Coronavirus Disease 2019 in Critically Ill Children: A Narrative Review of the Literature

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Abstract: Coronavirus disease 2019 has spread around the world. In the 3 months since its emergence, we have learned a great deal about its clinical management and its relevance to the pediatric critical care provider. In this article, we review the available literature and provide valuable insight into the clinical management of this disease, as well as information on preparedness activities that every PICU should perform. (*Pediatr Crit Care Med* 2020; XX:00–00)

Key Words: COVID-19; SARS-CoV-2; viral pneumonia

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in Wuhan, Hubei Province in December 2019 and has now circumscribed the globe, involving 168 countries outside of China at the time of writing. As of this writing, 1,000,000 cases have been confirmed globally (1), with 50,000 deaths, giving rise to an estimated case fatality rate (CFR) of 4%, although that number is expected to change. There has been significant regional and global variation in CFRs, with Hubei having a seven-fold increase of 2.9% versus 0.4% for the rest of China (2). Italy, the current epicenter of the European coronavirus disease 2019 (COVID-19) outbreak, currently stands at a CFR of 7.2% (3).

EPIDEMIOLOGY OF COVID-19 IN CHILDREN

Children do not appear to account for a large proportion of COVID-19 disease. In the largest series to date from China (2), pediatric patients less than 19 years old accounted for only 2% of confirmed cases. In Italy, COVID-19 cases in the pediatric cohort (0–18 yr old) account for only 1.2% (3). In Korea, children less than 19 years were 4.8% (4). In a series of 1,391 pediatric patients from Wuhan Children's Hospital who were screened from January 28, 2020, to February 26, 2020, SARS-CoV-2 was confirmed in 171 patients (12.3%) (5). This is higher than a previously described cohort of 366 children from Tongji Hospital in Wuhan that only found six positive cases (1.6%) (6). In Guangzhou, China, of 745 children who were in close contact with COVID-19 infected adults, only 10 tested positive (1.3%), suggesting a great deal of variation (7).

SEVERITY OF DISEASE IN CHILDREN

Children also appear to be relatively spared of severe disease. In the largest published COVID-19 retrospective case review in children ($n = 2,143$) to date (8), 94.1% of the children were either asymptomatic (4.4%) or had mild (50.9%)/ moderate disease (38.8%). This series was predominantly suspected, not-confirmed (65.9%), cases from winter with a variety of circulating viruses, and it is unclear what the true positive rate is in this series. In the case series of true positives from Wuhan Children's Hospital (5), 15.8% ($n = 27$) were asymptomatic and 19.3% ($n = 33$) only had an upper respiratory tract infection. The most common symptoms were cough (48.5%) and fever (41.5%)—this is supported by several other smaller case series already in the literature (6, 7, 9, 10).

In adults (2, 3), approximately 5% of patients will require intensive care. Information on pediatric patients requiring intensive care is very limited. In the large nationwide pediatric series (8), 5.2% ($n = 113$) of the 2,143 children had respiratory distress or hypoxia and 0.6% ($n = 13$) progressed to acute respiratory distress syndrome or multiple organ dysfunction. However, infants under 1 year appear to have an increased risk of severe disease with 10% ($n = 40$ out of 379 cases) of the cohort fulfilling severity criteria, defined as an oxygen saturation less than 92%. The rate of severe or critical disease in the

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other age groups was lower (7.3% in 1–5 yr, 4.2% in 6–10 yr, 4.1% in 11–15 yr, and 3% > 16 yr), with a death in a 14 year-old. The infant group had the highest proportion of clinically diagnosed disease, and there remains the possibility that other viruses such as influenza A/B and respiratory syncytial virus may have caused severe disease.

In the cohort with 1,391 children from Wuhan Children's Hospital (5), only three children required intensive care. One child had preexisting immunosuppression (leukemia on maintenance chemotherapy) and the other two had preexisting though perhaps unrelated conditions (hydronephrosis and intussusception). Unfortunately, the child with intussusception died of multiple organ failure 4 weeks after admission.

In the small cohort from Tongji Hospital (6), Wuhan, one out of the six children with COVID-19 was admitted to intensive care. This child received antiviral therapy (ribavirin, oseltamivir), glucocorticoids, pooled immunoglobulin from healthy donors as well as supplemental oxygen. It is unclear if she required mechanical ventilation. There were no deaths in this cohort. Other published small cohorts have also not had documented admission to the PICU (7, 11, 12).

