REVIEW ARTICLE

Pediatric Coronavirus Disease 2019: Clinical Features and Management

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There is a lack of clarity regarding management of COVID-19 infection in children. This review aims to summarize the key clinical presentations and management of Pediatric COVID-19. The Medline database was searched for seminal articles and guidelines on COVID-19 presentation and management in children less than 18 years of age. COVID-19 has a lower incidence (1-5% of reported cases worldwide), causes milder disease with lower need for intensive care admission and lower mortality rate (0-0.7%) in children compared with adults. Multisystem inflammatory syndrome is a rare but severe complication in children. Majority of patients require supportive care including adequate hydration, nutrition and antipyretics. Supplemental oxygen therapy should be given in moderate to severe cases with all precautions to prevent air-borne COVID-19 spread. Steroids may be helpful in severe cases. Anticoagulation is indicated in moderate to severe cases with risk factors. More data on the efficacy and safety of antivirals and immunomodulators in children is needed.

Keywords: *Coronavirus, Dexamethasone, Remdesivir, SARS-CoV-2, Treatment*.

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The novel coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. The causative agent, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), attaches through its viral surface spike proteins to the angiotensin converting enzyme-2 (ACE-2) receptors on the respiratory epithelial cells. Although several months into the pandemic, there is a lack of clarity regarding management of COVID-19 infection in children. This review aims to summarize the key clinical presentations and management of Pediatric COVID-19 based on most pertinent available evidence. The Medline database was searched for seminal articles on COVID-19 presentation and management in children less than 18 years of age. The latest guidelines from World Health Organization (WHO) and Ministry of Health and Family Welfare (MoHFW), Government of India were also reviewed [1,2].

EPIDEMIOLOGY IN CHILDREN

Children account for less than 5% of diagnosed COVID-19 infections worldwide [3]. As per the MoHFW, 8% of the COVID-19 positive cases in India were contributed by people below 17 years of age [4]. Reports show a lower need for hospital and intensive care unit (ICU) admission and lower mortality rate (0-0.7%) in children compared to adults [5]. This may be due to lower exposure, strong innate immune response due to trained immunity, healthier blood vessel endothelium, excellent alveolar epithelium regeneration capacity and fewer co-morbidities [6]. The community spread of virus by children is of concern as a high rate of asymptomatic infection is seen in younger age groups. However, data show lower transmission rate by children than adults [7,8].

CLINICAL FEATURES

The median age of presentation in children ranged from 3.3-11 years in different studies with a male preponderance [5,9,10]. When compared to adults, majority of COVID-19 infected children are asymptomatic with gastrointestinal and mild respiratory manifestations being the commonest [5,9-11]. Anosmia and ageusia are difficulty to elicit in young children and reported less commonly [5]. Other symptoms include lethargy, altered sensorium, seizures, sore throat, fatigue, myalgias, oligo-anuria, and skin rash. Severe or critical disease (acute respiratory distress syndrome, respiratory failure, shock, myocardial failure, and multiorgan dysfunction) is described in less than 1-3% children [10]. Viral co-infections have been reported in around 6% patients. Underlying co-morbidities (underlying malignancy, nephrotic syndrome, chronic disease of kidney, lung, or liver) are associated in 9.9 - 42% of SARS-CoV-2 positive children [12,13]. It is imperative to evaluate and treat these common infections and co-morbidities as COVID-19 may just be a bystander.

The COVID-19 disease severity classification is presented in **Table I** [1,14]. Indications for admission include children with moderate, severe or critical COVID-

