11,12,20,37,43,46,47]. Stool sample has been were found to be positive for a prolonged period, up to 18-51 days after symptom onset [11,25,43,48,49].

Pathophysiology

The S protein on its surface reacts with the molecules of the ACE2 in the alveolar epithelium (mainly type 2 pneumocytes), resulting in alveolar damage [50,51]. In children the development and function of ACE2 is imperfect, and the intracellular response induced by ACE2 in alveolar epithelial cells is lower than in adults [51-54]. Children has higher ACE activities, from 4 to 13-years-old, before gradually decreasing till it reaches adult values [55].

The composition and functional responsiveness of the children's immune system (IS) may be the reason for the milder symptoms and prolonged incubation period [12,56]. The dominant innate immunity and the underdeveloped adaptive immune response results in a qualitatively different response to the SARS-CoV2 virus [48,51,53,56]. The IS does not mount an acute inflammatory response to SARS-CoV-2, contributing to the better outcome [48,51,57]. They have a lower prevalence of increased C-reactive protein (CRP) suggesting a milder immune response and thus less immune damage [25]. Lymphopenia which is a predominant feature in severe infection occurs due to a combination of viral particle induced cytoplastic damage and apoptosis [58]. It may not occur in children due to the relative immaturity of their immune system and differences in immune response compared to adults, with children maintaining normal white cell and lymphocyte counts [58,59]. CD4 are higher, while CD8 T lymphocytes are lower in children, which may be related to the development and atrophy of the thymus [55].

Children are susceptible to a variety of viruses and the presence of the other simultaneous viruses in the airway mucosa, which may limit the growth of SARS-CoV-2 by direct interactions and competition, and the antibodies produced may cross-react with that of SARS-nCoV-2 to provide some protection, thus supporting the IS [51,52,56]. In addition, the frequent viral infections and vaccines in children may induce an enhanced state of activation of the innate IS, which result in more effective defence against different pathogens [54,60]. Bacillus Calmette-Guerin vaccine has been associated with heterologous immunity to other pathogens resulting in "trained immunity" involving innate cells like macrophages [61]. Lymphocytes count is high early in life and decreases later in childhood, and may also be higher due to frequently experienced viral infections [60]. In addition, they are gen-

Table 1: Reported clinical symptoms in the literature.

Symptoms	
Fever	36-80%
Headache	8-20%
Myalgia	
Fatigue	5-7.6%
Cough	30-75%
• **Dry**	19-44%
• **Expectoration**	50%
Nasal obstruction/congestion	5.3-30%
Rhinorrhoea	7.6-20%
Sneezing	20%
Dyspnea	3-100%
Hypoxia (< 92% oxygen saturation)	2.3%
Wheezing	
Pneumonia	53%
Sore Throat	5-40%
Tachycardia	42.1%
Abdominal discomfort/pain	8%
Nausea & vomiting	5-50%
Diarrhea	5-57.1%

Table 2: Reported bloodwork findings in the literature.

Bloodwork	
White Cell Count	
- Leucocytes:	Normal 69.6-70% Increase 10-28.6% Decrease 20-53.5%
- Neutrophils	Lymphopenia 3-30.6% Neutrophilia 4.6% Neutropenia 6% Thrombocytosis 14.3%
C-Reactive Protein	↑ 2.7-45%
Creatine Kinase	↑ 2.7%
- Creatine Kinase MB	↑ 25-75%
Alanine Aminotransferase	↑ 5.6%
Aspartate Transferase	↑ 8.3%
Procalcitonin	↑ 10.6-80%
D-Dimer	↑ 8.3%

erally healthier with less exposure to pollution and cigarette smoked resulting in in healthier respiratory tracts [61].

Clinical presentation

In Italy, children constitute 1.2% of the cases. In China, 2.16% are ≤ 18-years-old with < 1% are < 10-years-old [58,62,63]. In South Korea, where testing are done on a massive scale, 6.3% of the confirmed cases are < 20-years-old [25,48,56]. In the US, it is 1.7% [64]. In Madrid, 0.8% are < 18-years-old [65].

The clinical course is generally milder in children than adults [2,12,31,32,43-46,48,51,66-72]. 2.5-10% have severe disease, and 0.6% have critical disease; 10.6% are < 1-year-old, 7.3% 1-5 years, 4.2% 6-10 years, 4.1% 11-15 years and 3% 16-17 years [29,58,71,73].

Some are asymptomatic (1.3-60%), which may be an underestimation as they are not usually tested for obvious reasons [12,25,33,43,45,47,48,58,63,64,74-77]. Chan JF, et al. reported an asymptomatic 10-year-old, who had ground class changes on lung computed tomography (CT), and high viral load in the sputum sample [15].

