COVID - 19

CRITICAL CARE MANAGEMENT OF PEDIATRIC COVID-19

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Abstract: *Children tend to have relatively milder COVID-19 illness compared to adults. However, a small proportion of children may need critical care support either due to hypoxic respiratory failure or due to multi-system inflammatory syndrome (Pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2). While the principles of management are consistent with any other severe acute respiratory illness, there are numerous challenges to ensure that the healthcare workers are adequately protected. Significant planning and prior preparation are required to overcome these challenges. Even in the rare circumstances of severe illness in children, good outcomes are possible. The role of specific therapies is unclear and a brief review of medication is presented.*

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Children have been relatively less affected than adults in both frequency and severity of COVID-19 caused by the SARS-CoV-2 virus.[1] Given the rarity of severe disease in children, international critical care community response, including in the USA and UK, has largely been focused on expansion of adult critical care units and redeployment of personnel and equipment from pediatric critical care into adult critical care units to cope with the surge in numbers of critically ill adults with COVID-19. While children needing critical care with COVID-19 is a relatively rare occurrence, severe disease and COVID-19 related deaths in children have also been reported.[2] More recently, a possibly SARS-CoV-2 related, multi-system inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome affecting children has been reported.[3] While debate about appropriate nomenclature for this condition is still ongoing, it is currently referred to as 'pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2' (PIMS-TS).[4] It is therefore of utmost importance that the pediatric critical care community is well versed with strategies and considerations for managing children with confirmed or suspected COVID-19.

PICU admission- Indications

Assessment of children should follow established institutional policies. However, given the high infectivity of SARS-CoV-2 virus, risk-assessment to identify appropriate level of personal protective equipment (PPE) to protect the health care workers (HCW) should be performed. This may include obtaining information about symptoms and signs, travel, contact history and the results of any recent tests for SARS-CoV-2 virus before reviewing the children. Where this is not practical or feasible in situations when urgent assessment is required, high level of personal protective equipment (PPE) including that used for aerosol generating procedures (AGP) may be the safest option. This 'full PPE' includes water-repellent protective

body suit or long-sleeved gown, double gloves, wipeable shoes or shoe covers, N95 mask or filtering face piece 3 (FFP3) or FFP2 mask fit-tested for each staff member and visor/goggles ± head cap. There is no clear evidence to suggest a different threshold for PICU admission related to COVID-19 infection compared to other childhood pneumonias or severe acute respiratory infections (SARI). In general, the following clinical scenarios may necessitate a PICU admission.

- Requirement for significant respiratory support that cannot be provided elsewhere such as non-invasive or invasive ventilation. This may be due to hypoxia, hypercarbia or increased work of breathing.
- Requirement for cardiovascular support including multiple fluid boluses or inotropes. This may be because of hyperinflammatory syndrome, myocarditis or significant co-infections.
- Deterioration of neurological status. This may be due to direct COVID-19 related neurological complications (e.g. seizures, encephalopathy) or related to respiratory complications such as hypoxia.
- Any child considered to be at risk of further deterioration requiring continuous or close monitoring requiring higher nurse: patient ratios.

PICU management - General principles

Hypoxic respiratory failure has been widely reported in adults with SARS-CoV-2 infection and is the most common indication for ICU admission. Respiratory illness related to COVID-19 in children may resemble other causes of SARI including other bacterial or viral pneumonias. While characteristic radiological and laboratory features have been described in adults, non-specific changes are the norm in children with COVID-19. A high-index of suspicion and low threshold for testing for SARS-CoV-2 antigen by PCR is required. Due to sub-optimal sensitivity of the SARS-CoV-2 PCR test, a single negative test is not sufficient to exclude COVID-19 with high-level of certainty in patients with a high pre-test probability. The pre-test probability also depends on the population prevalence of COVID-19 and therefore will need to be interpreted in context of wider picture of the stage of the pandemic within the local area. Therefore repeat testing with nasal, throat or nasopharyngeal swabs in patients who are not invasively ventilated or lower airway specimen such as endotracheal aspirates in invasively ventilated patients may be required. Two or more tests may be required before full PPE precautions are stepped down to droplet PPE precautions (aprons, gloves, fluid-repellent surgical mask ± visor/ goggles), especially in those admitted with a SARI without an alternative diagnosis.