Table I COVID-19 Disease Severity Classification

Clinical severity	*Clinical presentation*	*Clinical parameters*
Mild	Symptomatic patients meeting the case definition for COVID-19	Fever, cough, sore throat, fatigue, anorexia, nasal congestion, malaise, headache, diarrhoea vomiting, nausea *without* evidence of viral pneumonia or hypoxia.
Moderate	Pneumonia	Child with clinical signs of pneumonia (cough or difficulty breathing *and* fast breathing *and/or* chest indrawing) *and* no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥60; 2-11 months: ≥50; 1-5 years: ≥40; 5-10 years: ≥30; 11-18 years: ≥24. Chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe	Severe pneumonia	Child with clinical signs of pneumonia at least one of the following: 1. Central cyanosis or SpO2 < 90% 2. Severe respiratory distress (e.g. grunting, very severe chest indrawing) 3. Any of the general danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.Chest imaging may provide corroborative evidence and identify or exclude complications.
Critical	Pediatric Acute Respiratory distress syndrome (PARDS) [14]	PARDS is said to occur in child with *all* of the following: 1. Acute onset (within 7 days of known clinical insult) 2. Respiratory failure (not fully explained by cardiac failure or fluid overload) with 3. Chest imaging findings of new infiltrate consistent with acute parenchymal disease with 4. Exclusion of perinatal related lung disease with 5. Oxygenation requirement as (a) or (b) (a) Non-invasive mechanical ventilation: Full face mask bi-level ventilation *or* CPAP ≥5 cm H_2O with PaO2: FiO2 ratio ≤300 *or* SpO2:FiO2 ratio ≤264 (b) Invasive mechanical ventilation: Mild: 4 ≤OI <8 *or* 5 ≤OSI <7.5) Moderate: 8 ≤OI <16 *or* 7.5 ≤OSI <12.3; Severe: OI ≥16 *or* OSI ≤12.3
	PARDS at risk [14]	PARDS at risk is said to occur in child with all of the above points 1 to 4 with oxygenation requirement as (a) or (b) (a) Non-invasive mechanical ventilation: Nasal mask CPAP or BiPAP requiring FiO2 ≤40% to attain SpO2 of 88-97%; or, Oxygen via mask, nasal cannula or high flow: SpO2 88-97% with oxygen supplementation at minimal flow as age <1 year: 2 L/min; 1-5 years: 4 L/min; 5-10 years: 6 L/min; >10 years: 8 L/min (b) Invasive mechanical ventilation: Oxygen supplementation to maintain SpO2 ≥88%, but OI< 4 *or* OSI <5
	Sepsis	*Suspected or proven infection and ≥2 of 4 age-based systemic inflammatory response syndrome (SIRS) criteria of which one must be (a) or (b)* a) Abnormal temperature (> 38.5 °C or < 36 °C) b) Abnormal white blood cell count for age or > 10% bands c) Tachycardia for age or bradycardia for age if < 1 year d) Tachypnoea for age or need for mechanical ventilation
	Septic shock	Any hypotension (SBP < 5th centile or > 2 SD below normal for age) corroborating with clinical markers *or* More than two of the following: a) altered mental status b) bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children) c) prolonged capillary refill (> 2 sec) or weak pulse d) mottled or cool peripheries e) reduced urine output

OI (Oxygenation index) = (FiO2 × mean airway pressure × 100)/PaO2; OSI (Oxygen saturation index) = (FiO2 × mean airway pressure × 100)/SpO2

19 disease. Mild disease can be managed at home. However, if the child has any underlying co-morbidity or if home isolation is not feasible, the child may managed at a COVID care centre or hospital.

INVESTIGATIONS

All patients with moderate to severe COVID-19 should undergo investigations as detailed in **Box I.** Investigations to rule out other possible differentials (like enteric fever, dengue, malaria, etc.) should be done as indicated.

MANAGEMENT

Mild Cases

Mild cases should be isolated at home, a community facility (COVID care-center) or a health facility decided on a case-to-case basis [1,2]. Pre-requisites for home isolation include apt residential conditions for quarantine of patient and family contacts, absence of co-morbidities and presence of a caregiver with communication link to the hospital. Strict adherence to home quarantine guidelines is necessary [22]. Any difficulty in breathing, grunting, inability to breast feed, bluish discoloration of lips or face, dip in oxygen saturation <95%, chest pain, mental confusion, inability to arouse and reduced interaction when awake should prompt urgent referral to a dedicated COVID health center or hospital. Symptomatic treatment should be given with antipyretic (Paracetamol) for fever and pain when necessary, adequate nutrition and rehydration, and identification and treatment of any underlying co-morbidities or co-infections. In children with symptomatic respiratory tract infection, routine use of antibiotics is not recommended except in situations of suspected or confirmed bacterial co-infection. Respiratory tract infection management should be followed as per existing protocols [23].