The reported clinical symptoms are shown in Table 1 [25,31,47,63-65,70,76-78]. The symptoms are variable and may be atypical. Children ≤ 5-years-old are more likely to develop severe clinical manifestations due to the immaturity of the respiratory tract and immune system [75,79]. Respiratory distress occurs in premature infants and children with underlying chronic condition [47,80]. Apart from younger age, other risk factors for a more severe outcome include pulmonary pathology and immunocompromise [12,73]. Children with co-morbidities (hydronephrosis, leukemia and intussusception) are more likely to require mechanical ventilation [63]. Pneumonia may develop, and some may progress rapidly, resulting in respiratory failure within 1-3 days [81].

Bloodwork findings are summarised in Table 2 [47,58,63,70]. Most children have leucocytosis rather than the leucopenia found in adults [70]. The features that distinguish mild to the more severe disease are decrease in CD4 and CD8 T cell subsets, decrease in neutrophil-to-lymphocyte ratio, decrease lymphocytes ($p = 0.008$), raised body temperature ($p = 0.002$), elevated procalcitonin ($p = 0.004$), elevated D-dimer ($p = 0.03$), and creatine kinase MB ($p = 0.008$) [25,43]. High IL-6 levels are associated with increased mortality in < 5-years-old with severe pneumonia [58]. This trend follows CRP [58]. Procalcitonin is thought to be induced by bacteriotoxin but suppressed by interferon, and in children is associated with bacterial co-infection (40%) [31,58]. Some authors reported up to two third of the cases have viral co-infections [76].

Most children recover within 1 to 2 weeks [29,32,43,51,68,70,74,82]. Disease duration in those with severe disease is over 10 days, but in critically ill, over 20 days [62].

Diagnosis

Diagnosis is based on epidemiological history, clinical symptoms and laboratory tests.

Nucleic acid testing via real time reverse transcription PCR assay, or viral gene sequencing of throat swabs, sputum, stool or blood samples.

Chest X-ray (CXR) is usually non specific [61]. CT plays

an important role in surveillance and diagnosis of COVID-19 pneumonia with higher sensitivity than CXR [10]. Children with mild disease does not routinely need CT chest due to the radiation exposure. Its sensitivity as diagnostic tool to detect COVID-19 pneumonia has been reported to be between 80-100% [48,50].

CT findings are diverse from normal (20-50%) to a few lesions including ground glass opacification (30-60%), fine mesh shadow (20%), tiny nodules (15%), or consolidation with a surrounding halo (50%) [10,29,31,49,63,70,77,78,83]. The lesions are generally small nodular ground glass opacities or subpleural patchy opacities [48,83]. 20-60% have unilateral, while 20-70% bilateral involvement [31,74,77,78]. Despite CT findings of chest lesions, children can remain asymptomatic (7.02%) [15,47,48].

Complication

While early reports from China are encouraging with only two deaths: 14-years-old (risk not elaborated) and a 10-months-old (intussusception and multi-organ failure 4 weeks after admission), there has been several reports so far [63].

Septic shock and multi organ failure are the most common complications in critically ill patients [62]. Others include toxic encephalopathy, status epilepticus, renal insufficiency, metabolic acidosis, cardiac insufficiency and coagulopathy [62]. Mortality is the main cause of death in < 5-years-old [25].

The higher rate of asymptomatic patients, the potentially prolonged shedding of virus in nasal secretion and stool have substantial implications of children in its transmission in day care, school and home [25,43,73]. It is hard for children to be aware of their personal hygiene, and if infected, they can result in cluster outbreaks. Schools closure early in outbreaks is believed to reduce transmission [84]. However, school closures may not only result in loss of education, but also negative effects on physical and mental health to be considered due to children being confined to their homes. This includes longer screen time, irregular sleep, nightmares, poor appetite, less healthy diet that results in weight gain, and a loss of cardiorespiratory fitness [52,68,85].

The stocking up on shelf stable food as part of the preparedness results in a calorie dense diet in children [85]. There are others in whom free school meals are an important source of nutrition [84]. The increases in weight found to occur during summer recesses is reported to be maintained during the school year and accrues from summer to summer, with lasting effect even into adulthood [85]. Social distancing and stay at home orders may result in physical inactivity, especially those living in dense urban area [85].

Psychological impact may result from physical and social isolations, as well as stressors like fears, uncertainties, frustration, boredom, lack of in-person contact with peers, being exposed to large amount of information, high levels of stress and anxiety in adults around them, and family financial loss [52,68,86]. Children experience substantial changes to their daily routine and social infrastructure, which ordinarily foster resilience in challenging events [86]. Clinginess in the 3-6 years age group, and inattention, irritability and challenging externalising behaviours in the older age group are some of the psychological manifestations reported [68,86]. Some reports that harms to child welfare with violence and vulnerability increasing during periods of school closures associated with health emergencies [84,87]. Isolation or quarantine during pandemic have been reported to result in acute stress disorder, adjustment disorder and grief, with 30% meeting clinical criteria of post-traumatic stress [88].

