Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Resuscitating Children with COVID-19: What the Pediatric Anesthesiologist Needs to Know

TO ADDRESS the challenges of resuscitating cardiac arrest victims in the setting of the coronavirus disease 2019 (COVID)-19 pandemic, the American Heart Association, in collaboration with the American Academy of Pediatrics, America Association of Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, American Society of Anesthesiologists, American Association of Critical Care Nurses, and National EMS Physicians, recently published an interim guidance for conducting cardiopulmonary resuscitation (CPR) in basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19.[1] Pediatric-specific resuscitation guidelines also were published in *Pediatrics* in early May 2020.[2] Over the past couple of decades, there have been significant improvements in outcomes after witnessed cardiac arrest in children, mostly due to the initiation of high-quality, early chest compressions and early cardiac defibrillation. During this COVID-19 pandemic, there is an urgent need to maintain this progress by ensuring best practice CPR is performed and, at the same time, balance the need to protect rescuers from acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the administration of CPR.

There are significant concerns that the time it takes to arrive at a patient's room, don personal protective equipment (PPE), and secure an invasive airway, may delay the initiation of effective CPR by 10 minutes.[3] Many hospitals are testing all inpatients weekly for SARS-CoV-2 to clearly identify infected patients. To minimize delays in initiating CPR, advanced directives and goals of care must be in place in known, severely ill SARS-CoV-2 patients. Ideally, all patients under treatment or investigation for SARS-CoV-2 should be treated in negative- pressure rooms. Healthcare teams should have clearly defined (or well- thought- out) resuscitation plans and actively monitor these patients for any signs of clinical deterioration. Healthcare teams should be ready to escalate critical care in any infected SARS-CoV-2 patient who may require endotracheal intubation and mechanical ventilation nonemergently to minimize the risk of having to initiate CPR.

This freestanding editorial aims to examine some of the reasons for the different pathophysiologies of SARS-CoV-2 infection in children compared with adults and highlight the critical resuscitation recommendations in neonates and children with COVID-19 for the pediatric anesthesiologist.

Pathophysiology of COVID-19 in Children

A paradox of the COVID-19 pandemic is that children have been relatively spared from severe clinical disease, even though the pediatric population is typically vulnerable to infectious diseases, especially from respiratory viruses.[4] Only about 1% to 5% of COVID-19 cases diagnosed so far have been reported in children. They often have milder disease than adults and death associated with the disease has been extremely rare.[4,5] Consider respiratory syncytial virus (RSV) infection that may cause severe respiratory disease in young children with long-term sequelae, especially those with comorbidities such as congenital heart disease. However, in older children and adults, RSV infection is generally not clinically severe.[6] SARS-CoV-2 behaves in the opposite direction, with evidence suggesting that children are just as likely as adults to become infected with SARS-CoV-2, but are less likely to be symptomatic or develop severe symptoms.[7-9] The incubation period of SARS-CoV-2 in children was found to be about 2 days, with a range of 2- to- 10 days.[10] The importance of children transmitting the virus remains uncertain. A recent systematic review concluded that children have seldom been the index case, and thus far, children with SARS-CoV-2 infections have seldom caused outbreaks.[11]

Why do most children with COVID-19 disease have a milder disease? There are several plausible explanations.[12,13] The first explanation is that the immune systems of children and adults are different in respect to their composition and functional responsiveness.[14] Milder disease presentation might be due to trained immunity when innate immunity cells become memory cells after antigen exposure.[15] Both frequent viral infections and vaccines in children induce an enhanced state of activation of the innate immune system that results in more effective defense against different pathogens.[16] This also may explain the more severe infection from SARS-CoV-2 in young infants, as they have not received all of their vaccinations and have not been exposed to many childhood viruses to

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develop this cross-reactive viral immunity.[17] The adaptive immune response also may play an important role in COVID-19 adults infected with SARS-CoV-2, especially those with severe disease, as they usually have a decreased lymphocyte count. Children infected with SARS-CoV-2 have normal lymphocyte counts, secondary to the frequent viral infections experienced during childhood and hence frequent activation of the immune system.[15,16] There also are data to suggest that after a child's first exposure to SARS-CoV-2, there is a rapid development of protective antibodies, with initial immunoglobulin M production switching rapidly to immunoglobulin G within 1 week. This efficient humoral immune response might explain why children have milder symptoms and recover more quickly than adults.[17,18]

A second explanation for a milder COVID-19 disease in children is the presence of other viruses in the mucosa of the lungs and airway that could limit the growth of SARS-CoV-2 by direct virus-to-virus competition and interactions.[19] Data from the current pandemic suggest that a higher number of viral copies of SARS-CoV-2 results in a more significant disease severity.[20] In the Italian experience, 9% of hospitalized patients with COVID-19 were healthcare workers, who were probably exposed to large amounts of the virus.[21,22]

The third possible explanation for a milder COVID-19 disease in children is related to the differences in the expression of the angiotensin-converting enzyme (ACE) 2 receptor, which is necessary for the binding of the spike protein on SARS-CoV-2 for entry into the host cell.[23] This receptor is expressed in the airways, lungs, and intestines. ACE 2 is counterregulatory to the activity of angiotensin II generated through ACE 1 and is protective against the detrimental activation of the renin-angiotensin-aldosterone system. Angiotensin II is catalyzed by ACE 2 to angiotensin I, which exerts vasodilatory, anti-inflammatory, and antifibrotic effects. There is age-dependent ACE-2 gene expression in nasal epithelium, with significantly higher levels in adults than children.[24,25] This lower ACE 2 expression in children may explain why SARS-CoV-2 may not be able to enter the host cell efficiently, and so COVID-19 is asymptomatic or only causes a mild disease. It is also possible that ACE inhibitor use in adults is protective and may be associated with better survival among patients with COVID-19.[26,27]

