

## COVID-19 In Children

M M Z Islam<sup>1</sup>, B H N Yasmeen<sup>2</sup>

### Abstract

Diagnosis of SARS-CoV-2 infection is based on detection of viral RNA by RT-PCR of nasopharyngeal or oropharyngeal swabs. Consider alternative diagnoses in children who are unwell, even in the presence of a positive SARS-CoV-2 PCR result. Children with mild to moderate Covid19 do not routinely need admission or investigations such as blood tests and radiology, unless otherwise clinically indicated. Children with severe or critical disease as a minimum should have the following investigations: Blood cultures, Full Blood Count (FBC), Coagulation profile, D-dimer, Urea and Electrolytes, LFT, CRP, Troponin, Ferritin, Lactate dehydrogenase (LDH) and Blood Gas Analysis.

Remdesivir may be considered for children > 12 years and >40kg with COVID-19 requiring supplemental oxygen. Consider chest x-ray in children who do not follow the expected clinical course, for example, those still requiring oxygen on day three of admission, those with worsening hypoxemia or those requiring respiratory support. Decision to escalate respiratory support to Non-Invasive Ventilation (NIV) should be made by a senior member of the pediatric team, in discussion with critical care. For children with clinical findings consistent with the Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) should be managed as per specialized guidelines.

**Key Words :** COVID-19, SARS-CoV-2, RT-PCR, PIMS-TS.

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### Introduction

COVID-19 is a respiratory illness caused by a novel coronavirus (SARS-CoV-2). COVID-19 was first described in Wuhan, China in December 2019 and is now a global pandemic. The most common symptoms include fever, fatigue, dry cough, and shortness of breath. Most of those affected patients have milder illness (80%), rest will be severely ill (15%), and few(5%) will require ICU care. Compared with adults, children are less likely to become severely unwell with the infection.<sup>1</sup> Although majority of children will have self-limiting illness without any complications, it is important to follow local guidelines on sepsis, acute kidney injury, and respiratory failure. Of those who are critically ill, most require early intubation and mechanical ventilation. Other complications include septic shock and multi-organ failure, including acute kidney injury and cardiac injury. The multidisciplinary team must work together to ensure the best outcome for the child.<sup>2</sup>As the virus is highly contagious, minimizing the spread of the virus in hospital is crucial.<sup>3, 4</sup>

### Pathology of COVID-19

SARS-CoV-2 virus is extremely contagious, it spreads via respiratory droplets, direct contact, and airborne routes if aerosolized, particularly where there is close contact between people. The incubation period may range from 2-14 days. Prolonged detection of SARS-CoV RNA has been reported in respiratory specimens and stool specimens.

The virus directly infects cells via the ACE2 receptors, expressed in multiple organs including the lung. Receptor expression is lower in children's airways than adult airways and is one hypothesis to explain why children experience less severe infections.<sup>5</sup> One proposed disease mechanism in adult severe cases is a 'cytokine storm'. This describes a cascade process whereby the virus leads to increased levels of cytokines that cause direct tissue damage, recruitment of neutrophils to tissues, and other pro-inflammatory effects. This damage can lead to organ failure including acute respiratory distress syndrome (ARDS). Extrapulmonary involvement and other organ failure have been

<sup>1</sup>Dr. Mirza Md. Ziaul Islam  
Associate Professor  
Pediatric Infectious Diseases  
and Community Pediatrics Dept.  
Bangladesh Institute of Child  
Health  
Dhaka Shishu (Children)  
Hospital, Dhaka

<sup>2</sup>Prof. B H Nazma Yasmeen,  
Professor and Head  
Dept. of Pediatrics  
Northern International Medical  
College (NIMC), Dhaka

Correspondence  
Dr. Mirza Md. Ziaul Islam  
Associate Professor  
Pediatric Infectious Diseases  
and Community Pediatrics Dept.  
Bangladesh Institute of Child  
Health  
Dhaka Shishu (Children)  
Hospital, Dhaka  
Email: mirzamd.ziaulislam@yahoo.com

identified in people with severe or fatal illness. Some patients develop cardiac dysfunction. This may be due to viral-induced direct damage, or hypoxic damage in people with respiratory failure. Liver damage and renal failure have been associated with severe infection.<sup>6</sup>

### Clinical Features in Children<sup>7-9</sup>

The most common presenting symptoms are fever, cough, nausea/vomiting, and dyspnea. In the children who are admitted to hospital and tested positive for COVID-19, fever is the most common presentation. Three clusters of presenting features are usually identified:

- A respiratory cluster in which children presented with a discrete respiratory episode of cough, upper and lower respiratory symptoms, and fever
- A mucocutaneous-enteric cluster of headache, myalgia, gastrointestinal symptoms, lymphadenopathy, fatigue, rash and conjunctivitis - and this cluster largely reflects the symptoms seen in children with Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS).
- A rarer cluster of neurological features – particularly seizures and confusion

Altered taste and smell are common features in adults with COVID-19, but rare in children.