Where possible, children with suspected COVID-19 should be treated in single-occupancy negative pressure cubicles, at least until COVID-19 is excluded with reasonable certainty. Where this is not possible, every effort should be made to minimise exposure of other patients admitted to PICU for reasons unrelated to COVID-19. Consideration of additional visiting restrictions and arrangements for isolation of parent/carers along with the children where appropriate may be required. Significant planning and re-organisation of the physical ICU footprint and staffing models may be required to ensure that this is possible. Communication between team members can be difficult while wearing PPE. Similarly the use of phones, computers and other resources may be limited inside the cubicles with COVID-19 patients. Working in full PPE for prolonged periods may cause dehydration of the health care worker (HCW). It is important to stress, however, that while significant changes may be required for infection prevention and control purposes, the clinical management principles of a child with COVID-19 are identical to any other SARI.

Respiratory failure - Management

There is no specific evidence to guide a different management strategy for respiratory failure in children with COVID-19, compared to children with other causes of SARI. However, minimising HCW' exposure to aerosols by reducing AGP and where this is unavoidable, using appropriate PPE precautions is the key.[5] Having minimal number of personnel, reducing equipment in close proximity, decontamination of exposed equipment, use of disposable equipment where possible are all important. Significant uncertainties related to procedures which are associated with aerosol generation exists. While there is a school of thought that early invasive ventilation, avoiding non-invasive ventilation and/or high flow nasal cannula (HFNC) oxygen therapy minimises HCW exposure to aerosols, it may not be practicable or safe in all circumstances. Therefore, step-wise escalation of respiratory support as with other causes of SARI may be the best course of action in children with COVID-19 also.[6] Management principles for ARDS in adults with COVID-19 may largely apply to pediatric critical care management also. An informative summary of escalation of respiratory support and management of COVID-19 related acute respiratory distress syndrome (ARDS) can be found in website of 'The Society of critical Care Medicine'.[7]

High flow nasal cannula (HFNC) oxygen therapy

Children with hypoxia (oxygen saturation <92%) should receive supplemental oxygen. In children who

require higher concentration of supplemental oxygen, heated and humidified oxygen with HFNC may be well tolerated and may reduce the need for invasive ventilation. There is limited evidence behind the concerns about aerosol generation due to HFNC. In fact a recent study showed that the aerosol production from HFNC was no worse than spontaneous respiration regardless of presence or absence of cough and regardless of higher or lower flows used in HFNC.[8] Some North American centres do not consider HFNC as an AGP. It is probably safe to use HFNC for children with mild-moderate disease severity, especially if the HCW uses full PPE and children are nursed in cubicles. Routine monitoring of heart rate, respiratory rate, fractional inspired oxygen (FiO_2), work of breathing and comfort levels are essential to assess the effectiveness of HFNC therapy. In fact, nearly a quarter of the children in the North American cohort of COVID-19 were managed with HFNC only.[2] HFNC therapy therefore is a useful immediate respiratory support. However, treatment failure needs to be promptly recognised and respiratory support rapidly escalated to either non-invasive ventilation (NIV) or invasive mechanical ventilation.

Non-invasive ventilation

NIV using a full face or oro nasal mask interface can be tried in selected patients based on local experience. Bubble CPAP may especially be a useful mode of support in young infants. As with HFNC, effectiveness and response to therapy should be carefully evaluated. Escalation to invasive ventilation should not be delayed especially in those children with a rapidly deteriorating disease trajectory. Intubation must be recommended if there is no improvement in oxygenation (target SpO_2 92 - 97% and FiO_2 < 0.6) within 60-90 minutes of initiating NIV.[9] As with HFNC, the risk associated with aerosol generation and exposure to HCW should be carefully considered and appropriate PPE worn.