Another vulnerable group are those quarantined in hospitals, or have lost their caregivers due to COVID-19. Separation from caregivers may result in a state of crisis, increasing the risk of psychological disorders as companionship is essential for children's normal psychological development and well-being [88]. Separation from parents or parental loss during childhood is associated with a higher risk of developing mood disorders and psychosis, death by suicide in adulthood [88].

Treatment

The mainstay of treatment is symptomatic with respiratory support, and treatment of complications. Anti-virals may be helpful in severe cases: Virazole, oseltamivir, arbidol, ribavirin, lopinavir/ritonavir and interferon [25,62,78]. The data on efficacy is unavailable. Table 3 summarises the recommended treatment [2,25,32,62,63,78,89].

IFN-α nebulisation has shown good safety profiles under most circumstances [32,89,90]. IFN-α spray has been used for high risk populations with close contact with suspected COVID positive patients or those in early phase with only upper respiratory tract symptoms [32]. The dose is one to two sprays into each nostrils, 8-10 sprays into the oropharynx for 5-7 days [32].

Children are sensitive to accumulation of chloroquine which may induce severe retinopathy, ototoxicity and cardiotoxicity [89].

Antibiotic, glucocorticoid and immunoglobulin therapies are used as indicated [78]. Steroid should be avoided but a short course (3-5 days of 1-2 mg/kg/day of methylprednisolone) can be considered in acute respiratory distress syndrome (ARDS), and other complications like toxic shock [2]. Intravenous immunoglobulin may be used in severe cases (1 g/kg/day for 2 days, or 400 mg/kg/day for 5 days) [2].

During delivery, delayed cord clamping's benefit outweighs the unlikely risk of acquiring COVID-19 in suspected or confirmed COVID-19 mothers [28]. The optimal mode of nutrition of infant born to COVID-19 mother is unknown, and the benefits of breastfeeding should be weighed against the risk of transmission [28]. There have been no reports demonstrating SARS-CoV-2 in breastmilk.

For neonates with ARDS, high dose pulmonary surfactant, inhaled nitric oxide, high frequency oscillatory ventilation and extracorporeal membrane oxygenation have been recommended [30].

Children are attuned to adults' emotional states [86]. Strategies to nurture resilience include increasing communication with children to address their fears and concerns

Table 3: Recommended treatment in the literature.

Drugs	Mode of action	Recommended dosing	Precaution	Side effects
IFN-α	Broad spectrum antiviral Inhibit viral RNA synthesis, viral replication and spread	Nebulised (mild cases) 100,000-200,000 IU/kg, (severe cases) 200,000-4000,000 IU/kg or 2-4 μg/kg (in 2 mL sterile water) BD-TDS for 5-7 days	Liver & renal dysfunction, mental illness (suicidal ideation more common in adolescents vs adults), severe or unstable heart disease or aplastic anaemia Used with caution in < 2-months-old	Low grade fever, flu-like symptoms, growth suppression (when used with ribavirin) Overdose: Myelosuppression, liver dysfunction, renal failure, coagulopathy
Lopinavir/ritonavir	Lopinavir is a substrate of CYP3A enzyme; ritonavir is a strong inhibitor of CYP3A enzyme	Oral ≤ 15 kg: 12 mg/3 mg/kg per dose 15-40 kg: 10 mg/2.5 mg/kg per dose ≥ 40 kg: 400 mg/100 mg per dose BD for 1-2 weeks	Liver dysfunction, jaundice, increase PR interval, heart blocks and hypokalemia Contains 42% ethanol and 15% propylene glycol, which is not recommended in < 14-days-old	Diarrhea, vomiting, rash
Ribavirin	Broad spectrum antiviral with inhibitory effects on RNA & DNA viruses	Intravenous: 10-15 mg/kg per dose (maximum of 500mg per dose) divided into BD-TDS dosing	Liver & renal dysfunction, cardiac disease Not recommended < 3-years-old orally	Fever, headache, neutropenia, fatigue Overdose: Haemolytic anaemia, myocardial injury
Chloroquine Dipohsphate	Anti-malarial	No recommendation	Liver & renal dysfunction, haematoprophyria, mental illness. Use with caution in children	Dizziness, headache, loss of appetite, ocular toxicity, arrhythmia, psychosis, leukopenia Overdose: Fatal with a dose of 50 mg/kg
Arbidol		No recommendation	Liver dysfunction Use with caution in children	Nausea, dizziness, diarrhea, elevated aminotransferase

(taking into account their age and level of understanding), playing collaborative games to alleviate loneliness, encourage activities that promote physical activities, using music therapy to reduce stress, fear and worry, improve sleep hygiene, relaxation therapy, model a positive psychological attitude to reduce stress [68,86].

Conclusion

Our understanding of COVID-19 is evolving, as more reports are published. Continued research to understand its effect in children is important to help us manage the disease in these vulnerable population in a timely fashion.

Competing Interests

No relevant disclosures.

Conflict of Interest

None to declare.

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