Several reports suggest the potential for clinical deterioration during the second week of illness.

### Diagnosis of SARS-CoV-2 Infection

Tests to detect SARS-CoV-2 may be performed on symptomatic children, children admitted to hospital either electively or as an emergency, prior to surgical procedures or, as part of screening in high-risk areas (e.g., PICU, transplant or dialysis centers). Samples that can be collected include nasopharyngeal/oropharyngeal swabs or saliva.

Reverse-transcription polymerase chain reaction (RT-PCR) assay, to detect SARS-CoV-2 RNA from the upper respiratory tract is the standard of care. A positive RT-PCR confirms the diagnosis of SARS-CoV-2 infection. Patients may have detectable SARS-CoV-2 RNA for weeks after the onset of symptoms; however prolonged viral RNA detection does not necessarily indicate ongoing infectious condition. A single negative RT-PCR is sufficient to exclude the diagnosis of COVID-19 in most children, however if there is high suspicion of COVID-19 (suggestive symptoms, clinical findings and investigations), a further test may be performed for infection control reasons. It is usually

recommended to repeat this test after 24 hours.<sup>10</sup>

### Blood tests

No additional blood tests are required for the children, if admitted requiring only supportive care, beyond those required to exclude alternative diagnoses. Alternative diagnoses must be considered in unwell children presenting, following the same pathways in place prior to the outbreak.<sup>11</sup> Children with severe COVID-19, the following blood tests may have some diagnostic and prognostic value: blood cultures, full blood count, coagulation profile, D-dimer, renal function, liver function, bone profile, CRP, ESR, ferritin, LDH, troponin and pro-NT-BNP. Blood gases should be monitored in children with respiratory distress.<sup>12</sup>

### Radiology<sup>13-14</sup>

Consider chest x-rays in children whose clinical course is not following an expected disease progression, or who deteriorate. For children with proven COVID-19 infection but minimal or no respiratory symptoms chest CT is unlikely to be helpful.

### Management

#### 1. Supportive medical care<sup>14</sup>

Most children with COVID-19 do not require admission and may be managed at home. Pediatricians should consider the child's clinical presentation, requirement for supportive care, underlying medical conditions and the ability for caregivers to care for the child at home when deciding whether to admit a child with COVID-19. All children and young infants including those who are clinically extremely vulnerable should be considered on a case-by-case basis.

#### 2. Fluids<sup>15</sup>

Most children with mild illness do not require fluid restriction below normal maintenance values. Fluid restriction may be indicated in children with moderate to severe respiratory compromise as this may reduce the risk of acute respiratory distress syndrome (ARDS). Be aware that febrile children, and those who are tachypneic, may have increased insensible losses. Monitor fluid balance and measure daily weight in those children in whom fluid intake is a concern. Diuretics are not indicated routinely but should be considered in children with worsening respiratory failure, particularly if there is evidence of pulmonary oedema on chest x-ray.

#### 3. Antipyretics<sup>14</sup>

Paracetamol is the first line antipyretic. Ibuprofen should be avoided in children with poor fluid intake or suspected AKI, but

this is related to the risk of kidney damage rather than worsening COVID-19.

#### 4. Antibiotics<sup>15</sup>

Consider antibiotics if

- They are unusually sick at admission or if there is a clinical deterioration. Antibiotics should be prescribed based on usual grounds and clinical judgment. Teams should ensure they have sought a focus of infection (urine, throat swab, blood culture +/- CSF as appropriate prior to starting antibiotics, as is best practice).
- Blood tests are suggestive of bacterial infection, e.g., increased CRP and neutrophil count.
- CXR changes reveal a pneumonic picture, e.g., lobar pneumonia and this is consistent with the clinical picture.
- An alternative or co-incidental diagnosis is considered, don't forget sepsis, which may have overlapping clinical features.

Bacterial co-infection is not common in COVID-19. For children with co-morbidities, such as cystic fibrosis, antibiotic choice should be based on known bacterial colonization where available. Antibiotic choice, duration, route of administration should be reviewed daily in the context of clinical progression and microbiology results.