Invasive ventilation

Strategies to minimise HCW protection from aerosols during invasive mechanical ventilation of suspected or confirmed COVID-19, may include the use of appropriate full PPE, inline suction, minimise circuit disconnection, temporary clamping of endotracheal tube (ETT) when disconnection is essential, passive humidification with a heat moisture exchanger (HME) filter rather than active humidification, viral filter in the expiratory limb of the ventilator circuit and pre-attached viral filters in bagging circuits for use in emergencies.

In children requiring mechanical ventilation, established strategies for lung protective ventilation should be followed. Initial setting should aim to achieve tidal volumes between 4 to 8 mL/kg of ideal body weight, with a PEEP between 6 to 10 cm H_2O and plateau pressure under 28 cm H_2O.[10,11] Permissive hypoxia (SpO_2 88-92% if PEEP >10, or else 92-97% if PEEP <10cm H_2O) and permissive hypercapnia (if pH >7.15) are acceptable to achieve optimal lung protection.[10, 11] Deep sedation with or without muscle relaxation may be needed to facilitate this.

Prone position has been thought to provide survival advantage in adults with severe hypoxemia (PaO2/ FiO_2 ratio < 150). Prone ventilation can improve oxygenation and lung homogeneity in children, although a survival advantage has not been demonstrated.[12] Proning is recommended for 12-16 hours/day in adults and due precaution needs to be taken to avoid complications like pressure sores and ET tube obstruction/displacement. It is likely that pediatric critical care units have had already experience with proning and have set policies and procedure which would help them to adapt to it. For e.g., adaptation would need to ensure that disconnection of ventilator circuit does not occur.

Trial of inhaled Nitric Oxide is warranted in children with persistent hypoxemia. High frequency oscillatory ventilation (HFOV) has been used in neonates and children with severe hypoxemia as a rescue therapy. However, the disadvantage with HFOV is that it is an open circuit with potentially significant aerosol generation. HFOV circuits with viral filters are available and are strongly recommended if that is considered.

Extra-corporeal oxygenation

Extra-corporeal oxygenation (ECMO) has been used in adults with SARS-CoV-2 in established and adequately resourced ECMO centres with variable outcome. This has usually been necessitated for refractory hypoxemia despite conventional ventilator management strategies including the use of prone positioning and inhaled nitric oxide. Very few children with COVID-19 have required ECMO.[13] Children have also been placed on ECMO for PIMS-TS (rather than acute COVID-19) for cardiovascular support if significant myocardial impairment exists.[3] Given the rarity, it is unlikely that clearly defined indications for ECMO support in children with COVID-19 can be agreed upon. Individualised decision making with adaptations of existing ECMO guidelines and wider consultation with various team-members will therefore be required. Key components of planning for ECMO use during a pandemic include: resource planning, personnel assignment, training, infection control on ECMO, planning for ECMO transfers etc.[14] The use of ECMO should be

restricted to experienced centres and the effect on resource utilisation in the midst of a pandemic should be carefully considered.

Other supportive care

Judicious fluid management is the key to the care of any critically ill child. Fluid overload is associated with increase in morbidity and mortality in critically ill children. Following restoration of intravascular volume, a restriction of daily allowance to 70-80% of calculated fluid requirement using Holliday-Segar formula is a good starting point. Fluid balance should be assessed clinically and using input/output chart daily, allowance made for ongoing fever and associated insensible losses and with measured body weight when feasible and safe to do so. Enteral feeding should be commenced at the earliest possible opportunity, if safe to do so. Empirical antibiotics are justified until a diagnosis is established and/or co-infections are excluded even if the SARS-CoV-2 PCR is positive. Choice of antibiotics depends on local prevalence of the various bacteria.