WHY ARE CHILDREN RELATIVELY SPARED FROM SEVERE DISEASE?

The published data and anecdotal evidence from PICU colleagues globally supports the notion that most children do not exhibit severe disease. Most children who tested positive in China were identified because of screening of household contacts and family clusters rather than because of signs and symptoms of disease (5–7). This experience is in keeping with the previous coronavirus outbreaks of Middle East respiratory syndrome coronavirus and SARS CoV where children had a milder manifestation of disease (10).

Why children appear to be less severely affected, compared with adults, by SARS-CoV-2 is unknown. Lessons gleaned from adults may provide some clues. In adults, the pathophysiology of COVID-19 appears to be related to immune dysregulation and a resultant cytokine storm (13, 14). Adults with COVID-19 presenting with progressive and/or severe lymphopenia and an increasing neutrophil count have been associated with higher disease severity (13–16). In addition, adults who have required ICU care have had higher levels of circulating cytokines associated with the innate immune response (16). Clinical worsening in the adult population has been described to occur in the second week of illness, in keeping with the proposed pro-inflammatory pathophysiology, resulting in progressive lung injury (15). It has been postulated that SARS-CoV-2 induces a delayed or suppressed interferon response during the initial phase, resulting in subsequent uncontrolled viral replication and a hyperinflammatory response by the body (13).

Children, on the other hand, have not displayed a similar tendency toward immune dysregulation. Lymphopenia was present in only 3.5% of pediatric cases in the Wuhan Children's Hospital Series (5), compared with 70.3% in hospitalized adults (17). Also, other markers of a pro-inflammatory response such as C-reactive protein, deranged liver function tests, and D-dimers are not common in children as compared with the adult population (5–7).

Children may be also less susceptible as a result of possible age-related differences in the expression of angiotensin-converting enzyme 2 (ACE2) in humans (18). SARS CoV and SARS-CoV2 both use ACE2 as the cell receptor in humans, predominantly in type II pneumocytes, and its presence appears to protect against lung injury (18, 19). In rat lung, however, the expression of ACE2 decreases with age which runs counter to the proposed mechanism of protection (20). The variation of ACE2 expression and activity with age and its impact on disease is a major knowledge gap in our understanding of pediatric COVID-19.

We have little data on the impact on SARS-CoV-2 on children with chronic illnesses. Many children are likely to suffer these comorbidities with advanced treatment and hence will need to monitored closely for severe disease.

DIAGNOSIS

The main method for detection for SARS-CoV-2 has been by real-time polymerase chain reaction (RT-PCR) testing on upper or lower respiratory tract secretions. As the majority of children have had mild symptoms, the vast majority of samples have been obtained via nasopharyngeal swabs. Viral shedding via the fecal route has been detected in children, although implications for transmission are unclear (7).

As compared with adults, children have also not consistently demonstrated abnormal chest radiographs on presentation. In a case series of 20 children from Wuhan, CT scans of the chest were performed in order to support the diagnosis of COVID-19, with 80% of the children ($n = 16$) showing some abnormality, including 60% with ground-glass opacities and 50% with consolidation with surrounding halo sign (21). However, given children have generally mild disease, and turnaround time for RT-PCR is generally improving, the use of CT scan as a diagnostic tool may have limited uptake.

It is also worth noting that coinfection with other respiratory viruses has been described. Forty percent of children in the same radiological case series above were noted to be coinfected with other pathogens such as influenza A/B, respiratory syncytial virus, and mycoplasma (21). This is in keeping with prior studies showing that other viruses can be isolated from up to two-thirds of children with coronavirus infection (22).

SPECIFIC THERAPIES

A number of clinical trials are underway to evaluate different agents. However, very few of these studies involve children, and data will have to extrapolated from adult studies. Remdesivir, lopinavir/ritonavir, favipiravir, chloroquine, and a number of other agents have all been postulated to be effective, and trials are underway to further evaluate their role. Use of these agents should be as part of a clinical trial

to better understand their role, and trials should enroll children to better understand their safety and effectiveness in this population.

SPECIFIC MANAGEMENT CONSIDERATIONS IN THE PICU

Despite likely small numbers, caring for children with COVID-19 will require careful considerations in clinical care, staffing and isolation requirements, and all PICUs should be prepared for these possibilities.