#### Respiratory support<sup>16</sup>

Most children, even those with lung involvement, are unlikely to develop respiratory failure. Children should initially receive low flow nasal cannula (LFNC) oxygen if they are hypoxic, rather than high flow nasal cannula (HFNC). Decision to use of HFNC should be made by a senior team member. Blood gas analysis be used in children who appear to require escalating respiratory support. In such children capillary blood gas (not arterial or venous) may be used to evaluate for pH and pCO<sub>2</sub>. Early use of CPAP and non-invasive ventilation (NIV) may prevent deterioration requiring invasive mechanical ventilation.

#### Treatment of children with asthma attacks<sup>17</sup>

Wheeze is not a common problem in children with COVID-19. Bronchodilators should not be used routinely unless there is strong suspicion of bronchoconstriction. The side effects of bronchodilators include pro-inflammatory effects on the alveoli, worsening of Ventilation/Perfusion (V/Q) mismatch, and tachycardia.

In children with acute wheeze or asthma attacks, prompt treatment with salbutamol and systemic steroids can reduce the

risk of hospitalization, and further need for nebulization.

Salbutamol given via Metered dose inhaler (MDI) is as effective as nebulization, and less likely to lead to admission. If nebulization is required because a child is hypoxic and tachypneic, salbutamol and ipratropium bromide may be given concomitantly.

#### Endotracheal Intubation<sup>18</sup>

Intubation should be performed early for a number of reasons, including the rapid disease progression. The most experienced person should perform endotracheal intubation to reduce exposure to the healthcare team and all team members should be in appropriate PPE during intubation. For patients with a normal airway assessment, awake intubation should be avoided and modified rapid sequence intubation with sufficient muscle relaxation is strongly encouraged.

#### Management of ARDS<sup>19</sup>

##### Non-invasive ventilation (NIV):

It is recommended to avoid NIV because there is no exhalation filter.

##### High-flow nasal cannula (HFNC):

Although an area of controversy, early expert opinion favors HFNC over other non-invasive modalities because it appears to be well tolerated, more efficacious and less provider intensive.

##### Mechanical Ventilation:

COVID-19 does not appear to cause substantially reduced lung compliance as is typical with ARDS, but rather atelectasis and interstitial pneumonia.

- a. Target ARD Snet high Positive End Expiratory Pressure (PEEP) lung-protective tidal volume (4-8 mL/kg ideal body weight), and lower inspiratory pressures (plateau pressure <30 cm H<sub>2</sub>O)
- i. Start with 6 mL/kg ideal body weight tidal volume and titrate as needed
- ii. In patients with moderate to severe ARDS, suggest higher PEEP instead of lower PEEP.
- iii. In younger children, maximal PEEP setting is 15 cm H<sub>2</sub>O as higher PEEP can result in decreased cardiac output.
- b. Permissive hypercapnia ensuring adequate hemodynamics and a pH >7.15 may be tolerated

##### Proning<sup>20-23</sup>

Patients who are unable to adequately ventilate in the supine

position may benefit from being placed in the prone position to improve oxygen saturation (PaO<sub>2</sub>), pulmonary mechanics, and arterial blood gases (ABGs).

Prone positioning requires proper sedation/pain medications and paralytic agents if necessary. Length of pronation cycle should be a minimum of 16 hours in the prone position with a return to supine positioning at least once a day.

### Oxygen Therapy and Monitoring

Give supplemental oxygen therapy immediately to patients with respiratory distress, hypoxemia, or shock and target SpO<sub>2</sub> 92-96%. Patients that have a persistent requirement for 5-6 L/min to maintain target SpO<sub>2</sub> should be considered for early intubation/mechanical ventilation given risk of deterioration. If persistent requirement for 5-6 L/min and lacking resources for invasive ventilation, consider use high flow nasal oxygen (HFNC) or a face mask with a reservoir bag at 10-15 L/min if the patient is in critical condition. HFNC is a more effective intervention for non-invasive management of ARDS that requires less staff intervention.<sup>24</sup>

For children, use of nasal prongs or nasal cannula may be better tolerated, but the goal is to target SpO<sub>2</sub> >94% during resuscitation, and >90% once stable. Patients may deteriorate rapidly, so continuous monitoring is critical. Aggressive fluid resuscitation may worsen oxygenation and outcomes, so in the absence of shock, fluid boluses should be minimized. Avoid routine steroids in patients without acute respiratory distress syndrome (ARDS) except under certain circumstances. However, consider methylprednisolone for intubated patients with ARDS. For intubated patients with ARDS and a PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150, recommend early proning and consideration for transfer to an extracorporeal membrane oxygenation (ECMO) center.<sup>24</sup>