Other considerations

Intubation and extubation

Intubation is probably the pediatric critical care procedure associated with the most amount of aerosol production. Therefore it is done with utmost care with PPE including careful donning and doffing and use of a donning/doffing buddy. Medical literature, especially the social media, is flooded with various improvisations of the procedure to minimise HCW exposure to aerosols. Examples include perspex boxes, plastic cling film covering the patient etc. However, the unproven but potential additional protection offered by these devices should be carefully weighed against difficult ergonomics, human factors, operator difficulty related to unfamiliar equipment, spreading the infection while removing the additional device and consequences of intubation failure. Regardless of any new equipment used, team simulation for intubating a COVID-19 patient is essential to fine tune the procedure and adapt it to the local environment and personnel. The challenges of performing pediatric critical care procedures while wearing full PPE cannot be underestimated. The use of a checklist, such as the one produced in conjunction with the UK Pediatric Intensive Care Society can be invaluable.[15] It is recommended that the most experienced airway operator intubates the child and where possible cuffed endotracheal tubes should be used to minimise leak around the tube. The use of video laryngoscopes has been recommended in several guidelines. However, familiarity is the key. Routine induction medications used by pediatric critical care physicians to provide optimal intubating conditions in other critically ill children can also be used for children with COVID-19. This often includes a combination of ketamine, and/or an opioid and/or a benzodiazepine. Bag and mask ventilation is avoided to limit aerosol generation, if clinical situation permits. If required, as low a tidal volume as possible with a low respiratory rate may be prudent. A heat moisture exchange (HME) filter can be placed between the mask and the bagging circuit. Prior to connecting to ventilator, the ETT can be temporarily clamped while attaching to the ventilator circuit. Viral filters are recommended in the expiratory limb (between the circuit and machine), but significant variations in compatibility based on the make and model of the ventilators may exist.

Extubation may also produce significant aerosols and therefore similar appropriate precautions apply.

Intra-and inter-hospital transport considerations

The key principles relevant to the transport of a child with COVID-19, whether within the hospital (e.g. for a CT scan) or between hospitals (e.g. for enhanced care), are similar. The primary consideration is always to maintain patient safety; however, the additional consideration of staff safety is important when dealing with COVID-19 due to its highly infectious nature.

Preparation for transport: It is important to identify early, the COVID-19 status of the patient, either suspected (based on the case definition) or confirmed by laboratory testing. COVID-19 status will affect several aspects of the transport: the type of PPE needed, the seniority of staff involved (most senior personnel), logistics of moving the patient (ground ambulance, air ambulance, trolley push within the hospital), the choice of respiratory support provided (non-invasive versus invasive ventilation) and appropriate decontamination of transport equipment. All staff involved in the transport of children with COVID-19 should be in full PPE to protect against AGP.[16] Common AGP performed during transport include HFNC, NIV, endotracheal intubation and open endotracheal suction. If patients are self-ventilating, a surgical face mask can be considered to minimise aerosol spread.

Airway and respiratory management: Inter-hospital transfers of children on HFNC or NIV are challenging due to aerosolisation risk - staff must be in full PPE throughout and the ambulance must not re-circulate air (instead, should be set to exhaust). Where possible, NIV should be delivered using dual-limb circuits and unvented face masks.

Alternatively, a high-efficiency viral filter should be attached proximal to the expiratory leak.[9] Emergency intubation is a high-risk procedure even without the challenges of full PPE and therefore the need for intubation during patient transport should be avoided wherever possible by early identification of NIV failure and early intubation.[10] Use of a standardised checklist for intubation, as highlighted earlier, is recommended.[15] Transport ventilators are often turbine-driven and use ambient air rather than compressed medical air from cylinders, therefore viral filters are recommended on the inspiratory limb of the circuit (to prevent the patient being infected) as well as expiratory limb of the circuit (to prevent the ventilator being contaminated by the patient).

Patient handover: To avoid contamination of clean areas of the receiving hospital, a secure and dedicated pathway for accessing the relevant areas (e.g. ICU, CT scanner) should be identified and followed during intra and inter-hospital transfer. Following verbal handover, transfer documentation may be transmitted by electronic means, where possible, due to the risk of contamination of paper notes during transport.