Use of Noninvasive Ventilation and High-Flow Nasal Cannula

Given that children appear to have mild disease and may have a clinical picture similar to that of viral bronchiolitis, the use of noninvasive ventilation (NIV), and/or high-flow nasal cannula (HFNC) for respiratory support would likely be preferred amongst PICU clinicians. Some institutional guidelines would, however, suggest avoiding NIV and HFNC in open wards to reduce the risk of aerosolization of droplets and move patients toward early intubation, if negative pressure rooms are unavailable. There are, however, concerns about balancing the potential morbidity of intubation for the pediatric patient with mild respiratory distress with the theoretical risk of increased aerosolization. At present, as rates of severe pediatric COVID-19 remain low and the rates of other viral etiologies remain unchanged, individualized institutional practice in the use of NIV/HFNC may be considered in appropriate pediatric patients.

Intubation of Pediatric COVID-19 Patients

Several guidelines about airway management for COVID-19 have been made publicly available from ICUs and anesthesia societies (23–26). Local guidelines are largely in place for many hospitals. The principles of maintaining safety for both patient and the intubating team remain paramount.

Prior to intubation, it is important to minimize the number of staff in the room and all staff to apply good hand hygiene and don full personal protective equipment (PPE). The patient should ideally be admitted to a negative pressure isolation room. A clear checklist for drugs and equipment should be in place and roles clearly delineated (**Table 1**). Most importantly is acknowledging the potential for aerosolization and ensuring that all staff present are familiar and comfortable with required PPE.

Communication is critical and made particularly challenging by the use of PPE during intubation, especially in units with powered air-purifying respirator use. Closed-loop communication is crucial and members of the team should monitor each other for potential contamination.

The most experienced practitioner should perform intubation. Several centers do advocate the use of video laryngoscopy if available, and if the practitioner is trained in its use—this may reduce distance to the patient airway. Rapid sequence induction with paralysis to avoid coughing is ideal. Adult guidelines suggest apneic oxygenation and minimal bagging to reduce aerosol generation, but this will be challenging in infants and small children with a small functional residual capacity and limited space. As such, bag valve mask ventilation can be considered with great care, with a tight mask seal (two-handed technique might be required) and small tidal volumes. Cuffed tubes can be selected to minimize significant air leaks during high-pressure ventilation and possibly minimize transmissibility.

Once the child is intubated, disruptions to the ventilator circuit should be minimized, with closed in-line suction. Staff should don appropriate PPE and be prepared to clamp the tube if ventilator circuit breaks are anticipated. Doffing PPE after the procedure requires equal care and is a high-risk period for contamination risks.

Given the complexity of the process, it is strongly recommended that hospitals and units run simulations to practice each step of the intubation and extubation process prior to having a real patient in the unit. The complex process of donning and doffing PPE, the need for anticipating far more than usual, and the challenges of communication cannot be over-emphasized.

Caregivers and Parents

One or more caregivers usually accompany pediatric patients and this too needs to be taken into account when considering the care of COVID-19 patients. Caregivers are close contacts of the infected patient, although they may be asymptomatic at the time—in the Wuhan Children's Hospital series with active case finding of close contacts, 90% of confirmed cases had family members who were either confirmed or suspect disease (5). Many centers have limited the number of caregivers at the bedside to one caregiver, restricting movement of the caregiver in the hospital, and ensure that staff maintains PPE when at the bedside. Clearly, given the high rates of familial clustering, there is a high likelihood of these family members being similarly infected, and local public health guidance should be followed to ensure minimal risk of nosocomial spread. Within this environment, the ability to deliver the same standard of family-centered care that is given during peacetime will be significantly compromised. The significant psychologic stress that may be experienced by a solo caregiver, coupled with staff time constraints, impaired communication potentially generated by full PPE, and the urgency of multiple sick patients create a perfect storm of challenges. In this scenario, the creation of a family liaison contact may alleviate some of the burden and allow a basic level of family-centered care to be delivered (27).