Although SARS-CoV-2 causes mild symptoms in most children, it also can cause severe cardiorespiratory failure, requiring life-sustaining interventions including CPR, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). In the United States, children comprise 1.7% of all COVID-19 cases, and less than 2% of these patients require admission to the intensive care unit.[28] A recent study published in May 2020, described 48 children with COVID-19 admitted to 46 participating pediatric intensive care units in North America.[28] The median (range) age of the patients was 13 (4.2-16.6) years. Thirty-five (73%) patients presented with respiratory symptoms and 18 (38%) required endotracheal intubation and mechanical ventilation. At the end of the study period, 2 patients (4%) died, and 15 (31%) remained hospitalized, with 3 still requiring ventilatory support and 1 receiving ECMO.[28] There also have been reports of COVID-19- associated pediatric multisystem inflammatory syndrome not unlike Kawasaki disease.[29] Some children have developed significant myocarditis and myocardial dysfunction, which has required the initiation of ECMO.[28-30] To date, 3 pediatric patients have required ECMO support, which is likely to increase as the virus continues to spread.[31]

Guidelines for the Safe Resuscitation of COVID-19 Patients

The resuscitation algorithms have not changed in the new guidelines.[1,2] Important additions include the emphasis of protecting the rescuers performing CPR.[1,2] Among in-hospital patients with suspected or confirmed COVID-19, healthcare workers should don PPE before entering a patient's room, even in an emergency such as CPR, and airway management.[1,2,32] This may be more difficult emotionally for healthcare providers, especially when a child's life is at stake.[3] The current resuscitation guidelines also advocate the importance of limiting personnel attending to in-hospital resuscitations.[1,2,33] Clear communication of the patient's COVID-19 status to newly arriving rescuers or when the patient is transferred to a new setting is also critical.

During CPR, bag-mask ventilation, chest compressions, and endotracheal intubation are all aerosol-generating medical procedures. Therefore, all rescuers should wear PPE, consisting of either a powered air-purifying respirator or an N95 mask, in addition to goggles or a face shield, gown and gloves.[1,2,32] Bag-mask ventilation should be initiated with an in-line high- extraction particulate air filter. A tight face mask seal should be ensured to minimize any air leak and possible aerosolization of viral particles. Endotracheal intubation should be prioritized early during the resuscitation in these patients, with the cessation of chest compressions during intubation. If intubation is delayed, a supraglottic airway device with a filter should be placed early, again aimed at minimizing the aerosolization of viral particles and protecting the rescuers. Ideally, the closed airway circuit should not be disconnected.[1,2] The guidelines also recommended the consideration of video laryngoscopy for endotracheal intubation by the most experienced provider, increasing the likelihood of first-pass success.[1,2] An appropriately sized, cuffed endotracheal tube is recommended to minimize aerosolization of viral particles. Following intubation, an in-line high- extraction particulate air filter should be placed and ideally, the patient placed on a ventilator as soon as possible.

If the patient is already intubated at the time of the cardiac arrest, the guidelines recommended leaving the patient on the mechanical ventilator to maintain a closed circuit and minimize the risk of aerosolization.[1,2]. Suggested changes to the ventilator settings include increasing the fraction of inspired oxygen to 1.0, changing to pressure-controlled ventilation and limiting pressures as needed to achieve adequate chest rise, and adjusting positive end-expiratory pressure levels to balance lung volumes and venous return.[1,2] Accidental extubation should be avoided to minimize the risk of aerosolization.

Another special consideration is the stabilization and resuscitation of the newborn born to a mother with suspected or

confirmed COVID-19. The risk of vertical transmission of COVID-19 during pregnancy remains unclear. Neonatal resuscitation may be performed in the delivery room 6 feet away from the mother, with a curtain/physical barrier or in an adjacent negative- pressure room.[33] Current American Academy of Pediatrics and Neonatal Resuscitation Program guidelines should be followed.[1,2] The initial steps of resuscitation such as drying, tactile stimulation, placement of pulseoximetry, and electrocardiograph leads are not aerosol- generating.[1,2] However, suctioning of the airway, endotracheal intubation, and administration of medications through an endotracheal tube (especially uncuffed tubes) are considered aerosol-generating medical procedures. The current guidelines recommend obtaining prompt access of umbilical vessels and administration of resuscitative medications here rather than administration into the endotracheal tube.[2,33] All providers must wear appropriate PPE, and the most experienced provider must perform the endotracheal intubation.[1,2,33]

Summary

Despite the lower incidence of serious COVID-19 infection in children, healthcare teams must be prepared to resuscitate these patients. To reduce the risk of transmission of SARS-CoV-2 during the resuscitation of cardiac arrest victims, the American Heart Association recently published interim guidance, emphasizing the importance of donning appropriate PPE, limiting the number of personnel involved, and achieving early airway control.

Conflict of Interest

None.

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