Equipment and decontamination: To avoid equipment wastage due to contamination, they should be in wipeable, closed, small pouches (e.g. airway equipment, resuscitation drugs) that should be opened only if required. Decontamination of equipment such as the patient trolley, transport ventilator, infusion pumps and patient monitor should be performed using universal detergent wipes followed by a 1:1000 chlorine-based solution/wipes. The exposed surfaces of the ambulance will require similar decontamination, especially if an AGP was performed during transport.

Cardiopulmonary resuscitation (CPR)

Cardiac arrest due to COVID-19 in children is an extremely unlikely event. However, in children who unfortunately have an in-hospital cardiac arrest, the COVID-19 status may be unclear either because of unclear history, awaiting test results, or because of a concern that a repeat test is warranted due to the sequence of events leading to the cardiac arrest. In any case, HCW protection is an important consideration in CPR as with the other pediatric critical care aspects mentioned here. There is limited evidence base related to status of CPR as an AGP.[17] However, it has been helpful that various life support organisations have produced consistent consensus statements recommending that the HCW donning PPE before commencing CPR in patients with suspected or confirmed COVID-19 because of concerns related to aerosol generation with CPR.[18,19]

In essence, therefore the adaptation required for patients with suspected or confirmed COVID-19 are two-fold, i) Donning full PPE prior to any contact with patients to commence CPR and ii) Early intubation, as soon as it is practical, following initial bag and mask ventilation. Potential delays in initiating CPR can be minimised by close monitoring, anticipation of deterioration, preparedness and simulation of donning PPE.

Specific therapies for SARS-CoV-2 infection

The vast majority of children with COVID-19 only require routine supportive treatment as described above. However, a number of specific therapies to treat COVID-19 have been proposed, especially in adults given that the severity of disease and case-fatality rate are significantly worse than in children. Many of these are repurposed medications used in COVID-19 because of in-vitro evidence or hypotheses only. None have been convincingly shown to be of benefit yet, in either adults or children. Adults have been recruited to several large scale clinical trials.[20] Therefore, literature related to this is rapidly evolving and multiple trials are due to publish their findings within the next few weeks to months. A summary of mechanism of action, dose ranges and recommendations for some of the COVID-19 specific medications is listed in Table I.[21-23] Additional details related to a few of the proposed specific therapies are provided below.

Remdesivir: In the United States, the Food and Drug Administration (FDA) authorized the emergency use of remdesivir to treat hospitalized adult and pediatric patients with suspected or laboratory confirmed SARS-CoV-2 infection and severe COVID-19.[24] Although, the double-blind placebo controlled Adaptive COVID-19 Treatment Trial showed a significantly faster time to recovery in hospitalized adults, the differences in mortality rate was minimal and did not reach significance.[25] Children were excluded from this study. Therefore caution is warranted.

Chloroquine/Hydroxychloroquine: The repurposed anti-malarial/immune-modulator medications, used sometimes in combination with a macrolide such as Azithromycin attracted significant media attention during the early stages of the pandemic due to a much publicised study with significant limitations.[26] 239 clinical trials of either chloroquine or hydroxychloroquine are currently ongoing.[20] Therefore it is likely that a definitive answer about effectiveness of these medications will be obtained soon. Recently, data from a large-scale multi-national registry analysing drug regimens that used either hydroxychloroquine or chloroquine, with or without a macrolide for COVID-19 revealed an association with more

Table I. Specific therapies in children with COVID-19 [21-23]