Asymptomatic cases who are incidentally detected like contacts of a diagnosed case or planned for an elective surgery may be isolated and monitored. A COVID positive status during surgery may pose a risk for infection spread and portend poor surgical outcome [24]. Therefore, elective surgeries should be delayed until patients test negative for COVID-19 [25,26].

Moderate Cases

Moderate cases should be treated in a dedicated COVID health center or hospital with detailed clinical history and regular assessment for vital signs, work of breathing and oxygen saturation (SpO2). Investigations as described in

Box I Suggested Investigations and Typical Findings in Children With Moderate to Severe COVID-19

Required	
Complete blood count (CBC):	Leucopenia has been reported in 6-26.3% children and lymphopenia in 3.5-40% children [15].
Liver function tests (LFT):	Persistent leucopenia, lymphopenia, and thrombocytopenia suggest severe disease.
Kidney Function test (KFT):	Raised liver transaminases may be seen in one-third children.
Chest *X*-ray (CT Thorax is best avoided for diagnostic screening routinely):	Milder and more focal findings than adults, typically as ground-glass opacities and consolidations with unilateral lower-lobe and peripheral predominance, which regress during recovery time [16].
Preferred	
D-dimer, coagulation profile, serum ferritin, C-reactive protein:	Raised D-dimer and fibrinogen degradation products (found in 12-17.5% children), ferritin and CRP (found in 13.6% cases) levels are associated with severe disease, cytokine storm and multi-organ dysfunction [17]. Prolongation of aPTT and INR may be seen.
Electrocardiogram (ECG), Echocardiography (ECHO), Cardiac biomarker levels (troponin, CK and CK MB):	Prolonged PR interval, ST-T segment changes, atrioventricular block, arrhythmia, tachycardia, and low voltage are suggestive of cardiac injury, dysfunction in severe COVID-19. Raised cardiac enzymes indicate myocarditis or myocardial injury; are associated with severe disease ECHO may identify myocarditis, valvulitis, pericardial effusion, and coronary artery dilatation [18].
Desired	
LDH levels, serum IL-6 serum procalcitonin:	Higher IL-6 and LDH levels are shown to correlate with disease severity but not routinely recommended [19,20]. Raised procalcitonin levels may indicate a bacterial co-infection or severe COVID-19 disease while a lower level has a high negative predictive value for a bacterial co-infection [21].

CT-computerized tomography; CK-creatine kinase; CK-MB-creatine kinase myocardial band; IL-6-interleukin-6; LDH-Lactate dehydrogenase.

Table II should be done at admission [1,2]. General management should be done as stated above. Additionally, the following may be considered [1,2].

i) Supplemental oxygen therapy should be used for distressed breathing or hypoxia (detailed below with management of severe cases). Bronchodilators if required are preferably delivered with an MDI and spacer instead of a nebulizer.

ii) Empiric antibiotic therapy may be given in under-five children. In the absence of hypoxia, an oral antibiotic (amoxycillin-clavulanic acid/azithromycin) may be added while intravenous ceftriaxone (50-100 mg/kg/day in two divided doses) may be started for moderate COVID-19 cases with hypoxia or infiltrates on chest X-ray.

iii) Chloroquine (5–10 mg/kg/day for 5-10 days) was used in children with moderate to severe COVID disease in initial months of the pandemic [27]. However, latest evidence shows no role of chloroquine or hydroxychloroquine in treatment of COVID-19 [28].

Close monitoring for disease progression, repeat investigations at 48-72 hours if needed and provision of transportation to dedicated COVID care hospital should be available.

Severe and Critical Cases

All severe and critical COVID-19 cases should be admitted in a dedicated COVID care hospital with detailed work-up as elucidated above. Continuous monitoring of vitals, work of breathing and SpO2 should be done.

i) All patients should be started on empirical intravenous antibiotics (third generation cephalosporins) within an hour of arrival which should be escalated as per clinical assessment.

ii) Aggressive intravenous fluid resuscitation should be avoided as it may worsen oxygenation.

iii) Experience of awake proning in children is limited as their tolerance may not be good and any agitation can worsen hypoxia.

iv) Supplemental oxygen therapy is required to maintain SpO2 ≥ 94% while taking all precautions to minimize aerosol generation.