### Prevention of Complications<sup>25</sup>

Troponin and Basic Natriuretic Peptide (BNP) should only be measured if clinical evaluation suggests acute coronary syndrome or heart failure. Recommend ECG in suspected or acute coronary syndrome. An echocardiogram should only be ordered if it is likely to provide clinical benefit. Recent reports found that 7-17% of hospitalized patients with COVID-19, have a combination of elevated cardiac biomarkers, in addition to electrocardiographic and echocardiographic abnormalities. This myocardial injury appears to be a late manifestation. Supportive care depending on hemodynamic status. Once the diagnosis of acute coronary syndrome is made, medical management should be coordinated with cardiology. In a recent report it was observed that 23% of patients with COVID-19 had presentations

consistent with heart failure. Fulminant cardiomyopathy can occur and is thought to be a late feature described in patients recovering from respiratory failure. Cardiogenic shock and cardiac arrest contribute to 7-33% of deaths. SARS-CoV-2 is thought to infect host cells through ACE2 to cause COVID-19, while also causing damage to the myocardium, although specific mechanisms are uncertain. In the absence of high-grade AV block or unstable bradycardia, cardiogenic shock, or acute kidney injury (AKI), guideline directed medical therapies should be continued in patients with heart failure.

Acute Kidney Injury (AKI) requiring dialysis is reported in a subset of patients admitted to ICU. The exact mechanism is unclear at this point, but AKI is present in ~7% of patients with pathology demonstrating acute tubular necrosis (a reflection of multiorgan failure). AKI correlates with an overall poor prognosis and seems to be the strongest predictor of mortality.

### Management of Septic Shock and Cardiac Arrest<sup>26</sup>

Recognize septic shock in children with any hypotension or two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. Recognition and appropriate treatments within 1 hour of recognition include: antimicrobial therapy, and initiation of fluid bolus and vasopressors for hypotension. Give 10-20 mL/kg crystalloid fluid as a bolus as quickly as possible and reassess after each bolus. Avoid Excessive Fluid Resuscitation. The cause of death from COVID-19 is most often ARDS and subsequent complications. Patients usually present with normal lactate and blood pressure, but some patients do suffer from superimposed bacterial septic shock. Conservative fluid therapy should be considered for patients with evidence of hypoperfusion and a history suggestive of total body hypovolemia (e.g., prolonged nausea/vomiting and diarrhea). If there is no response to fluid loading or signs of volume overload appear, then reduce or discontinue fluid administration. This step is particularly important in patients with hypoxemic respiratory failure. Resuscitation endpoints include perfusion targets (e.g., urine output > 1 mL/kg/hr in children; improved level of consciousness; and lactate). Do not use hypotonic crystalloids, starches, or gelatins for resuscitation. Vasopressors should be administered when shock persists during or after fluid resuscitation to maintain Mean Arterial Pressure (MAP) goal 60-65 mmHg. If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and

vasopressors, consider an inotrope such as dobutamine. In children, epinephrine is considered first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine.

### **Steroids** <sup>27</sup>

Corticosteroids (Dexamethasone or equivalent) should be considered for use in children > 5 years with severe or critical COVID-19.

Dosing of Dexamethasone should be 150 micrograms/kg IV or PO (maximum 6mg) once daily for 10 days or until day of discharge from hospital if this is before completion of 10 days.

Corticosteroids should also be considered for children aged between 44 weeks gestational age and 5 years with severe or critical COVID on a case-by-case basis.

### **Investigational therapy** <sup>28-29</sup>

There is currently limited evidence of efficacy of antiviral and immunomodulatory therapy for COVID19 in adults, and no high-quality evidence in children. The decision to start specific treatment should therefore be made carefully on a case-by-case basis.

Antiviral treatment is likely to have the most benefit in the first phase of illness. Immunomodulatory therapy may only be indicated if clear evidence of hyperinflammation, or in the second phase of the illness, and evidence is currently extremely limited. Antiviral treatment and immunomodulatory treatment should be restricted for hospital use only and preferably in a clinical trial setting.

### **Remdesivir** <sup>30-31</sup>

Remdesivir is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related beta coronaviruses.