Drug	Mechanism of action	Pediatric recommendations Comments	Dosing guidance*
Remdesivir	Inhibits viral RNA - dependent RNA polymerase	May be considered on a case-by-case basis in children with severe disease unresponsive to standard management without specific COVID-19 therapy	<40 kg: 5 mg/kg IV loading dose on day 1; then 2.5 mg/kg IV OD. ≥40 kg: 200 mg IV loading dose on day 1; then 100 mg IV OD. 5-10 days
Chloroquine(CQ) Hydroxychloroquine (HCQ)	Inhibits viral entry and endocytosis. Inhibition of glycosylation of ACE-2 receptor. Additionally, host immune-modulatory effects postulated to be beneficial	May be considered on a case-by-case basis in children with severe disease without access to Remdesivir. No evidence related to prophylaxis. Co-administration with Azithromycin not recommended. Monitor QTc	CQ: 10mg/kg base stat followed by 5mg/kg base BDHCQ: 8mg/kg stat, followed by 4mg/kg BD for 5 days.
Lopinavir-Ritonavir	Inhibits proteolysis	Recommendation unclear. Do not co-administer with Ribavirin Major p450 interactions	14 day-12 months: 16 mg/kg/dose [Lopinavir dose]15-25kg: 200/50mg 26-35kg: 300/75mg >35kg: 400/100mg 12 hourly PO, BD, 5-14days
Tocilizumab	Binds IL6 receptor and prevents IL6 activation	Has been used in COVID-19 cytokine storm in adults. Limited pediatric data. Recommendation unclear. May be considered in PIMS-TS patients who are unresponsive to standard management, as part of clinical trial.	<30 kg-12 mg/kg/dose >30 kg-8 mg/kg/dose IV infusion. Further single dose after 12h, if required.

** Other drug dosing suggestions exist. Please consult local formulary prior to prescribing.*

frequent ventricular arrhythmias and decreased survival which was retracted later.[27] This stresses the importance of balancing hypothetical benefits of treating children with COVID-19 with specific therapies, against the real treatment related risks.

Steroids: The role of steroids is unclear. There are concerns that steroids may be associated with prolonged viral shedding and therefore not routinely recommended. However, there is a weak consensus for the use of steroids in select circumstances such as refractory shock (low, replacement dose of steroids) or in patients who fail to improve with conventional management for severe ARDS.[7]

Convalescent plasma: A systematic review and meta-analysis of convalescent plasma for treatment of SARI of viral aetiologies suggested a significant reduction in mortality.[28] Indeed, various reports of improved outcomes with the use of convalescent plasma from donors with sufficient titres of neutralizing antibody to SARS-CoV-2 exist. However, the Surviving Sepsis campaign COVID-19 panel recommended against the routine use of convalescent plasma on the basis of limited trial evidence.[7] Important knowledge gaps regarding optimal titres of neutralizing antibodies to SARS-CoV-2 and availability of a sufficiently large enough donor pool with optimal antibody titres exist. However further trials are ongoing, including at least two in India.[20]

Pediatric Inflammatory Multisystem Syndrome, Temporally associated with SARS-CoV-2 (PIMS-TS)

In April 2020, pediatric critical care clinicians in the UK and elsewhere witnessed clusters of children requiring PICU admission for an inflammatory syndrome which appeared to have overlapping features of Kawasaki disease (KD), toxic shock syndrome and potentially macrophage activation syndrome or hemophagocytic lymphohistiocytosis. This syndrome is commonly being referred to as PIMS-TS or Multisystem Inflammatory Syndrome in Children (MIS-C).[4, 29]

Case definition: The UK Royal College of Paediatrics and Child Health (RCPCH), Centers for Disease control (CDC) and prevention in the US and the World Health Organization (WHO) have all put forward case definitions

Table II. Case definition and additional features of PIMS-TS, adapted from the UK Royal College of Pediatrics and Child Health guidelines

RCPCH Case Definition

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features listed below.This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative

Additional Features

Clinical:	**Imaging and ECG:**	**Laboratory:**
All: • Persistent fever >38.5°C Most: • Oxygen requirement • Hypotension Some: • Abdominal pain • Confusion • Conjunctivitis • Cough • Diarrhoea • Headache • Lymphadenopathy • Mucus membrane changes • Neck swelling • Rash • Respiratory symptoms • Sore throat • Swollen hands and feet • Syncope • Vomiting	• Echocardiogram & ECG - myocarditis, valvulitis, pericardial effusion, coronary artery dilatation • CXR - patchy symmetrical infiltrates, pleural effusion • US abdomen - colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly • CT chest – patchy symmetrical infiltrates, pleural effusion, may demonstrate coronary artery abnormalities if with contrast	All: • Abnormal fibrinogen • Absence of potential causative organisms (other than SARS-CoV-2) • High CRP • High D-Dimers • High ferritin • Hypoalbuminemia • Lymphopenia • Neutrophilia in most - normal neutrophils in some Some: • Acute kidney injury • Anemia • Coagulopathy • High IL-10 • High IL-6 • Neutrophilia • Proteinuria • Raised CK • Raised LDH • Raised triglycerides • Raised troponin • Thrombocytopenia • Transaminitis