The following modes of oxygen delivery may be used:

Conventional oxygen therapy may be given using nasal prongs/cannula, oxygen mask or hood. Non-rebreathing mask can provide up to 95% FiO2 at oxygen flow rate of 10 -15 L/ min and can be used for short periods initially [29].

HHHFNC/HFNC (Heated humidified high flow nasal canula**)** [30], is indicated in patients with mild ARDS without evidence of hemodynamic instability, altered mental status or multi-organ failure. However, in absence of response, consider early escalation to BiPAP/invasive ventilation. Although, increased aerosolization risk with HHHFNC has been speculated, the certainty of evidence is low and it is a widely preferred option in resource poor settings. A triple layer mask may be used to cover the mouth and nose of the patient over the nasal cannula to decrease aerosolization [29].

Non-invasive Ventilation

BiPAP (*Bilevel Positive Airway Pressure*): It is indicated for mild acute respiratory distress syndrome without hemodynamic instability, altered mental status or multi-organ failure. However, its use is feasible only in an older, cooperative child accepting of oronasal BiPAP mask [29].

Bubble CPAP (*Continuous positive airway pressure*) may also be used for newborns and children with severe hypoxemia.

Invasive Ventilation

Tracheal intubation should be performed when failure/ contraindication of BiPAP/HFNC occurs. The following specific precautions are needed:

- Pre-oxygenate with a non-rebreathing mask (NRM) or tight-fitting face mask attached to a self-inflating bag with100% oxygen for 5 minutes. Avoid bag and mask ventilation (BMV) to limit aerosolization and if required, use low tidal volumes.
- Follow Rapid sequence intubation using sedation and analgesia (to avoid cough reflex).
- Use a cuffed endotracheal tubes (ETT)
- Ensure intubation by most experienced person to minimize attempts and use video laryngoscope for intubation to maintain safe distance from patient.
- May use a plastic sheet to cover the head, neck and chest of patient to minimize contamination.
- Use disposable ventilator circuits and hydrophobic viral filter between the ventilator circuit at the expiratory end.
- Use closed suction to minimize contact with secretion and aerosol release.

The pediatric ARDS protocol for management should be used. Prone ventilation may be difficult to conduct in a child and may unnecessarily increase the risk of infection to the healthcare workers.

Extracorporeal membrane oxygenation (ECMO) may be considered in patients with continued severe hypoxemia despite maximal ventilatory support.

Management of Shock

Standard care includes early recognition and the initiation of antimicrobial therapy and slow crystalloid fluid bolus within 1 hour of recognition and vasopressors for fluid non-responsive hypotension. Further management may be as per the Surviving Sepsis Campaign guidelines for the management of septic shock in children [31].

Adjunctive Therapies for COVID-19

Steroids: Glucocorticoids may be considered for patients with severe or critical COVID-19 disease with progressive deterioration of oxygenation indicators, rapid worsening on imaging and excessive activation of the body's inflammatory response. The recommended doses include intravenous methylprednisolone 1 – 2mg/kg/day (maximum 80 mg) for 10 days or oral/ injectable dexamethasone 0.2-0.4 mg/kg/day OD (maximum of 6 mg) for 5 days [1,2]. These recommendations have been extrapolated from studies conducted chiefly in adults. The UK-based RECOVERY trial) reported dexamethasone to reduce mortality in patients who required respiratory support [32]. The proportion of children enrolled and analysed was not clear.

Anticoagulation [17,33]: Recommendations for use in children are listed in **Box II**. Thromboprophylaxis, both mechanical (with sequential compression devices, where feasible) and anticoagulation are recommended. Low molecular weight heparin (enoxaparin) 1.5 IU/kg/dose subcutaneous twice a day for <2 months age and 1 IU/kg/ dose twice a day for >2 months should be used. Unfractionated heparin may be used for children who are clinically unstable or have severe renal impairment as loading dose 75-100IU/kg intravenous in 10 min followed by initial maintenance dose of 28 IU/kg/hour for age <1 year and 20 IU/kg/hour for 1-18 years (target aPTT between 65-80 seconds). Anticoagulation therapy may be continued till resolution of the hypercoagulable state or resolution of the clinical risk factors for venous thrombo-embolism [17].