### **Chloroquine (CQ) and Hydroxychloroquine (HCQ)** <sup>32-33</sup>

These drugs have been widely used as anti-malarial treatment and prophylaxis and to treat autoimmune conditions. No high-quality evidence exists to support use at present. Potential toxicities include QTc prolongation and risk for arrhythmias. In vitro studies have reported antiviral activity against SARS-CoV and more recently against SARS-CoV-2. Studies conducted in China indicate in vitro activity of these agents against SARS-CoV-2, and a survey in French patients showed reductions in viral load. Significant use is occurring overseas and in some US

hospitals. A variety of dosing regimens have been in use, including: Hydroxychloroquine 400 mg PO BID x 1 days, then 200 mg PO BID x4 days.

### **Lopinavir/Ritonavir** <sup>32-33</sup>

Coronavirus cellular infectivity and replication are dependent on virally-encoded and cellular protease activity. Clinically used protease inhibitors effective for HIV and HCV infection have been examined for potential utility in treatment of SARS, MERS, and COVID19. Reports from China suggested this combination to be effective for COVID-19 treatment.

### **Host-directed anti-inflammatory strategies** <sup>34</sup>

ARDS and sepsis, life-threatening downstream complications of COVID-19 remain significant unmet therapeutic gaps. Numerous anti-inflammatory and anti-cytokine agents, as well as many other drug candidates, have been tried.

### **Anti-IL6 monoclonal antibodies** <sup>29</sup>

One anti-inflammatory agent that is receiving substantial attention currently is an anti-IL6 receptor humanized monoclonal antibody, tocilizumab. Several additional agents are under investigation and information is expected to emerge rapidly.

Caring for Infants and Mothers with COVID-19: Infection Prevention Control (IPC) and Breastfeeding <sup>35</sup>

Vertical transmission does not appear to occur, but perinatal infection leading to severe manifestations has been documented. It is unknown whether newborns with COVID-19 are at increased risk for severe complications, but transmission after birth via contact with infectious respiratory secretions is a concern. In addition to face mask and hand hygiene, consider temporarily separating a symptomatic PUI or COVID-19 mothers from her baby (e.g. separate rooms) depending on clinician judgement and individual circumstances. This carries risks as well (e.g., delayed maternal-child bonding, poor breastfeeding relationship, etc.). COVID-19 positive postpartum mothers as well as postpartum Patients Under Investigations (PUIs) will be counseled about the risks and benefits of colocation vs. separation. Postpartum patients who elect to 'rooming in' with their infants will be encouraged to wear a facemask and gloves and to practice hand hygiene before each feeding. They will also be encouraged to wash any skin that may come in contact with the infant (e.g., breasts, chest, arms, etc.). They will be encouraged to limit other close contact with the infant(s) and a separate non-infected caregiver should be present to help care for the infant. This separate noninfected caregiver should perform a majority of the infant's care. While not breastfeeding,

infants should be kept greater than 6 feet away from the mother within the room.

### Expressed Breast Milk<sup>36</sup>

Mothers who wish to breastfeed should be provided with a dedicated breast pump. Postpartum patients who are pumping should follow guidelines on equipment use and feeding. Wipe the surface where syringes/bottles will be placed after collection with a germicidal disposable wipe, and cover surface with clean paper towel or cloth. Mother will wash hands and breasts before use and cleaning equipment before and after use. Mother will wear a mask while pumping. Mother collects breast milk by hand or by pump into clean syringes or bottles then ensures syringe/bottle cap is secured.

### Infants<sup>37</sup>

Infants born to mothers with confirmed COVID-19 should be considered PUIs. All infants born to mothers with suspected or confirmed COVID-19 should be bathed immediately following delivery. These infants should be tested for COVID-19 before hospital discharge. Prior to discharge, inpatient providers will directly discuss care of the infant with the follow-up provider.

### Neonatal Intensive Care Unit (NICU)<sup>37</sup>

COVID-19 positive postpartum mothers and their household contacts should not be allowed to visit in the NICU. Any infant who has symptoms that meet criteria for NICU admission will be assessed by the NICU team and admitted to a COVID-19 cohort pod or other segregated section of the unit. For care teams assigned to infants requiring CPAP, or undergoing aerosolizing procedures such as intubation, full personal protective equipment (PPE) including N95 (or PAPR), eye shields, gown, hair cover, and gloves should be worn when caring handling the infant. Patients requiring nasal cannula or those who are intubated on mechanical ventilation (closed circuit) require contact/droplet precautions when handling to include surgical mask, gown, hair cover, and gloves.

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