for this condition.[30-32] While subtle variations exist, they refer to a combination of fever, evidence of hyper-inflammation, multiple organ involvement, a link to SARS-CoV-2 infection and exclusion of other underlying etiologies. The exact nature of this illness and its association with COVID-19 is far from clear at this moment. While the RCPCH case definition (Table II) merely mentions that the SARS-CoV-2 PCR may be positive or negative, the CDC and WHO criteria go further in suggesting an aetiological link with SARS-CoV-2 serology testing or contact with COVID-19. Indeed, several patients with PIMS-TS were found to have either SARS-CoV-2 RNA by PCR or more commonly IgG and IgM antibodies to SARS-CoV-2.[3,33] This raises the possibility of this being an immune-mediated disease process in children who had either asymptomatic or mildly symptomatic recent COVID-19 illness.

Clinical features and investigations: While some variability within individual patients existed, they were generally older (6-15 years of age) than the usual age-group affected by KD (<5 years of age). Patients often presented with fever for several days. While the CDC case definition suggested fever for longer than 24 hours, the WHO case definition requires presence of persistent fever of at least 3 days. Gastro-intestinal manifestations such as abdominal pain, diarrhea and vomiting were common. The abdominal signs and symptoms may be severe enough to mimic an acute abdomen such as appendicitis in some patients. Rash and mucositis were also common, however, they were less consistent than GI symptoms. Patients were noted to have high inflammatory markers (C-reactive protein, procalcitonin, ferritin). Various interleukins, especially IL-6 levels may be elevated. CRP has good correlation to IL-6 levels and may be used as a proxy marker. Warm shock with significant vasoplegia requiring vasopressors is common. Myocarditis and development of coronary artery aneurysms are the potentially life-threatening short and long-term consequences respectively. Myocarditis and reduced cardiac function have been severe enough in some patients to necessitate ECMO support.[3] Serial troponins, brain natriuretic peptides (BNP) or N-terminal-pro hormone brain natriuretic peptides (NT-proBNP), ECG and echocardiography may be useful to track the cardiac

Table III. Suggested investigations in children suspected to have PIMS-TS. Adapted from the UK RCPCH guidelines

Blood Tests: • Full blood count, blood film • Urea, creatinine, electrolytes • Liver function tests • CRP • ESR • Glucose • Blood gas with lactate • Prothrombin time, partial thromboplastin time, fibrinogen • D-Dimer • LDH • Triglycerides • Ferritin • Troponin I • BNP or NT-proBNP • Creatine kinase • Vitamin D • Amylase • Save blood, serum sample (pre IVIG) for any other investigations that may be required later	Microbiology: • Blood culture • Urine and stool culture • Throat swab culture • Nasopharyngeal aspirate or throat swab for respiratory virus /bacterial panel • Mycoplasma antibody titres • Pneumococcal, Meningococcal, Group A Streptococci, Staph aureus Blood PCR [include locally prevalent pathogens] • ASO Titre • EBV, CMV, Adenovirus, Parvovirus, Enterovirus PCR on Blood • Consider blood for enterotoxin/staph toxins • Stool for virology
Cardiac investigations: • ECG • Echocardiogram	SARS-CoV-2 Investigations: • SARS-CoV-2 Respiratory PCR • Consider SARS-CoV-2 PCR on stool and blood, if available • SARS-CoV-2 serology

involvement and help prognosticate. Coagulation abnormalities such as elevated fibrinogen, elevated D-dimers, thrombocytopenia or thrombocytosis were also frequently observed. The implications of these are not yet well understood. Heightened anxiety related to potential for new thrombosis or embolism to occur exists. However, this has not been well characterised in the literature as yet. Surveillance for thrombosis and precautions to prevent thrombosis from occurring are essential. A suggested list of investigations as per the UK RCPCH is provided in Table III. This needs adaptation to include investigations for ruling out common causes of sepsis as per the local situation.