Thromboprophylaxis is contraindicated in active/ major bleeding, need for emergency surgery, platelets < 20,000/mm^3, concomitant aspirin administration at doses >5 mg/kg/d and malignant hypertension.

Remdesivir: There are no comparative clinical data evaluating the efficacy or safety of remdesivir for COVID-19 in pediatric patients. Although, initial guidelines contraindicated its use in children < 12 years, the US Food and Drug Administration issued an Emergency Use Authorization (EUA) to permit the use of remdesivir for treatment of COVID-19 in hospitalized pediatric patients [34]. As per NIH guidelines, remdesivir is indicated only in moderate COVID-19 with supplemental oxygen requirement where it shortens the time to recovery [34,35]. It may be considered in severe to critical COVID-19 (high flow oxygen device, NIV, invasive ventilation or ECMO) with dexamethasone (expert opinion) [34]. The latest guidelines are similar for children albeit extrapolated from adult data and recommended as a part of clinical trials [36]. Few case series in children show promise [37].

For children weighing > 40 kg, a single loading dose of 200 mg on day 1 followed by once daily dose of 100 mg from day 2 for 5-10 days is used. For children weighing 3.5-40 kg, a single loading dose of 5 mg/kg on day 1 followed by 2.5 mg/kg once daily from day 2 for 5-10 days may be given. The contraindications for its use include AST/ALT > 5 times upper limit of normal (ULN) and severe renal impairment (eGFR <30mL/min/m^2 or need for hemodialysis). Remdesivir should not be used in combination with chloroquine or hydroxychloroquine [34].

Tocilizumab (TCZ): It is a monoclonal antibody against interleukin-6 (IL-6) receptor which emerged as an alternative treatment for COVID-19 patients with cytokine

Box II Recommendations for Use of Thromboprophylaxis in Children With COVID-19

Moderate to severe COVID with any one of the following:

- D-Dimer levels more than 5 times the upper limit of normal
- One or more non-COVID risk factor for hospital acquired thrombo-embolism
  (Central venous catheter, mechanical ventilation, prolonged length of stay, complete immobility, obesity, active malignancy, nephrotic syndrome, cystic fibrosis exacerbation, sickle cell disease vaso occlusive crisis, flare of underlying inflammatory disease, congenital or acquired cardiac disease with venous stasis, previous history of VTE, First degree family history of VTE before age 40 years or unprovoked VTE, known thrombophilia, pubertal, post pubertal, or age >12 years, receiving estrogen containing oral contraceptive pill or post splenectomy for underlying hemoglobinopathy)
- Children with MISC with coronary artery aneurysms or low left ventricular ejection fraction

VTE: Venous thromboembolism; MISC: multisystem inflammatory syndrome in children.

storm. While initial systematic reviews show that TCZ resulted in reduction of mortality in severe COVID-19 cases compared to the standard treatment, the latest trials showed no benefit [38-40]. A larger ongoing RCT which is also enrolling children may provide clearer answers [41]. The use of TCZ is suggested only in context of clinical trials [34] in those with moderate/severe disease where oxygen/ventilation requirement is increasing after use of steroids with extensive bilateral lung disease on radio-imaging [2,17]. The dose of TCZ for >30 kg is 8 mg/kg (up to maximum of 800 mg) and <30 kg is 12 mg/kg given as intravenous infusion over 1 hour once, may be repeated if required at 12-24 hrs.

Contraindications to use include patients with HIV, those with active infections (uncontrolled systemic bacterial/fungal), tuberculosis, active hepatitis (total bilirubin or AST/ALT raised > 5 times ULN), ANC < 500-2000/mm3 and platelet count <50,000-1,00,000/mm3. Recipients should be carefully monitored for secondary infections, neutropenia, and thrombocytopenia. All patients should obtain a latent tuberculosis (TB) test before TCZ therapy. If the text is positive, treatment for tuberculosis should be started prior to administration although, the risk for latent TB reactivation is very compared to the benefit of administering TCZ. Safety profile of TCZ in COVID-19 patients is yet to be understood.