Patient Flow

As point-of-care testing is unavailable, in the setting of widespread community transmission, it is currently recommended that hospitalized children who fit local case definitions for COVID-19 be treated as a patient under investigation until tests come back negative. This implies using the same levels of infection prevention and control, speaking to the tremendous importance of rapidly and widely available testing, given the

TABLE 1. Airway Checklist for Intubation

Checklist for intubation
Plan ahead
1) Make sure you have practiced donning and doffing and have a buddy. Know your PPE
2) Assign tasks—intubator (most experienced with airways), team leader, airway assistance, second nurse for medications. Minimize staff in room
3) Negative pressure room, if available
4) Establish clear strategy for communication
Intubation
1) Don PPE
2) Establish monitoring, IV access, intubation equipment (consider video laryngoscopy, if available), filter between face-mask and bag
3) Preoxygenate
4) Plan for rapid sequence induction, with minimal bag mask ventilation
5) Intubate and confirm
6) Attach to ventilator, with inline suction
7) Clean relevant surfaces
8) Disposable equipment should be disposed of via hospital protocol
9) Ensure proper doffing, monitored by buddy

PPE = personal protective equipment.
Adapted from Paediatric Intensive Care Society Society UK: Paediatric Critical Care Coronavirus Disease 2019 Guidance (26).

resource and personnel requirements involved in this process. Given the low rates of critical illness due to COVID-19, this process will likely exert more impact on day-to-day processes in PICUs than sick patients with confirmed infection.

Preparing Your PICU for Surge Capacity

Although pediatric cases requiring critical care might be low, it is important to anticipate that exposures may occur and staff are quarantined for a period of time. It may be necessary to use a segregated roster where two or three groups of clinical staff are completely separated from each other such that if one group is exposed, the entire team may be quarantined together and the next team can take its place. In lean PICU teams, this may be extremely challenging but the scenario needs to be considered carefully and backup plans established.

Identifying potential surge capacity in the form of extra beds, staff, and equipment should also be anticipated and published guidance on early planning for pandemics is already available (27, 28). This may necessitate reducing elective work and anticipating the need for high dependency areas to be converted to intensive care space. Identifying clinical staff who may be able to bolster the PICU response, for example, pulmonologists, and anesthetists may be necessary at an early stage. Nursing staff may need to look to up-skilling general ward staff to help look after the less critically ill patients, allowing the PICU nursing staff to focus on the sickest patients.

It is imperative that clear guidelines about the use of appropriate PPE are established and training done at all levels. This is to ensure appropriate usage and prevent PPE from being wasted unnecessarily. In a global pandemic, stocks of necessary items are likely to run low and hospital/national workflows should be established to maintain staff safety.

Given the burden of disease on adult ICUs, it is also possible that pediatric units may be called upon to help look after adult patients so as to increase COVID-19 capacity in adult units. Feasible options such as increasing the age limit for the PICU to 25 years old or to consider accepting patients with shared PICU diagnoses, such as diabetic ketoacidosis, overdose, trauma, or congenital cardiac disease might have to be considered. These arrangements should be made early and the decisions made must reflect local and regional capabilities and in line with appropriate standards of care for the patient (29).

Global Resources

Setting up local and international communication groups over social media channels such as WhatsApp, Telegram, and Twitter have also proved to be very helpful in disseminating information and education for this emerging infection with rapidly generated data. The hashtags #PedsICU and #COVID19 have garnered high volumes of information for Twitter users online. These social media channels, in combination with Free Open Access Medical Education websites such as Open Pediatrics and the Life in the Fast Lane blog (www.litfl.com) have also served as international COVID-19 resources and facilitated knowledge sharing at a rapid rate and fostered a powerful sense of community amongst practitioners.

Care for Staff, Mental Well-Being

This is a stressful time for all clinical staff and the sense of isolation and fear can be profound. Social distancing has been implemented in several countries and regular hospital meetings, teaching sessions, and conferences have largely been canceled. Anxiety about personal welfare as well as the safety of family and friends cannot be underestimated. Hospital and ICU leadership is critical during this time and communication about plans and workflows needs to be measured and well-paced. It is wise to consider programs in the unit and hospital to encourage staff and to consider measures to cater to mental wellbeing of staff.

CONCLUSIONS

At present, critically ill COVID-19 pediatric patients remain rare, as the majority of pediatric cases have mild symptoms. The substantial rise in international numbers, however, necessitates early planning in consideration of a rise in pediatric cases. A comprehensive response will require cooperation at a local, regional, and national level. In addition, the international PICU community should act together to share information rapidly given the limited amount of information we have on these critically ill children.

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