Management: Given that this is a relatively new condition, knowledge and understanding related to this disease is evolving. Mainstay of treatment is supportive care. All patients should receive supportive therapies such as empirical antibiotics tailored to the local prevalence of bacteria, judicious fluid resuscitation and if required inotropes and/or vasopressors. Many centres used intravenous immunoglobulin (IVIG), aspirin (commonly 12.5mg/kg QDS, if no contra-indications exist) and steroids in line with existing guidelines for the apparently related Kawasaki disease with shock.[34]

If hyper-inflammation persisted, various other immunomodulators have also been tried on a case-by-case basis such as anakinra, tocilizumab and infliximab; although it is unclear whether they improve longer term outcomes. Clear definitions of failure to respond to treatment and indications to consider these immunomodulators are lacking. Tocilizumab has been considered for its inhibitory effects on IL-6. Anakinra has been used for blocking IL-1 receptor signalling which then acts on other pro-inflammatory cytokines.[35] Recovery of myocardial function after intravenous immunoglobulin has been reported.[29] However, there is limited evidence base to provide precise indications or to support one therapy over the other. In fact, coronary artery aneurysms have been reported to occur even in patients who had received tocilizumab for Kawasaki disease prior to this pandemic.[36] Concerns about re-activation of latent diseases such as tuberculosis must be borne in mind when immunomodulators are considered.

The role of anti-coagulation in management of PIMS-TS is unclear. However, several centres have used prophylactic low-molecular weight heparin after a case-by-case consideration weighing up the risks and benefits.

The key principle underpinning management of such patients is individualised management with a multi-disciplinary team approach with members of pediatric rheumatology, immunology, infectious diseases, hematology and cardiology. Serial blood tests, ECG and echocardiography may be indicated for surveillance. Frequency of monitoring and investigations has to be tailored to the individual depending on clinical, laboratory, ECG, echocardiographic response. Longer term follow-up of such patients may be essential, especially focusing on recovery of myocardial function and progression to coronary artery aneurysms. Information from global registries such as the recently established WHO Global COVID-19 Clinical Data Platform may help reduce some of the many uncertainties related to monitoring and management of this new entity.[32]

Conclusion

While children are relatively spared from the severity of COVID-19 infection, it is prudent for pediatric critical care physicians to get prepare. The challenges related to managing children with COVID-19 span every level of an organisation from procurement, estates to physicians and nurses. Simulation of a patient journey through the hospital including the critical care environment, with considerations including parents, families and other non-COVID-19 patients, can be invaluable in highlighting the lessons that need to be learnt and adaptations that must be performed. The challenges of communication and performing procedures while wearing full PPE cannot be underestimated. By following good critical care practice in airway, breathing and circulatory management with very careful attention to personal protection of staff with PPE practices and infection control for other patients, good outcome for children with COVID-19 can be achieved. Additional research into pharmacological treatments for adults and children with COVID-19 and PIMS-TS are needed to demonstrate their benefits and recommend use.

Points to Remember

- ***Though COVID-19 infection in children is less frequent and need for critical care is a relatively rare occurrence, severe disease and COVID-19 related deaths have been reported.***
- ***Indications for PICU admissions are similar to other emergencies.***
- ***In COVID-19 , step-wise escalation in respiratory support is considered as best practice . Compared to the early days of pandemic, NIV and HFNC use is increasing since it is believed that HFNC does not produce much aerosolisation.***

- ***Supportive management with repurposed or unproven medications is practised widely and more evidence for or against will be available in the next weeks or months from the ongoing studies.***
- ***A new clinical presentation reported recently is the PIMS-TS, a possibly SARS-CoV-2 related, multi-system inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome.***
- ***While managing PIMS-TS, concerns about re-activation of latent diseases such as tuberculosis must be borne in mind when immunomodulators are considered.***

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