Convalescent plasma therapy (CPT): It may be considered in patients with moderate disease who are not improving with steroids. Few reports of its use in children with severe COVID-19 show promise [42,43]. Special considerations while using CPT include ABO compatibility, neutralizing titre of donor plasma above the specific threshold and avoidance of use in patients with IgA deficiency or immunoglobulin allergy. While adult trials have used doses of 4 to 13 ml/kg (usually 200 mL single dose) given slowly over 2 hours, 2-4 mL/kg of convalescent plasma has been used in children [43].

Other Agents Under Evaluation

Ivermectin, a potent in vitro inhibitor of the COVID-19 causative virus (SARS-CoV-2) with an established safety profile for human use, was shown to be beneficial in COVID-19 [44]. A newer agent under evaluation is the interleukin (IL)-1 inhibitor anakinra which may be considered for immunomodulatory therapy (>4 mg/kg/day intravenous or subcutaneous) in COVID-19 with hyperinflammation. Initiation of anakinra before invasive mechanical ventilation may be beneficial [33]. Other potential treatments under evaluation include interferon-beta, anti-IL-6 receptor monoclonal antibodies (sarilumab), anti-IL-6 monoclonal antibody (siltuximab), Bruton's tyrosine kinase inhibitors, acalabrutinib, ibrutinib, zanubrutinib) and Janus kinase inhibitors (baricitinib, ruxolitinib, tofacitinib). A recent trial has shown benefit of baricitinib-remdesivir combination compared to remdesivir alone in reducing recovery time in COVID-19 patients [45]. However, there is insufficient data for recommending use of any of these agents in children except in the context of a clinical trial [34].

Discharge Criteria and Follow-Up

The patient with mild to moderate disease can be discharged after 10 days of symptom onset and no fever or oxygen requirement for three consecutive days with complete resolution of symptoms prior to discharge [48]. Negative RT-PCR before discharge is not required. Home quarantine for 7 days post-discharge is necessary. Patients with severe disease and immunocompromised states (like cancer transplant recipients and HIV) should have complete resolution of symptoms and negative RT-PCR test report prior to discharge [48].

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

MIS-C is a post-infectious inflammatory response syndrome (characterized by high levels of pro-inflammatory cytokines CTNF, IL-6 and IL-1β) following SARS-CoV-2 infection. Various diagnostic criteria have been provided by WHO and CDC [33]. A tiered investigational approach is followed in patients without life-threatening manifestations, while work-up is done simultaneously for the sick children [33]. Patients may require additional investigations to rule out any co-infection/other cause of illness.

Children with life threatening manifestations should be admitted in PICU management. Children with acute COVID inflammation (RT-PCR positive) with symptoms like Kawasaki disease (KD) should receive intravenous immunoglobulin (IVIG) (dose-2g/kg over 1-2 days) and remdesivir if available. Children with remote COVID infection with KD symptom overlap should receive IVIG and aspirin (20–25 mg/kg/dose every 6 hourly or 80-100 mg/kg/day) steroids may be added. In children with remote COVID infection with predominant cardiovascular involvement (myocarditis/cardiogenic shock/distributive shock) with or without KD symptom overlap IVIG, 3-day pulse of methylprednisolone with tapering and LMWH prophylaxis are to be considered as disease modifying agents [46].

Sick children should receive initial broad-spectrum antibiotics considering symptom overlap with severe bacterial infection. Ceftriaxone or meropenem with vancomycin or clindamycin or teicoplanin may be used

for the sickest children. In stable patients with MIS overlap, with mild lab abnormalities and lacking alternate diagnosis, ceftriaxone may be given. Metronidazole is added if gastro-intestinal symptoms are predominant.

All children with MIS-C require ongoing clinical monitoring while laboratory investigations may be repeated every 24-48 hourly as guided by the clinical condition [47].

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